Dementia Prevention

through Optimising Cardiovascular Risk Factor Management

Jakob Laurens Schroevers

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Dementia Prevention through Optimising Cardiovascular Risk Factor Management

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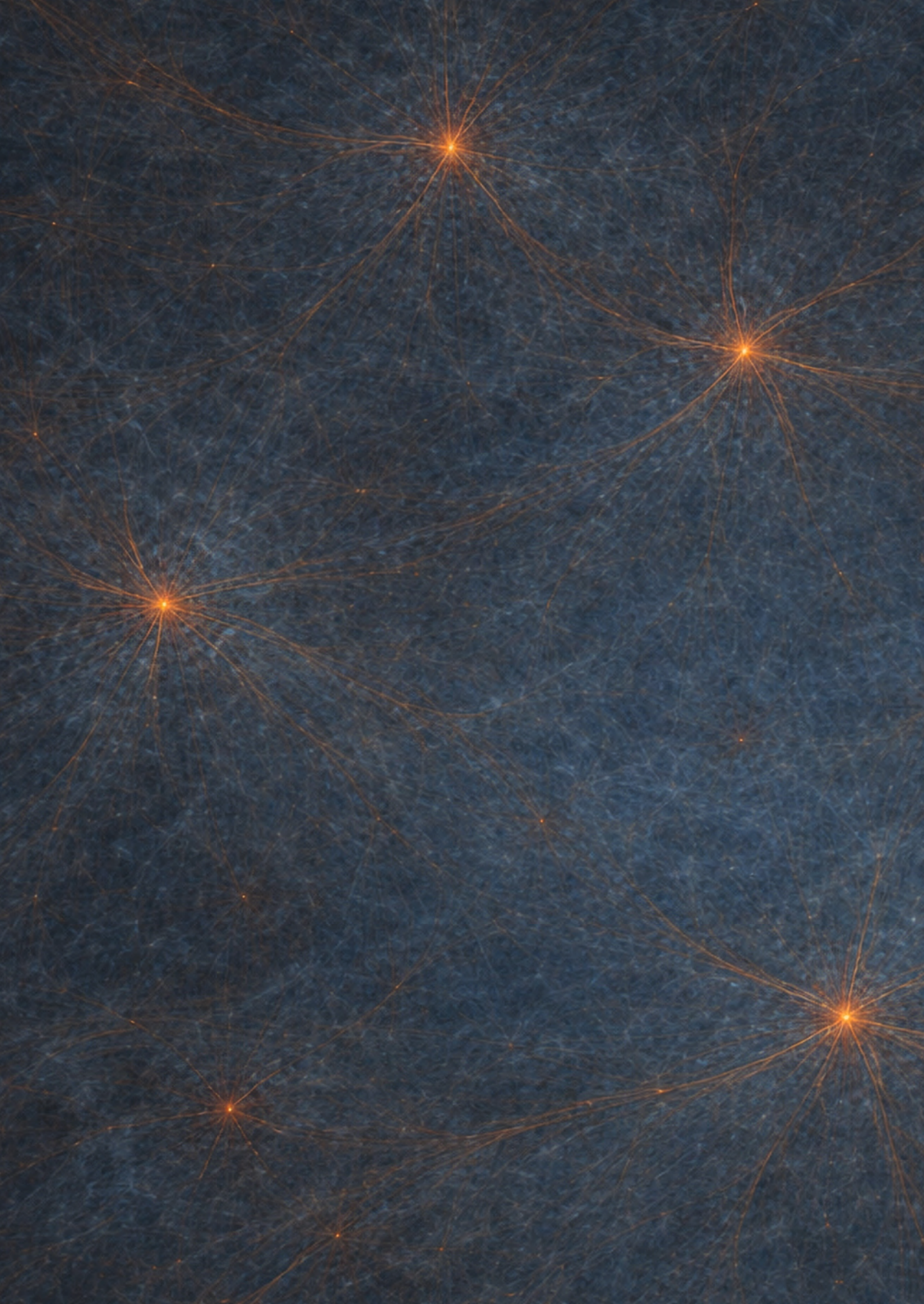
TABLE OF CONTENTS



Chapter I

General Introduction

Dementia is an umbrella term for a number of symptoms that occur in neurodegenerative diseases such as progressive decline of memory, other cognitive abilities, changes in mood and behaviour resulting and the inability to perform daily activities.[1] There are several forms of dementia, with the most common being Alzheimer's disease (AD), vascular dementia, Lewy body dementia, and mixed dementia. The global number of people living with dementia is projected to nearly triple, exceeding 150 million by 2050, with the largest rise expected in low- and middle-income countries due to increasing life expectancy and population growth.[2]

'Prevention is better than cure', often attributed to Dutch philosopher Desiderius Erasmus, is particularly apt in the context dementia.[3] Despite recent approvals by regulatory authorities for treatments targeting specific subgroups of patients with Alzheimer's disease, a widely accepted and impactful treatment, let alone cure, remains elusive and may still be years away.[4] Moreover, if a cure for dementia is discovered, it will likely be too expensive initially for regions with the highest dementia rates. This emphasises the importance of focussing on prevention of dementia by targeting modifiable risk factors, ideally through cost-effective and rapidly deployable interventions. In recent years, a number of potential modifiable risk factors for all-cause dementia have been identified, with the majority being closely linked to cardiovascular health.[5] However, trials targeting these multiple factors simultaneously have not provided clear evidence of the effectiveness of multidomain interventions in reducing dementia risk compared to usual care.[6,7] Focusing research on specific, single risk factors could help clarify their specific contributions to dementia risk, ultimately paving the way for the development of more effective multidomain prevention strategies in the future.

Hypertension, or chronically elevated blood pressure (BP), is one of these individual modifiable risk factors for all-cause dementia.[5,8] It affects approximately 70% of individuals over 60, and causes vascular damage throughout the body, including the brain.[9] Cerebrovascular injury increases the risk of dementia, contributing to specific vascular dementia, but also to more prevalent forms seen in older individuals, which are often characterized by a combination of vascular and other pathologies.[10-12]

Lowering BP through antihypertensive medication (AHM) may reduce the risk of dementia in middle-aged hypertensive individuals.[13,14] Several classes of AHM are available to lower BP, each acting through distinct mechanisms of action. The primary classes used for BP control are angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, (dihydropyridine) calcium channel blockers (CCBs), and (thiazide) diuretics. According to prevailing guidelines, these

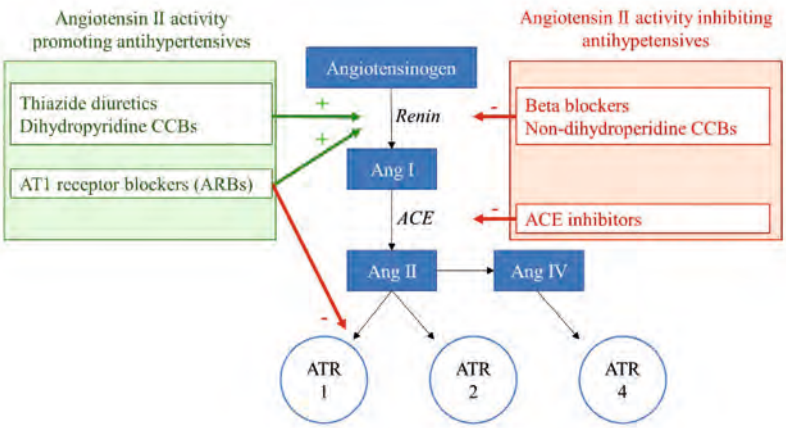
medications are generally considered equally effective for lowering blood pressure, giving physicians flexibility in their choice.[15-17]

However, some studies indicate that users of different types of antihypertensive classes have diverging risks of incident dementia. A post-hoc analysis of the Prevention of Dementia by Intensive Vascular Care (PreDIVA), a large-scale dementia prevention trial studying 6–8 years of cardiovascular risk management in over 3,500 older adults, indicated that both ARBs and CCBs were associated with lower dementia risk compared to other AHM classes.[18] More recently, a large network meta-analysis supported these findings, reporting similar lower dementia risk for ARBs and CCBs.[19] However, two smaller-scale individual patient data (IPD) studies did not report significant differences between classes.[20,21]

The potential underlying mechanisms by which specific AHM classes may contribute to a lower dementia risk are speculative but appear to be independent of BP control, suggesting these classes may exert pleiotropic effects.[13,18] For example, CCBs regulate cellular calcium influx, potentially preventing neuronal cell death, and they may even directly influence AD pathology by reducing amyloid beta production and neurofibrillary tangle formation.[22,23] ARBs may improve cerebral blood flow, enhance memory function, and reduce inflammation.[24] Furthermore, an autopsy study showed that individuals treated with ARBs had less AD pathology, including reduced amyloid beta deposition, compared to those treated with other AHM classes.[25] The recent "angiotensin hypothesis" groups the antihypertensive classes that have been associated with lower dementia risk under one overarching theory.[26-28] It divides AHM into two groups based on their presumed effects on cerebral angiotensin II type 2 and 4 receptor activity (**Figure 1**).

Detecting class-specific differences requires large, carefully selected populations: individuals with hypertension who need AHM therapy and are sufficiently at risk of developing dementia. Age is a critical factor in dementia risk, as the condition primarily develops later in life. Including younger participants (e.g., age 50) is impractical due to the extended follow-up required to diagnose sufficient dementia cases. Conversely, including older participants (e.g., age 80 and over) risks capturing individuals in whom the majority of preventable brain injury has already occurred, thereby limiting the potential protective effects of AHM. Trials primarily focused on cardiovascular outcomes, which included dementia as a secondary outcome, illustrate this issue. These trials often involve younger populations and shorter follow-up periods, limiting their ability to detect class-specific differences in dementia risk. Another important consideration is the method of comparison between AHM classes.

Figure 1. Angiotensin hypothesis.[29]



Angiotensinogen is converted by renin to angiotensin I (Ang I), which is subsequently converted by angiotensin-converting enzyme (ACE) to angiotensin II (Ang II). Angiotensin II may cause physiological effects by binding to angiotensin II receptor types 1 (ATR 1) and 2 (ATR 2), or may be metabolised to angiotensin IV (ang-IV), which binds to angiotensin II receptor type 4 (ATR 4). ATR 1 activity causes vasoconstriction, so its inhibition, for example through angiotensin receptor blockers (often also referred to as AT1 receptor antagonists), promotes vasodilation and lowers blood pressure. ATR 2 is associated with vasodilation, reduced oxidative stress, and inflammation, and ATR 4 with improved memory function.[30-33] Angiotensin receptor blockers, dihydropyridine calcium channel blockers, and thiazide diuretics (on the left) *increase* renin, thus promoting ATR 2 and ATR 4 activity. In contrast, beta blockers, non-dihydropyridines (on the right) *inhibit* renin, and ACE inhibitors *inhibit* the conversion of Ang I to Ang II, both resulting in reduced ATR 2 and ATR 4 activity.

Comparisons to users of placebo (in clinical research) or non-use (in observational studies) are highly problematic, as untreated hypertensive patients have an elevated dementia risk, diminishing the contrasts between AHM classes. Similarly, comparisons to "any other AHM" or non-hypertensive individuals may also obscure class-specific differences. Many studies rely exclusively on baseline data for exposure and confounders, ignoring changes in medication or health over time – an issue compounded by the long follow-up required in dementia research. Major adverse cardiovascular events and mortality, primary reasons for initiating AHM therapy, are often unaccounted for. Particularly mortality is a competing risk for dementia, as participants with high mortality rates may not survive to ages where dementia typically develops, potentially resulting in deceptively lower observed dementia rates. Observational studies face additional challenges from the risk of bias and confounding, particularly confounding by indication, where differences in dementia risk between AHM classes are attributed to varying underlying health profiles rather than the effects of the medication classes themselves. This type of confounding can affect data at multiple levels; for example,

cardiovascular comorbidities may simultaneously impact both the choice of AHM class and dementia risk, complicating efforts to isolate class-specific effects. Other factors that may systematically shape prescription patterns include medication availability, cost, reimbursement policies, patients' socioeconomic status, and physician preferences.

All these challenges are reflected in the existing body of evidence. To date, no trials have specifically investigated antihypertensive medication (AHM) classes with incident dementia as a primary outcome, and the available studies are consistently limited by at least some of the methodological issues outlined above. When moving towards a recommendation for a specific AHM class to prevent dementia, it is crucial to incorporate major adverse cardiovascular outcomes and mortality as key endpoints alongside dementia, as these remain the primary reasons for initiating AHM therapy. Additionally, physicians' perspectives on AHM must be carefully considered, as disregarding their views could hinder the adoption of guideline changes.

Recently, dyslipidaemia has been added to the growing list of modifiable risk factors for dementia as reported by the authoritative Lancet commission on dementia prevention, intervention, and care.[5] It refers to a metabolic disorder marked by abnormal serum levels of one or more lipids or lipoproteins.[29] Adverse lipid profiles are thought to contribute to dementia risk through atherosclerotic plaque formation, inducing vascular disease.[30] Additionally, genes involved in dyslipidaemia, such as the Apolipoprotein E (APOE) gene, are thought to alter brain cholesterol homeostasis, potentially promoting amyloid beta deposition and thus increasing Alzheimer's disease risk.[31] The association between dyslipidaemia in mid-life and increased risk of late-life dementia has been well investigated.[32,33] However, whether dyslipidaemia in older age is associated with increased dementia risk remains unclear, with perhaps, similar to hypertension, U-shaped associations at play.[34] This is particularly relevant because, although physicians often address adverse lipid profiles with dietary changes and cholesterol-lowering medications, there is frequent reluctance to start or continue these therapies in older, more frail individuals due to less certain long-term cardiovascular benefits and increased vulnerability to side effects.[35,36] Statins, the most commonly prescribed cholesterol-lowering drugs, are often associated with burdensome side effects, including muscle pain and fatigue.[37,38] Furthermore, studies have often investigated one or two lipid markers rather than a full lipid panel.[39-41] Examining the complete lipid profile allows for a more complete, nuanced understanding of how various lipid components may collectively relate to dementia risk.

Objectives and Chapter Summaries

In the first part of this thesis, potential differences between AHM classes and dementia risk were further investigated, addressing previously identified methodological challenges, particularly confounding by indication and the competing risk of mortality through the use of time-dependent models. Additionally, we examined physicians' preferences regarding AHM prescribing and explored differences between AHM classes in relation to major adverse cardiovascular events.

The second part, focused on exploration of another modifiable cardiovascular risk factor for dementia, dyslipidaemia, by investigating how various lipid profiles are associated with dementia risk in community-dwelling older adults, while addressing potential confounding mechanisms.

Chapter II describes whether the lower dementia risk for certain AHM classes, specifically ARBs and CCBs previously observed in the PreDIVA study were stable over prolonged follow-up. We additionally tested the aforementioned angiotensin hypothesis, by comparing angiotensin II-stimulating with angiotensin II-inhibiting antihypertensives. For this study, we used data from the PreDIVA trial and its Observational Extension.[6,42]

Chapter III expands upon previous methodologies by directly comparing AHM classes with one another in respect to dementia risk, employing a time-dependent model to account for dynamic changes in medication exposure and health status over time. For this study, we used routine-care data of over 130,000 older primary care patients. This large population allowed for extensive subgroup and sensitivity analyses to test the robustness and specificity of our findings, with a particular focus on addressing competing risk and confounding by indication.

Chapter IV investigates how previously observed differences between AHM (sub)classes extend beyond dementia and mortality risk, by include major adverse cardiovascular events – the primary reasons for initiating AHM therapy – alongside dementia and mortality as a composite outcome. In this study, we compared AHM (sub)classes based on the first occurrence of acute myocardial infarction, stroke, dementia, or mortality. To further mitigate confounding by indication, we specifically selected patients treated for primary hypertension only, excluding participants with a history of cardiovascular comorbidities, using dynamic routine-care data from over 80,000 older primary care patients.

Chapter V explores physicians' preferences for specific AHM classes, which may act as potential source of confounding between AHM classes and dementia risk. We interviewed 18 Dutch general practitioners (GPs) on their perspectives, preferences, and practices in prescribing AHM classes in patients with primary hypertension. Our aim was to gain further insights into how GPs interpret and apply guideline-proposed equivalence among AHM classes in practice, and how their prescribing patterns may influence clinical care and research that assumes AHM equivalence.

Chapter VI investigates the relation between various common serum lipids and incident dementia in community-dwelling, older adults using data from the aforementioned PreDIVA trial, specifically addressing potential biases, confounders and modifiers that may influence this relation in late-life.

Chapter VII presents the scientific discussion that followed the publication of Chapter VI. Through an exchange of correspondence we explored whether two potential mechanisms – frailty and the use of antidiabetic drugs – might partially explain our findings.

Chapter VIII synthesises and contextualises the findings from Chapters II through VII, providing a perspective on their broader significance. This chapter addresses key methodological considerations, including the strengths and limitations of the study designs, as well as potential biases and confounding factors encountered throughout the research process. Additionally, it delves into the clinical implications of the results, assessing how they might influence current practices in hypertension management and dementia prevention. Finally, the chapter outlines directions for future research, highlighting gaps in knowledge, opportunities for further investigation, and how subsequent studies could build upon our findings to advance understanding in this field.

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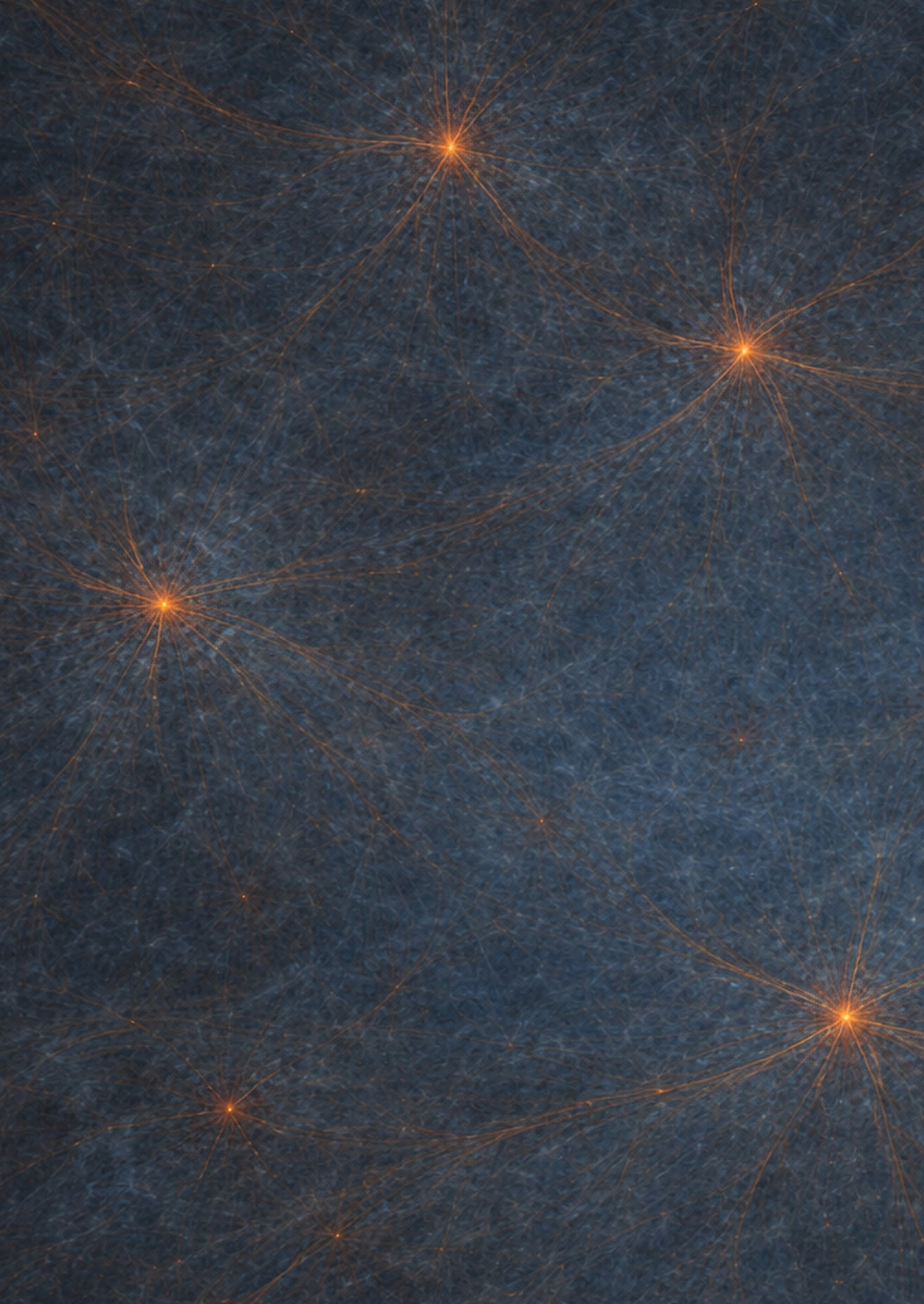

Chapter II

Antihypertensive medication classes and the risk of dementia over a decade of follow-up

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ABSTRACT

Introduction: Use of angiotensin II (ATII)-stimulating antihypertensive medication (AHM), including angiotensin receptor blockers (ARBs) and dihydropyridine calcium channel blockers (CCBs), has been associated with lower dementia risk. Previous studies had relatively short follow-up periods. The aim of this study is to investigate if these effects are sustained over longer periods.

Methods: This post-hoc observational analysis was based on data from a dementia prevention trial (preDIVA and its observational extension), among Dutch community-dwelling older adults without prior diagnosis of dementia. Differential associations between AHM classes and incident dementia were studied after 7.0 and 10.4 years, based on the median follow-up durations of dementia cases and all participants.

Results: After seven years, use of ATII-stimulating antihypertensives (HR=0.68, 95%CI=0.47-1.00), ARBs (HR=0.54, 95%CI=0.31-0.94) and dihydropyridine CCBs (HR=0.52, 95%CI=0.30-0.91) was associated with lower dementia risk. After 10.4 years, associations for ATII-stimulating antihypertensives, ARBs and dihydropyridine CCBs attenuated (HR=0.80, 95%CI=0.61-1.04; HR=0.75, 95%CI=0.53-1.07; HR=0.73, 95%CI=0.51-1.04 respectively), but still suggested lower dementia risk when compared to use of other AHM classes. Results could not be explained by competing risk of mortality.

Conclusion: Our results suggest that use of ARBs, dihydropyridine CCBs and ATII-stimulating antihypertensives is associated with lower dementia risk over a decade, although associations attenuate over time. Apart from methodological aspects, differential effects of antihypertensive medication classes on incident dementia may in part be temporary, or decrease with ageing.

INTRODUCTION

Dementia is a major global health problem, which is expected to increase over the coming years, due to global aging.[1] Results from several prospective studies suggest that hypertension is a risk factor for late-life dementia, in particular vascular dementia and Alzheimer's disease[2-5], with a population attributable fraction of approximately 5%.[6] Targeting hypertension may be a promising strategy to delay or prevent dementia, given its high prevalence and the wide availability of antihypertensive medication (AHM) worldwide.[7] Class-specific mechanisms of AHM may contribute to a differential effect on dementia risk[8-10], potentially explaining some of the inconsistent results of previous hypertension trials and meta-analyses.[11-13] A network meta-analysis of studies comparing dementia risks between users of different AHM classes suggests that users of angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs) had a 12-17% lower risk of dementia compared to individuals using angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, but less so versus diuretics.[14]

A potential mechanism underlying these findings is the 'angiotensin hypothesis', which suggests that antihypertensive agents that stimulate the angiotensin II type 2 (AT2) and 4 (AT4) receptors, including ARBs, dihydropyridine CCBs and thiazide diuretics, may reduce dementia risk by inhibiting neuronal damage and preserving memory function.[15,16] We observed that specifically these angiotensin II (ATII)-stimulating antihypertensive users had a 45% lower dementia risk compared to users of other AHM types in the Prevention of Dementia by Intensive Vascular care (preDIVA) population.[15] This finding was recently replicated in the SPRINT-MIND trial population, wherein ATII-stimulating AHM users had a 24% lower dementia risk when compared to other AHM users.[16] Moreover, we previously observed that individuals who used ARBs and CCBs at baseline had an approximately 40% lower dementia risk compared to individuals using other AHM types over 6.7 years of follow-up.[17]

It is unclear how these associations are affected by follow-up time, and whether they are sustained over long periods. A network meta-analysis suggests that protective effects are particularly observed in studies with longer follow-up.[14] Crucially however, these findings were nearly exclusively based on studies with a maximum follow-up of approximately 7 years. Duration of follow-up may be especially important in dementia, as it can develop insidiously over many years, implying that any protective effects of AHM classes may only become apparent in the long-term. Alternatively, protective associations may wear off over time, and/or attenuate due to changes in blood pressure and AHM regimen.

The preDIVA observational extension (POE) study yields longitudinal data on AHM use and dementia status of 3526 older adults up to twelve (median 10.4) years of follow-up. The aim of this study is to assess whether the associations between ARBs and CCBs, as well as dihydropyridine CCBs and ATII-stimulating AHM as a group and dementia persist, attenuate or increase over up to twelve years of follow-up, using the POE data.

METHODS

For the current study, we have used data from the preDIVA study and its observational extension. The initial preDIVA cluster-randomized controlled trial assessed the effect of intensive vascular care versus standard care on the incidence of all-cause dementia after a median intervention period of 6.7 years in 3526 Dutch community-dwelling, older adults (70-78 years) without dementia.[18] In the subsequent POE study, we included former preDIVA participants who had not deceased or developed dementia during that period. After adding another four years of observational follow-up, leading to a median follow-up of 10.4 years since baseline, information on dementia status or death could be obtained in 3491 (99.0%) and 3521 (99.9%) participants respectively. The study protocols and outcomes of the preDIVA and POE studies have been reported in more detail elsewhere.[18-20] The preDIVA trial was registered at the ISRCTN-registry (no.29711771). Both preDIVA and POE were approved by the medical ethics committee of the Academic Medical Centre, Amsterdam, the Netherlands. Participants gave written informed consent at the respective preDIVA and POE baselines. Since the preDIVA trial results for dementia and mortality were similar between the intervention and control groups, for the current analysis we considered the trial population as a single cohort, using additional adjustment for randomization group.

Independent variables

Demographics and data on other independent variables were collected at baseline and two, four, and six to eight years thereafter. Data on medication use and medical (cardiovascular) history gathered during these visits were crosschecked with participants' electronic health records (EHR). Blood pressure (BP) was assessed by taking the mean of two baseline BP measurements, performed at the same arm in sitting position with an automated BP monitor (M6,OMRON Healthcare Co., Ltd.,Kyoto,-Japan).[21] Body mass index (BMI) and low-density lipoprotein (LDL) cholesterol were measured using standardized devices and procedures. Self-reported data on education, smoking, and physical activity were defined according to WHO criteria.

We identified five main classes of AHM: ACE inhibitors, ARBs, beta-blockers, CCBs, and diuretics. We further distinguished between use of dihydropyridine and non-dihydropyridine CCBs, and between ATII-stimulating and inhibiting AHM, as this was differentially associated with dementia risk in previous studies.[15,16,22] ARBs, dihydropyridine CCBs or thiazide diuretics increase Angiotensin II levels and were thus included in the ATII-stimulating group.[15,23-25] AHM were (sub)-categorized into classes according to WHO Anatomical Therapeutic Chemical (ATC) codes (*Supplementary Table 1*).[26]

Outcome assessment

Diagnosis of dementia was defined according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV). An independent outcome adjudication committee, blinded for study allocation, evaluated the diagnosis of dementia, and re-evaluated the diagnosis after 1 year, to minimize the risk of false-positive diagnoses. In the POE study, the municipal death registry was consulted first. Of those participants who had deceased since the final visit of preDIVA, information on the development of dementia since the end of preDIVA was obtained from the general practitioner (GP). Those still alive were asked to participate in the telephone interview of cognitive status (TICS), which is an 11-item, validated screening tool (maximum score=41).[27] For participants with a TICS score >30 and no known diagnosis of dementia, we assumed no dementia had occurred. For those with a TICS score ≤30 or missing score, the EHR of the GP was checked for a diagnosis of dementia.[28]

Statistical analysis

We included all participants who used AHM at preDIVA baseline, with available baseline data on AHM use, covariates and outcome of dementia and mortality. Individuals who did not use AHM at baseline were excluded to limit the potential influence of selective dropout. In order to focus on the differential effects between AHM classes, we compared use of specific AHM classes with use of any other AHM classes. Participants who used multiple classes simultaneously (for instance those using fixed combination therapy) were represented in multiple classes or subgroups at once. The association between AHM class and dementia incidence was analysed using Cox proportional hazards regression models, using number of years from baseline to diagnosis of dementia, time of death, or date of outcome assessment as timescale. Model 1 was unadjusted. In model 2, we adjusted for age, sex, history of cardiovascular disease (CVD) (i.e. myocardial infarction, stroke and/or transient ischemic attack), and type 2 diabetes. In model 3, we additionally adjusted for randomization group and number of used AHM classes, as indicator for the intensity of treatment. Sensitivity- and subgroup analyses were adjusted according to model 2. In order to compare potential

differences between short- and long term results, we repeated the main analysis with a shorter follow-up period. Short-term was defined using the median follow-up of participants who developed dementia, ensuring even distribution of cases on either side of the cut-off value.

Several sensitivity analyses were performed to assess the robustness of the main analyses. First, we included all AHM classes in one model, to adjust for concurrent use of multiple AHM classes. Second, to assess the potential influence of AHM class changes during follow-up, we performed a sensitivity analysis for stable users, defined as use of the same AHM class at baseline and during at least one follow-up visit of preDIVA. Third, to assess the influence of the competing risk of death, we used the cause-specific hazard approach, repeating all analyses with mortality and dementia/mortality combined as outcomes. In a post-hoc sensitivity analysis, we compared use of ARBs and/or CCBs with use of any other AHM. As both classes have a presumed negative association with dementia risk, we used this approach to limit potential concealment of the effect between use of ARBs and dementia risk by use of CCBs in the reference group, and vice versa. Finally, we included dihydropyridine CCBs and ATII-stimulating AHM in (pre-specified) sensitivity- and subgroup analyses.

Subgroup analyses were performed for age (cut-off 75 years at baseline, based on the mean age at baseline in preDIVA), for participants with(out) CVD, type 2 diabetes, (un)controlled hypertension (systolic blood pressure cut-off at 150 mmHg, based on the prevailing primary care guideline on hypertension at the start of the preDIVA study[29]) at baseline, and on monotherapy vs. combination therapy, as these may be proxies for different cardiovascular risk profiles, with different dementia risks. Finally, a subgroup analysis for sex was performed, as previous studies have suggested that the relation between the RAS system and development of dementia may be different between males and females.[23]

No imputations were deemed necessary, due to the low number of missing values in both the preDIVA trial and observational follow-up (*Supplementary Table 2*). All analyses were performed in RStudio(v1.3) based on R(v4.0.2).

RESULTS

In total, 1907 (54.1%) AHM users out of 3526 participants were included in the analyses. Mean age of participants at baseline was 74.5 (±2.5) years, 1027 (53.9%) were female. Mean systolic blood pressure was 156.2 (±21.5) mmHg. Including combina-

tion therapy, 620 (32.5%) participants used ACE inhibitors, 390 (20.5%) ARBs, 958 (50.2%) beta-blockers, 512 (26.8%) CCBs, (51.1%) 974 (51.1%) diuretics. More specifically, within the CCB group 399 (77.9%) used dihydropyridines and 115 (22.5%) non-dihydropyridines. Within the diuretic group 752 (77.4%) used thiazides. **Table 1** gives an overview of baseline data for participants in each AHM class.

Among all participants, after a median 10.4 years (range 0.2-12.8, IQR 6.8-11.0) of follow-up, 225 (11.8%) participants had developed dementia (**Figure 1**). Risk of dementia was not significantly different for any of the AHM classes of interest as compared with use of any other AHM class in the crude and adjusted model (**Table 2**). Point estimates for use of ARBs (HR=0.75, 95%CI=0.53-1.07), dihydropyridine CCBs (HR=0.73, 95%CI=0.51-1.04), and ATII-stimulating AHM (HR=0.80, 95%CI=0.61-1.04) suggested a negative association with incident dementia (**Table 2**, **Figure 2**, and *Supplementary Figure 1*).

Short-term, with follow-up cut-off at 7 years (median follow-up of dementia cases), use of ARBs (HR=0.54, 95%CI=0.31-0.94), CCBs (HR=0.60, 95%CI=0.37-0.97), dihydropyridine CCBs (HR=0.52, 95%CI=0.30-0.91) and ATII-stimulating AHM (HR=0.68, 95%CI=0.47-1.00) was associated with reduced dementia risk (*Supplementary Table 4*). Results from the main analyses remained largely unchanged after additional adjustment for number of AHM and randomisation group (*Supplementary Table 5*) and when mutually adjusting for all main AHM classes in one model (*Supplementary Table 6*). When restricting analyses to participants in the stable-use group (*Supplementary Table 7*), use of ATII-stimulating AHM was associated with lower dementia incidence (HR=0.73, 95%CI=0.52-0.99). Use of ARBs, dihydropyridine CCBs, and ATII-stimulating AHM were not associated with increased mortality rates (HR=0.94, 95%CI=0.77-1.14; HR=0.99, 95%CI=0.82-1.20; HR=0.94, 95%CI=0.81-1.11 respectively), suggesting no evident influence of competing risk of death (*Supplementary Table 8*). Finally, use of ARBs and CCBs combined was associated with a lower dementia incidence (HR=0.69, 95%CI=0.52-0.92, *Supplementary Table 9*).

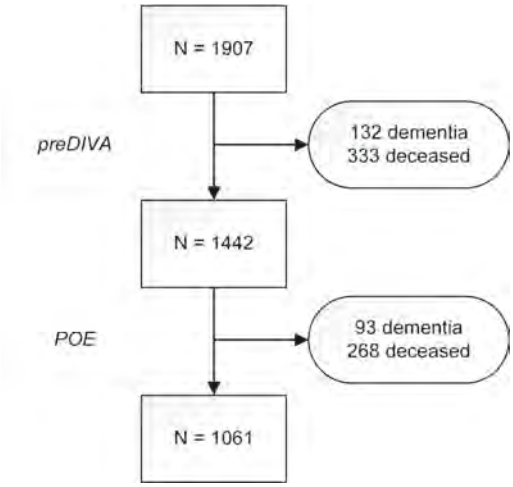
Associations between AHM classes and dementia were largely similar across the predefined subgroups (*Supplementary Table 10*), although in ARB users, the association with dementia was stronger in participants aged 75 and over (HR=0.60, 95%CI=0.36-0.99) when compared to those under 75 years of age at baseline (HR=0.95, 95%CI=0.57-1.58). In participants using ATII-stimulating AHM, the association was stronger in those with a history of diabetes (HR=0.58, 95%CI=0.36-0.94) when compared to individuals without history of diabetes (HR=0.90, 95%CI=0.65-1.25).

Table 1. Baseline characteristics of participants with different classes of antihypertensive medication.

	Total N=1907	ACEi N=620	ARB N=390	Beta-blocker N=958	CCB N=512	Diuretic N=974	Dihydropyridine CCB N=399	ATII-stimulating AHM N=1180
Sociodemographic								
Age (years), mean±SD [Range]	74.5 ± 2.5 [69-80]	74.5 ± 2.5 [69-80]	74.3 ± 2.5 [69-79]	74.4 ± 2.5 [69-80]	74.5 ± 2.5 [69-80]	74.5 ± 2.5 [69-80]	74.4 ± 2.5 [69-80]	74.4 ± 2.5 [69-80]
Sex (female), N (%)	1027 (53.9)	280 (45.2)	219 (56.2)	492 (51.4)	273 (53.3)	591 (60.7)	215 (53.9)	682 (57.8)
MMSE, median [IQR]	28 [27-29]	28 [27-29]	29 [27-29]	28 [27-29]	29 [27-29]	29 [27-29]	29 [27-29]	29 [27-29]
Cardiovascular risk factors and medication use								
CVD history (yes), N (%)	947 (49.7)	315 (50.8)	184 (47.2)	589 (61.5)	289 (56.4)	438 (45.0)	204 (51.1)	517 (43.8)
DM history (yes), N (%)	501 (26.3)	233 (37.6)	110 (28.2)	240 (25.1)	154 (30.1)	301 (30.9)	126 (31.6)	332 (28.1)
Systolic BP (mmHg), mean±SD [Range]	156.2±21.5 [100-232.5]	156.6±21.9 [100-233]	156.5±23.1 [103-222]	156.6±22.5 [100-233]	155.8±20.4 [109-218]	155.9±21.5 [100-233]	157.5±20.3 [109-218]	157.7±21.0 [101-233]
Diastolic BP (mmHg), mean±SD [Range]	81.4±11.2 [50-131]	81.4±11.9 [52-131]	81.5±11.2 [55-118]	80.9±11.4 [50-131]	79.4±10.4 [52-125]	81.3±10.8 [52-119]	79.7±10.4 [52-125]	81.6±10.9 [52-125]
BMI (kg/m^2), mean±SD	28.4±4.3	28.2±4.1	29.1±4.6	28.3±4.0	28.5±4.2	28.9±4.5	28.6±4.1	28.7±4.4
LDL (mg/dL), mean±SD	112.0±38.6	108.1±34.8	112.0±38.6	108.1±34.8	108.1±34.8	112.0±38.6	108.1±34.8	112.0±38.6
Current smoking (yes), N (%)	232 (12.2)	79 (12.7)	40 (10.3)	121 (12.6)	66 (12.9)	117 (12.0)	52 (13.0)	141 (11.9)
Physically active (yes), N (%)	1565 (82.1)	493 (79.5)	321 (82.3)	797 (83.2)	414 (80.9)	778 (79.9)	325 (81.5)	974 (82.5)
Number of AHM, median [IQR]	2 [2-3]	2 [2-3]	2 [2-3]	2 [1-3]	2 [2-3]	2 [2-3]	2 [2-3]	2 [2-3]

Individual participants are represented in different classes of antihypertensive medication when they use combination therapy. Data are presented as numbers (percentage), mean ± SD, median (IQR) or ranges. Physical activity was self-reported and defined according to WHO criteria. ACEi = angiotensin-converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; BP = blood pressure; CCB = calcium channel blocker; CVD = cardiovascular disease; DM = diabetes mellitus; LDL = low-density lipoprotein; MMSE = Mini-Mental State Examination

Figure 1. Overview of outcome assessment



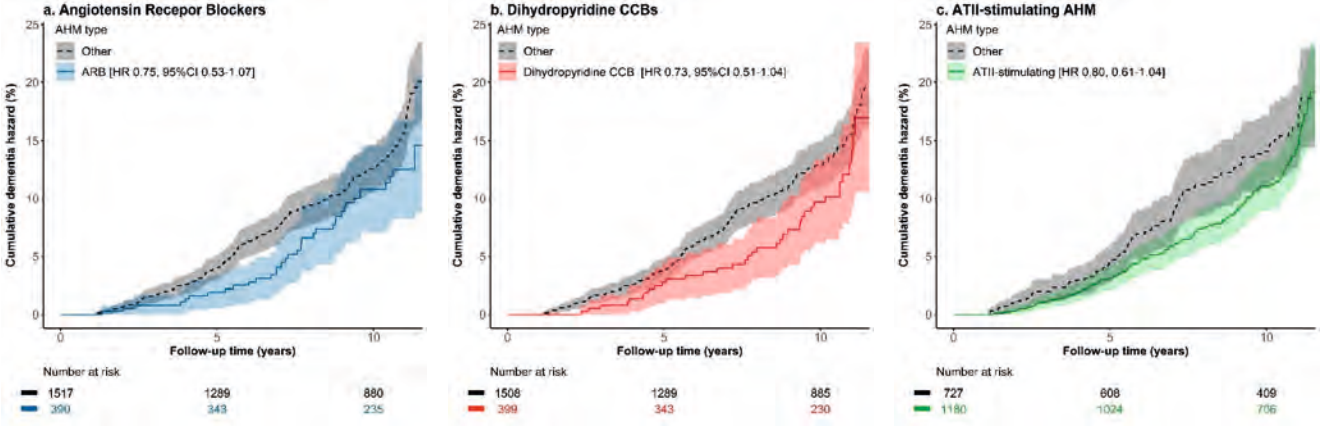
Participants who had dementia and subsequently deceased, were included in the number of people with dementia only. AHM = antihypertensive medication; preDIVA = prevention of dementia by intensive vascular care; POE = preDIVA observational extension; RCT = randomised controlled trial.

Table 2. Association between use of a specific antihypertensive medication class and incident dementia, compared with use of any other antihypertensive medication.

	Dementia cases (%) in AHM class of interest	Dementia cases (%) in other AHM users	Crude model HR (95% CI)	Model 2 HR (95% CI)
ACEi	72/620 (11.6)	153/1287 (11.9)	1.09 (0.82-1.44)	1.07 (0.81-1.43)
ARB	37/390 (9.5)	188/1517 (12.4)	0.75 (0.53-1.07)	0.75 (0.53-1.07)
Beta-blocker	113/958 (11.8)	112/949 (11.8)	1.01 (0.78-1.31)	0.99 (0.76-1.30)
CCB	58/512 (11.3)	167/1395 (12.0)	0.96 (0.71-1.29)	0.92 (0.68-1.25)
Diuretic	117/974 (12.0)	108/933 (11.6)	1.07 (0.82-1.39)	1.03 (0.79-1.34)
Dihydropyridine CCB	37/399 (9.3)	188/1508 (12.5)	0.74 (0.52-1.05)	0.73 (0.51-1.04)
ATII-stimulating AHM	129/1180 (10.9)	96/727 (13.2)	0.81 (0.62-1.05)	0.80 (0.61-1.04)

Median follow-up: 10.4 years. Model 2: adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. The dementia cases (percentages) represent the number of participants with incident dementia from the participants using the AHM class of interest. ATII-stimulating AHM include ARB's, dihydropyridine CCB's and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; ATII = angiotensin II; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Figure 2. Cumulative hazard of dementia for ARBs, dihydropyridine CCBs and ATII-stimulating antihypertensive medication



a. ARBs (blue), b. Dihydropyridine CCBs (red) and c. ATII-stimulating AHM (green) versus any other AHM classes (grey). ARB = angiotensin receptor blocker; CCB = calcium channel blocker; ATII = angiotensin II; AHM = antihypertensive medication; HR = hazard ratio, CI = confidence interval.

DISCUSSION

Main findings

In our population of 1907 AHM-using Dutch older adults, use of ARBs, dihydropyridine CCBs, and ATII-stimulating AHM was non-significantly associated with 20-27% lower risk of incident dementia over a median follow-up duration of 10.4 years, and significantly with 32-48% lower risk of dementia after 7 years follow-up, when compared to use of any other AHM class.

Interpretation of findings

The non-significant 20-27% lower dementia risks after median 10.4 years had decreased compared to the 30-45% lower risks over 7 years. This suggests that the associations of ARBs, (dihydropyridine) CCBs or ATII-stimulating AHM with decreased dementia risk might attenuate over time. Possibly, as many of the known risk factors for dementia are age dependent[8,30,31], differential effects of AHM classes partly decrease with aging. Analyses stratified by age however do not support this hypothesis. Another explanation may be that, with increasing follow-up time, baseline data on medication use have become less reliable indicators of actual medication use. Nevertheless, sensitivity analyses in participants who used the same AHM class at baseline and during at least one follow-up visit did not substantially alter our results. Thirdly, differential effects of AHM classes on dementia risk could have a temporary nature, regardless of age. Finally, regression to the mean could in part explain the difference between associations on the short and longer term.

Baseline blood pressure levels and number of prescribed AHM were comparable between the different AHM classes users. Any differential effects between AHM classes and incident dementia we observed are therefore likely caused by class-specific mechanisms rather than their effect on blood pressure. Several hypotheses exist around the potential neuroprotective effect of CCBs and ARBs, ranging from their abilities to improve cerebral blood flow, reduce cerebral oxidative stress markers, to protection against neuronal death.[32] In addition, dihydropyridine CCBs and ARBs stimulate AT2 and AT4 receptors through the ATII pathway, which potentially protects against ischemia and preserve memory respectively.[15,16,33-36]

An important potential challenge in studies with dementia as outcome is the competing risk of mortality before the development of dementia. In our study, we observed associations between use of ACE inhibitors and mortality (HR1.19, 95%CI=1.01-1.40) and dementia/mortality combined (HR1.18, 95%CI=1.02-1.36). This may be related to the high number of individuals with diabetes in this group. As no association be-

tween use of any other AHM class and mortality were observed, with HRs around 1.0, our results appear unaffected by the competing risk of death.

Strengths and limitations

Main strengths are the judicious assessment of the most clinically relevant outcome of incident dementia, the long follow-up period of up to twelve years, and completeness of follow-up on all-cause dementia (99.0%) and mortality (99.9%). Furthermore, our study population consists of a broadly representative sample of community-dwelling Dutch older adults.[18]

A limitation is potential confounding by indication, as former Dutch guidelines recommended a stepped approach for AHM prescriptions in which ARBs and CCBs represented second or later steps in treatment. In our study, baseline blood pressure values were comparable across classes, but beta-blockers, ACE inhibitors, and ARBs were more often prescribed among specific groups, including those with a history of CVD or diabetes. To address this issue, we adjusted for CVD and diabetes history in the main model, which did not change the results of the crude analyses. Additional adjustment for number of AHM classes did not change the results. Also, results were highly comparable in subgroup analyses for participants with and without diabetes, a history of CVD and uncontrolled hypertension.

A second limitation is the lack of complete data on medication history prior to baseline assessment, medication adherence, and dosage. In the main analysis, we only used data on AHM use collected at baseline, ignoring intermediate changes in AHM use. We repeated the main analysis in a sample of participants who used the same AHM class at baseline and at least one follow-up visit and observed similar results. The available data did not allow for a more thorough analysis on the effects of post-baseline AHM class switching and medication exposure over time.

Comparison with previous studies

The HRs for incident dementia ranging between 0.73 and 0.80 we found, are in line with findings from previous studies on class-specific effects of AHM. Two individual participant data (IPD) studies with dementia as secondary outcome compared use of various AHM classes with use of any other AHM class. Both studies reported negative, albeit non-significant associations with incident dementia. One study found that use of ARBs was associated with a 12-24% lower dementia risk and the other reported 7-24% lower ORs for ARBs and CCBs.[37,38] A recent network meta-analysis compared use of various AHM classes to each other and demonstrated that use of CCBs and ARBs was associated with a 12-17% reduced dementia risk compared to ACE inhibitors and beta

blockers, but less so versus diuretics (7-11%). However, all but one included studies had a follow-up period of less than approximately 7 years and most applied non-use of AHM classes, including individuals who did not use any AHM at all, as reference groups, hindering accurate comparison with our results.[14,22,39,40] One study with a follow-up of over 10 years compared use of CCBs with use of other AHM classes and found a significant 19% reduction of dementia risk in those using CCBs.[41] Our study is the first to assess the sustainability of class-specific associations between various AHM classes and incident dementia over a prolonged period of time.

Conclusion

In our study population of Dutch community-dwelling older persons, we did not observe statistically significant associations between use of any specific AHM class and dementia risk over a median 10.4 years of follow-up, although point estimates for ARBs, dihydropyridine CCBs and ATII-stimulating AHM suggest a lower risk of dementia when compared to use of any other AHM class. Possibly, significant associations observed in the short-term represented effects that were to some extent temporary, or could not be replicated over the complete follow-up period because baseline AHM data were not fully representative of actual medication use over time. However, even temporary effects, resulting in delayed manifestation of dementia, could be meaningful to both individuals and society. Further studies assessing the sustainability of class-specific associations in older adults should comprise detailed registration of AHM use over time, to account for intermediate class-changes and to assess potential dose-effect relationships.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1. AHM classes and corresponding ATC codes.

AHM class	ATC codes
ACEi	C09A; C09B
ARB	C09C; C09D
Beta-blocker	C07A; C07B; C07C; C07D; C07E; C07F; C09BX02, C09BX04; C09DX06
CCB	C08C, C08D, C08E, C08G; C07FB; C09XA53; C09XA54; C09DX01; C09DX03; C09DX07; C09DB; C09BX04; C09BX01; C09BX03; C09BB
Diuretic	C03A, C03B, C03C, C03D, C03E, C03X; C02L; C07B; C07C; C07D; C08G; C09BA; C09BX01; C09BX03; C09DA; C09DX01; C09DX03; C09DX07; C09XA52; C09XA54
Other	C02A, C02B, C02C, C02D, C02K, C02L, C02N, C09X
Dihydropyridine CCB	C08G; C07FB; C09XA53; C09XA54; C09DX01; C09DX03; C09DX06; C09DX07; C09DB; C09BX01; C09BX03; C09BX04; C09BB02; C09BB03; C09BB04; C09BB06; C09BB07; C09BB12
Angiotensin II-stimulating AHM	C02L; C03A; C03EA01; C03EA02; C03EA03; C03EA04; C03EA05;C03EA07; C03EA013; C03EA014; C07B; C07D; C07FB; C08CA; C08G; C09BA; C09BB02; C09BB03; C09BB04; C09BB05; C09BB06; C09BB07; 09BB12; C09BX01; C09BX03; C09BX03; C09BX04; C09CA; C09DA; C09DB; C09DX; C09XA52; C09XA53; C09XA54

Angiotensin II-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. AHM = antihypertensive medication; ATC = Anatomical Therapeutic Chemical; ACEi = angiotensin-converting enzyme inhibitor; ARB=angiotensin II receptor blocker; CCB = calcium channel blocker.

Supplementary Table 2. Number of participants with missing data for each variable of interest.

Variables	Participants with missing data (%)
Age	0 (0)
Dementia	21 (1.1)
History of CVD	24 (1.2)
Diabetes mellitus	0 (0)
Systolic blood pressure	0
Diastolic blood pressure	0
Smoking	3 (0.2)
Physical activity	41 (2.1)
LDL	53 (2.7)
BMI	1 (0.1)
MMSE	3 (0.2)

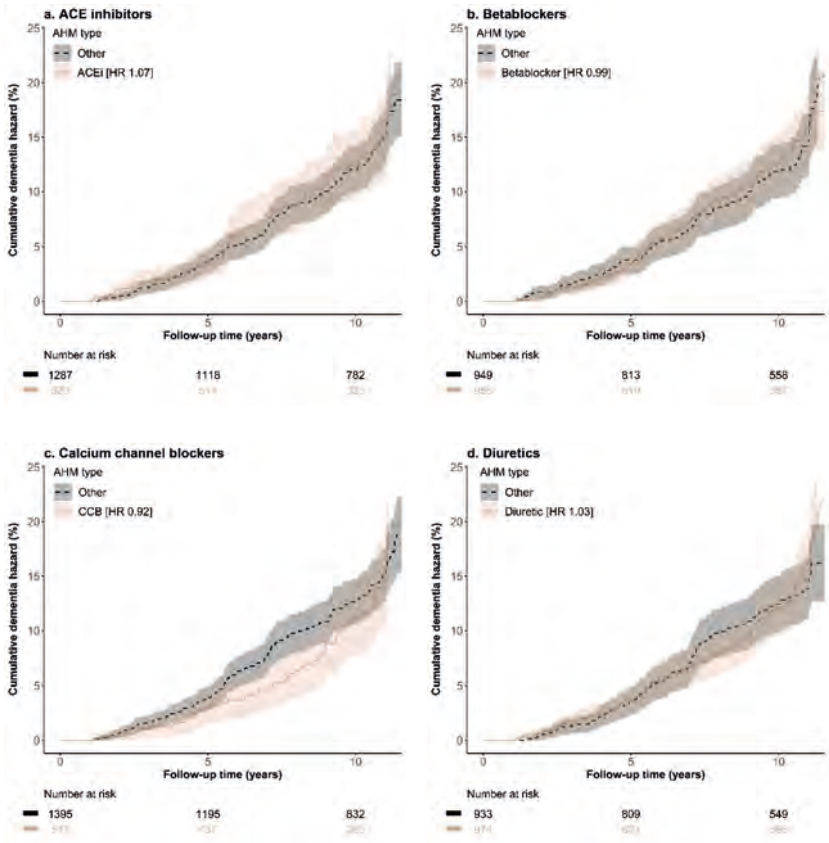
Data presented for all participants who used who used antihypertensive medication at baseline (n=1953). CVD = cardiovascular disease; LDL = low-density lipoprotein; BMI = Body-Mass index; MMSE = Mini-Mental State Examination.

Supplementary Table 3. Number of antihypertensive medication (AHM) classes and combinations of AHM at baseline.

	ACEi (N=620)	ARB (N=390)	Beta-blocker (N=958)	CCB (N=512)	Diuretic (N=974)
Number of AHM classes, N (%)					
1	137 (22.1)	90 (23.1)	282 (29.4)	104 (20.3)	182 (18.7)
2	247 (39.8)	164 (42.1)	364 (38.0)	172 (33.6)	457 (46.9)
3	181 (29.2)	101 (25.9)	233 (24.3)	157 (30.7)	255 (26.2)
≥4	55 (8.9)	35 (9.0)	79 (8.2)	79 (15.4)	80 (8.2)
AHM classes					
ACEi	620 (100.0)	13 (3.3)	258 (26.9)	161 (31.4)	342 (35.1)
ARB	13 (2.1)	390 (100.0)	150 (15.7)	107 (20.9)	201 (20.6)
Beta-blocker	258 (41.6)	150 (38.5)	958 (100.0)	225 (43.9)	434 (44.6)
CCB	161 (26.0)	107 (27.4)	225 (23.5)	512 (100.0)	230 (23.6)
Diuretic	342 (55.2)	201 (51.6)	434 (45.3)	230 (44.9)	974 (100.0)
Cholesterol lowering medication	346 (55.8)	183 (46.9)	528 (55.1)	266 (52.0)	448 (46.0)

Median follow-up: 10.4 years. Individual participants are represented in different classes of antihypertensive medication when they use combination therapy. ACEi = angiotensin-converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker.

Supplementary Figure 1. Cumulative hazard of dementia for ACE inhibitors, beta-blockers, calcium channel blockers and diuretics



a. ACEi, b. beta-blockers, c. CCBs, d. diuretics (brown) versus any other AHM classes (grey). ACEi = angiotensin-converting enzyme inhibitor, AHM = antihypertensive medication, HR = hazard ratio;CCB = calcium channel blocker, AHM = antihypertensive medication, HR = hazard ratio

Supplementary Table 4. Short-term associations between use of a specific antihypertensive medication class and incident dementia, compared with use of any other antihypertensive medication classes.

	Dementia cases (%)	HR (95% CI)
ACEi	39/620 (6.3)	1.12 (0.75-1.66)
ARB	14/390 (3.6)	0.54 (0.31-0.94)
Beta-blocker	58/958 (6.4)	1.05 (0.72-1.54)
CCB	21/512 (4.1)	0.60(0.37-0.97)
Diuretic	57/974 (5.9)	0.96 (0.66-1.40)
Dihydropyridine CCB	18/399 (3.5)	0.52 (0.30-0.91)
AT II-stimulating AHM	36/1180 (3.1)	0.68 (0.47-1.00)

Follow-up cut off at 7 years. Model 2: adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. The dementia cases (percentages) represent the number of participants with incident dementia from the participants using the AHM class of interest. ATII-stimulating AHM include ARB's, dihydropyridine CCB's and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; AT II = angiotensin II; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplementary Table 5. Associations between use of antihypertensive medication (AHM) classes and incident dementia, compared with use of any other AHM class – maximally adjusted model.

	Dementia cases (%) in AHM class of interest	Dementia cases (%) in other AHM users	Model 3 HR (95% CI)
ACEi	72/620 (11.6)	153/1287 (11.9)	1.13 (0.83-1.52)
ARB	37/390 (9.5)	188/1517 (12.4)	0.76 (0.53-1.09)
Beta-blocker	113/958 (11.8)	112/949 (11.8)	1.05 (0.78-1.37)
CCB	58/512 (11.3)	167/1395 (12.0)	0.96 (0.69-1.32)
Diuretic	117/974 (12.0)	108/933 (11.6)	1.10 (0.81-1.50)
Dihydropyridine CCB	37/399 (9.3)	188/1508 (12.5)	0.73 (0.50-1.07)
ATII-stimulating AHM	129/1180 (10.9)	96/727 (13.2)	0.79 (0.58-1.08)

Median follow-up: 10.4 years. Model 3: adjusted for age, sex, history of cardiovascular disease, history of diabetes mellitus, number of antihypertensive drugs, and randomization group. ATII-stimulating antihypertensives include ARBs, dihydropyridine CCBs, and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; ATII = angiotensin II; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplementary Table 6. Associations between use of antihypertensive medication class and dementia, mutually adjusted for use of multiple classes.

	HR (95% CI)
ACEi	0.98 (0.72-1.34)
ARB	0.74 (0.51-1.08)
Beta-blocker	0.96 (0.73-1.27)
CCB	0.92 (0.68-1.24)
Diuretic	1.01 (0.77-1.33)

Cox proportional hazard model adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

Supplementary Table 7. Associations between use of antihypertensive medication classes and dementia within stable users.

	Stable- /Total users (%)	Dementia cases (%)	HR (95% CI)
ACEi	418/620 (67.4)	50/418 (12.0)	1.12 (0.80-1.57)
ARB	302/390 (77.4)	29/302 (9.6)	0.78 (0.52-1.16)
Beta-blocker	713/958 (74.4)	87/713 (12.2)	1.01 (0.74-1.38)
CCB	372/512 (72.7)	40/372 (10.7)	0.87 (0.61-1.24)
Diuretic	685/974 (70.3)	73/685 (10.6)	0.79 (0.58-1.08)
Dihydropyridine CCB[a]	286/399 (71.7)	27/286 (9.4)	0.77 (0.51-1.17)
ATII-stimulating AHM[a]	883/1180 (74.8)	91/883 (10.3)	0.73 (0.52-0.99)

Median follow-up: 10.4 years. Cox proportional hazard model adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. Stable users as defined as using the same antihypertensive medication group at baseline and at one or more preDIVA follow-up visits. ATII-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

[a]Post hoc analysis.

Supplementary Table 8. Associations between use of antihypertensive medication classes and mortality, and dementia and mortality combined.

	Death cases (%)	HR death (95% CI)	Dementia or death cases (%)	HR dementia or death (95% CI)
ACEi	237/620 (38.2)	1.19 (1.01-1.40)	294/620 (47.4)	1.18 (1.02-1.36)
ARB	122/390 (31.3)	0.94 (0.77-1.14)	154/390 (39.5)	0.91 (0.77-1.09)
Beta-blocker	323/958 (33.7)	0.89 (0.76-1.04)	410/958 (42.8)	0.92 (0.80-1.05)
CCB	194/512 (37.9)	1.13 (0.95-1.34)	237/512 (46.3)	1.06 (0.91-1.24)
Diuretic	333/974 (34.2)	1.15 (0.98-1.34)	424/974 (43.5)	1.13 (0.98-1.30)
Dihydropyridine CCB[a]	135/399 (33.8)	0.99 (0.82-1.20)	165/399 (41.4)	0.93 (0.79-1.11)
ATII-stimulating AHM[a]	382/1180 (32.4)	0.94 (0.81-1.11)	486/1180 (41.2)	0.93 (0.81-1.07)

Median follow-up: 10.4 years. Cox proportional hazard model adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. ATII-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics.

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

[a]Post hoc analysis.

Supplementary Table 9. Association between use of ARBs or dihydropyridine CCBs and incident dementia**.**

	Dementia cases (%) in AHM class of interest	Dementia cases (%) in other AHM users	Crude model HR (95% CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)
ARB or dihydropyridine CCB	692/1907 (36.3)	65/692 (9.8)	0.69 (0.52-0.92)	0.69 (0.52-0.92)	0.67 (0.49-0.92)

Model 2: adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. Model 3: adjusted for age, sex, history of cardiovascular disease, history of diabetes, number of used AHM-classes, and randomization group. AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CI = confidence interval; HR = hazard ratio.

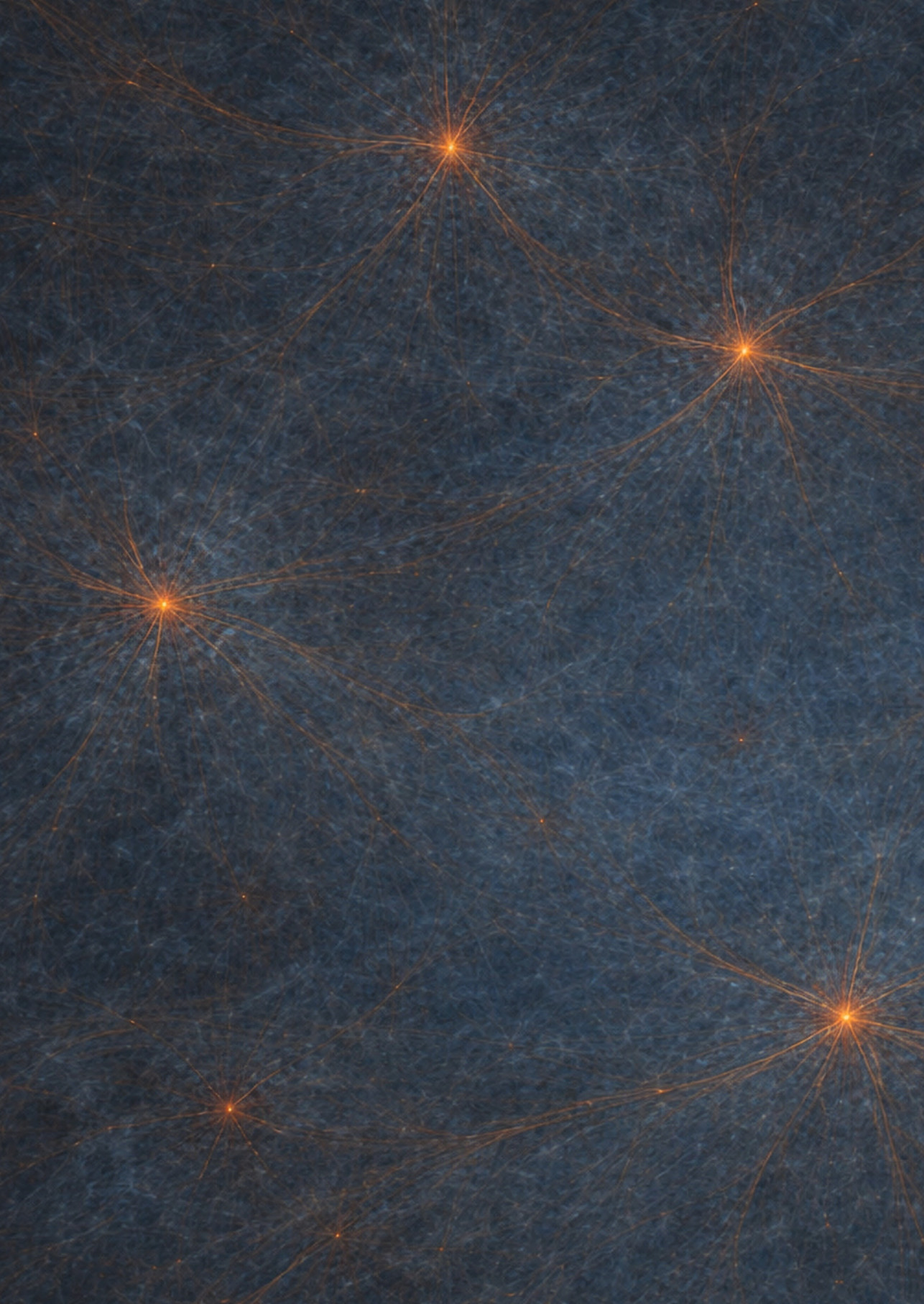
Supplementary Table 10. Subgroup analyses for the association between use of different antihypertensive medication classes and incident dementia.

	Sex		CVD history		DM history		Hypertension[b]		Mono vs. multi-therapy		Age	
	Female	Male	Yes	No	Yes	No	Uncontrolled	Controlled	Mono	Multi	< 75	≥ 75
ACEi												
Dementia cases (%)	33/340 (9.7)	39/280 (13.9)	34/315 (10.8)	38/305 (12.5)	33/233 (14.2)	39/387 (10.1)	40/385 (10.4)	32/235 (13.6)	19/137 (13.9)	53/483 (11.0)	32/309 (10.4)	40/311 (12.9)
HR	1.14	1.04	0.95	1.25	1.26	0.99	0.99	1.25	1.29	1.01	1.25	0.95
(95% CI)	(0.72-1.79)	(0.72-1.51)	(0.63-1.42)	(0.83-1.87)	(0.77-2.04)	(0.69-1.42)	(0.67-1.45)	(0.81-1.91)	(0.77-2.16)	(0.71-1.45)	(0.81-1.94)	(0.65-1.39)
P for interaction	*0.85*		*0.36*		*0.49*		*0.29*		*0.37*		*0.38*	
ARB												
Dementia cases (%)	10/171 (5.8)	27/219 (12.3)	18/184 (9.8)	19/206 (9.2)	12/110 (10.9)	25/280 (8.9)	17/226 (7.5)	20/164 (12.2)	7/90 (7.8)	30/300 (10.0)	19/201 (9.5)	18/189 (9.5)
HR	0.58	0.83	0.77	0.71	0.71	0.77	0.62	0.93	0.60	0.81	0.95	0.60
(95% CI)	(0.30-1.13)	(0.55-1.26)	(0.46-1.27)	(0.43-1.16)	(0.38-1.34)	(0.50-1.18)	(0.37-1.04)	(0.57-1.53)	(0.28-1.30)	(0.54-1.22)	(0.57-1.58)	(0.36-0.99*)
P for interaction	*0.42*		*0.70*		*0.86*		*0.27*		*0.52*		*0.82*	
Beta-blocker												
Dementia cases (%)	45/466 (9.7)	68/492 (13.8)	71/589 (12.1)	42/369 (11.4)	33/240 (13.8)	80/718 (11.1)	66/576 (11.5)	47/382 (12.3)	33/282 (11.7)	80/676 (11.8)	49/493 (9.9)	64/465 (13.8)
HR	1.08	0.96	1.09	0.91	0.90	1.03	1.11	0.85	0.97	1.06	1.04	0.97
(95% CI)	(0.69-1.70)	(0.68-1.34)	(0.74-1.60)	(0.62-1.34)	(0.56-1.47)	(0.75-1.43)	(0.78-1.57)	(0.56-1.30)	(0.63-1.51)	(0.73-1.53)	(0.68-1.59)	(0.68-1.37)
P for interaction	*0.91*		*0.54*		*0.80*		*0.56*		*0.66*		*0.58*	
CCB												
Dementia cases (%)	22/239 (9.2)	36/273 (13.2)	34/289 (11.8)	24/223 (10.8)	22/154 (14.3)	36/358 (10.1)	28/294 (9.5)	30/218 (13.8)	15/104 (14.4)	43/408 (10.5)	20/250 (8.0)	38/262 (14.5)
HR	0.98	0.89	1.00	0.84	1.09	0.88	0.80	1.07	1.22	0.84	0.79	1.01
(95% CI)	(0.60-1.59)	(0.61-1.30)	(0.66-1.49)	(0.53-1.32)	(0.61-1.97)	(0.59-1.31)	(0.52-1.22)	(0.70-1.66)	(0.70-2.12)	(0.58-1.22)	(0.48-1.29)	(0.69-1.48)
P for interaction	*0.89*		*0.58*		*0.50*		*0.24*		*0.30*		*0.51*	
Diuretic												
Dementia cases (%)	39/383 (10.2)	78/591 (13.2)	50/438 (11.4)	67/536 (12.5)	40/301 (13.3)	77/673 (11.4)	72/583 (12.3)	45/391 (11.5)	23/182 (12.6)	94/792 (11.9)	45/471 (9.6)	72/503 (14.3)
HR	1.25	0.92	0.90	1.15	0.86	1.10	1.25	0.80	0.96	1.18	0.95	1.07
(95% CI)	(0.80-1.94)	(0.66-1.29)	(0.61-1.31)	(0.79-1.69)	(0.53-1.39)	(0.80-1.53)	(0.87-1.78)	(0.53-1.21)	(0.59-1.56)	(0.79-1.78)	(0.62-1.45)	(0.75-1.51)
P for interaction	*0.28*		*0.62*		*0.42*		*0.15*		*0.66*		*0.36*	
Dihydropyridine CCB[a]												
Dementia cases (%)	15/184 (8.2)	22/215 (10.2)	19/204 (9.3)	18/195 (9.2)	15/126 (11.9)	22/273 (8.1)	19/240 (7.9)	18/159 (11.3)	9/6 (13.6)	28/333 (8.4)	14/203 (6.9)	23/196 (11.7)
HR	0.83	0.69	0.78	0.67	0.80	0.67	0.66	0.81	1.10	0.64	0.67	0.78
(95% CI)	(0.47-1.45)	(0.44-1.08)	(0.47-1.28)	(0.41-1.12)	(0.45-1.43)	(0.43-1.05)	(0.41-1.08)	(0.48-1.35)	(0.55-2.20)	(0.42-0.98)	(0.38-1.18)	(0.49-1.22)
P for interaction	*0.64*		*0.66*		*0.57*		*0.51*		*0.19*		*0.36*	

Supplementary Table 10. *(Continued)*

	Sex		CVD history		DM history		Hypertension[b]		Mono vs. multi-therapy		Age	
	Female	Male	Yes	No	Yes	No	Uncontrolled	Controlled	Mono	Multi	< 75	≥ 75
ATII-stimulating AHM[a]												
Dementia cases (%)	43/498 (8.6)	86/682 (12.6)	52/517 (10.1)	77/663 (11.6)	39/332 (11.7)	90/848 (10.6)	77/739 (10.4)	52/441 (11.8)	36/300 (12.0)	93/880 (10.6)	52/591 (8.8)	77/598 (13.1)
HR	0.80	0.81	0.69	0.90	0.58	0.90	0.79	0.83	0.91	0.67	0.78	0.79
(95% CI)	(0.51-1.23)	(0.57-1.14)	(0.48-1.01)	(0.60-1.34)	(0.36-0.94)	(0.65-1.25)	(0.55-1.13)	(0.55-1.27)	(0.59-1.39)	(0.44-1.01)	(0.51-1.19)	(0.55-1.12)
P for interaction	*0.89*		*0.49*		*0.13*		*0.91*		*0.27*		*0.32*	

Adjusted for age, sex, history of cardiovascular disease, and history of diabetes mellitus. ATII-stimulating AHM include ARBs, dihydropyridine CCBs and thiazide diuretics. ACEi = angiotensin converting enzyme inhibitor; AHM = antihypertensive medication; ARB = angiotensin II receptor blocker; ATII = angiotensin II; CCB = calcium channel blocker; CI =confidence interval; CVD = cardiovascular disease; DM = diabetes mellitus; HR = hazard ratio. [a]Post hoc analysis. [b]Cut-off for controlled hypertension is 150 mmHg.



Chapter III

Antihypertensive medication classes and risk of incident dementia in primary care patients: a longitudinal cohort study in the Netherlands

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RESEARCH IN CONTEXT

Evidence before this study: Hypertension is a modifiable risk factor for dementia. Some antihypertensive medication classes might reduce dementia risk more than other classes, potentially through angiotensin-II-receptor stimulating properties. We searched PubMed for articles published in any language between 1977 and September 2023, using the terms and variations for "antihypertensive medication", "angiotensin-converting enzyme inhibitors", "angiotensin II receptor blockers", "beta blockers", "calcium channel blockers", "diuretics", "hypertension", "blood pressure", "dementia", and "Alzheimer's disease". We found various observational cohort studies and meta-analyses; however, the results on whether specific antihypertensive medication classes were more effective in lowering dementia risk than others varied. These inconsistent findings may be attributed to several factors, including choice of comparator (i.e. comparing to 'non-users' or 'any other antihypertensive medication class users', reducing overall contrast), use of single time-point (baseline) rather than dynamic drug exposures over time, not accounting for competing risk of death, and insufficient exploration of potential confounding by indication.

Added value of this study: In this study, addressing some of the potential methodological flaws from previous studies, we further strengthened evidence that among patients, all receiving some form of antihypertensive medication, angiotensin II receptor blockers, calcium channel blockers, and thiazide diuretics might lower dementia risk more than angiotensin-converting enzyme inhibitors, potentially due to angiotensin-II-receptor stimulating properties. This supports previous findings and aligns with the angiotensin hypothesis. These results cannot be explained by excess mortality. Lastly, we used time-dependent variables for both medication exposure and a wide range of confounders, reducing misclassification over time.

Implications of all the available evidence: Ideally, randomised controlled trials with head-to-head comparisons between antihypertensive medication classes are needed to corroborate these findings before further recommendations can be made. If replicated in an RCT, preferential prescription of one commonly used guideline-equivalent antihypertensive class over another may provide a cheap, safe, and accessible way to reduce dementia incidence in aging populations worldwide.

ABSTRACT

Background: Hypertension is a modifiable risk factor for dementia affecting over 70% of individuals older than 60. Lowering dementia risk through preferential treatment with antihypertensive medication (AHM) classes that are otherwise equivalent in indication could offer a cost-effective, safe, and accessible approach to reducing dementia incidence globally. Certain AHM-classes have been associated with lower dementia risk, potentially attributable to angiotensin II-receptor (Ang-II) stimulating properties. Previous study results have been inconclusive, possibly due to heterogeneous methodology and limited power. We aimed to comprehensively investigate associations between AHM (sub-)classes and dementia risk using large-scale continuous, real-world prescription and outcome data from primary care.

Methods: We used data from three Dutch General Practice Registration Networks. Primary endpoints were clinical diagnosis of incident all-cause dementia and mortality. Using Cox regression with time-dependent covariates, we compared the use of angiotensin-converting enzyme inhibitors (ACEi) to angiotensin receptor blockers (ARBs), beta blockers, calcium channel blockers (CCBs), and diuretics; and Ang II-stimulating to Ang II-inhibiting AHM.

Findings: Of 133,355 AHM-using participants, 5877 (4.4%) developed dementia, and 14,079 (10.6%) died during a median follow-up of 7.6 [interquartile range = 4.1–11.0] years. Compared to ACEi, ARBs [HR = 0.86 (95% CI = 0.80–0.92)], beta blockers [HR = 0.81 (95% CI = 0.75–0.87)], CCBs [HR = 0.77 (95% CI = 0.71–0.84)], and diuretics [HR = 0.65 (95% CI = 0.61–0.70)] were associated with significantly lower dementia risks. Regarding competing risk of death, beta blockers [HR = 1.21 (95% CI = 1.15–1.27)] and diuretics [HR = 1.69 (95% CI = 1.60–1.78)] were associated with higher, CCBs with similar, and ARBs with lower [HR = 0.83 (95% CI = 0.80–0.87)] mortality risk. Dementia [HR = 0.88 (95% CI = 0.82–0.95)] and mortality risk [HR = 0.86 (95% CI = 0.82–0.91)] were lower for Ang-II-stimulating versus Ang-II-inhibiting AHM. There were no interactions with sex, diabetes, cardiovascular disease, and number of AHM used.

Interpretation: Among patients receiving AHM, ARBs, CCBs, and Ang-II-stimulating AHM were associated with lower dementia risk, without excess mortality explaining these results. Extensive subgroup and sensitivity analyses suggested that confounding by indication did not importantly influence our findings. Dementia risk may be influenced by AHM-classes' angiotensin-II-receptor stimulating properties. An RCT comparing BP treatment with different AHM classes with dementia as outcome is warranted.

INTRODUCTION

Approximately 55 million people worldwide have dementia. With global aging, this number is expected to increase to 153 million by 2050, making dementia prevention an international major health priority.[1,2] Hypertension is an important risk factor for all-cause dementia, including Alzheimer's disease (AD).[2,3] It affects over 70% of adults aged 60 and older.[4] RCT and observational evidence suggests that blood pressure (BP) lowering using antihypertensive medication (AHM) reduces dementia risk in hypertensive individuals.[5,6] Moreover, a recent network meta-analysis suggested that specific AHM-classes, particularly angiotensin receptor blockers (ARBs) and calcium channel blockers (CCBs), reduce dementia risk beyond their BP lowering effects.[7] These AHM-classes are commonly used and considered equivalent to other AHM-classes for lowering BP by guidelines worldwide.[8-11] Thus, preferential prescription of these classes for lowering BP may provide an easily accessible and cost-effective method to reduce dementia risk globally. However, two recent, relatively small individual participant data (IPD) collaborations did not find significant differences in dementia risk between AHM-classes.[12,13]

Several factors may underlie this heterogeneity. Studies used different comparator categories, including non-users and "any other AHM-class", instead of comparing individual AHM-classes directly.[7,12,13] This may have diminished contrast and caused insufficient power to detect the approximated 10-30% risk differences between AHM classes.[7] Furthermore, studies based on AHM exposure at single time points may not reflect the clinical reality, as AHM regimens are likely to change over time. The resulting potential exposure misclassification may attenuate class-specific associations, especially with extended follow-up durations,[14] which are required when researching dementia, due to its gradual onset.[15] Finally, studies often do not separately investigate subclasses of diuretics (thiazides/K-sparing/loop) and CCBs (dihydropyridine/non-dihydropyridine), despite these subclasses having considerably varying clinical indications and mechanisms of action.[8-10,16] Recent studies suggest that specifically angiotensin-II-receptors type 2 and 4 (Ang-II) stimulating AHM-subclasses (ARBs, dihydropyridine CCBs, thiazides), lower dementia risk compared to Ang-II-inhibiting subclasses (angiotensin-converting enzyme inhibitors [ACEi], non-dihydropyridine CCBs, beta blockers).[14,17-19] Not distinguishing between these subclasses in exposure or comparator groups may have further diminished contrast and increased heterogeneity based on differences in AHM-subclass usage between studies.

This study aims to address these issues by comprehensively investigating the associations between AHM-(sub)classes and incident dementia risk, using large-scale re-

al-world primary care data, incorporating time-dependent diagnoses and medication changes from over 130,000 Dutch community dwelling, AHM-using older adults from 1988 to 2022. In addition, we explore the extent to which competing risk of mortality and confounding by indication may influence these results.

METHODS

Population

We used routine care data from three Dutch General Practice Registration Networks (GPRN) registered from January 1988 to December 2022. GPRNs record individuals' demographics, medical history, and prescriptions, retrieved from electronic health records (EHR) of general practitioners (GP), >98% of the Dutch population is registered at a GPs-office. Diagnoses and medication use in GPRNs are considered representative of the Dutch population.[20] We included all participants with any AHM use during the observed period who were aged ≥65 years when reaching an endpoint (dementia diagnosis, death, or deregistration), without further in-/exclusion criteria. Data use approval was obtained from each GPRN. Data were anonymously aggregated, requiring no ethical approval.

Endpoints

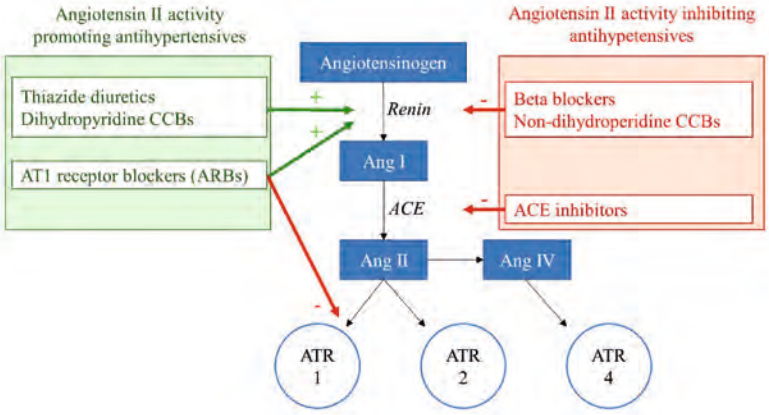
The primary outcome was all-cause dementia using International Classification of Primary Care (ICPC) codes (*Supplementary Methods 1*). Dutch GPRNs include diagnoses made by hospital specialists (e.g. neurologists, geriatricians) following clinical guidelines. Hypertension is primarily managed by GPs. For a brief overview of the role of the GP in Dutch Healthcare, please refer to *Supplementary Methods 2*. All-cause mortality was collected as secondary outcome.[21] Participants leaving the participating GPRNs (e.g. moving from the region) were censored at the deregistration date.

AHM exposure

AHM-use was based on successive prescriptions using ATC codes. We investigated five main AHM-classes: ACEi, ARBs, beta blockers (BBs), CCBs and diuretics. All included ATC codes divided by class are described in *Supplementary Methods 4*. We distinguished between dihydropyridine and non-dihydropyridine CCBs, and thiazide(-like), loop- and potassium-sparing diuretics. Additionally, we compared Ang-II-stimulating AHM (ARBs, dihydropyridine CCBs and thiazide diuretics) to Ang-II-inhibiting AHM (ACEi, BB, non-dihydropyridine CCBs), adjusting for K-sparing and loop-diuretics, as these are not categorised as either Ang-II-stimulating or inhibiting (**Figure 1**).[14,17-19] Over 8 million prescriptions in 133,355 individuals were used to create a detailed, continuous

medication overview for each patient. Within chronic medication regimens, gaps may occur between recurring prescriptions, since arrangements with pharmacies allow for multiple retrievals based on one prescription. Therefore, for chronic users with ≥3 successive prescriptions of an AHM-class, we assumed continuous exposure to that AHM-class from the first to the last prescription date.

Figure 1. Angiotensin Hypothesis.



Thiazides and dihydropyridine calcium channel blockers (dihydropyridine CCBs) increase renin. Beta–blockers reduce β_1-mediated renin production. Long-acting forms of verapamil nor diltiazem CCBs (non-dihydropyridine CCBs) affect or reduce renin. Renin generates angiotensin-I which is converted by angiotensin converting enzyme (ACE) to angiotensin-II, which has physiological effects by binding to ATR1 or ATR2 or it may be metabolised to Ang-IV, which binds to ATR4. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor-1 blockers (ARBs) impact on the Renine-Angiotensine System (RAS) via different Ang-II effects. ACE is reported to degrade Amyloid-β, a major component of dementia plaques in the brain. This degradation may be reduced by ACE-Is. ARBs selectively inhibit Ang-II at angiotensin-receptor 1 (ATR1) without inhibiting ACE. Ang-II and Ang-IV activity may protect from ischemia via activity at ATR2 and possibly ATR4. Ang-II and Ang-IV may directly affect memory. Green arrows and text: Ang-II stimulating antihypertensives; red: Ang-II inhibiting antihypertensives; blue boxes: Angiotensin peptides; blue circles: angiotensin receptors.

Covariates

Age, sex, diabetes, and history of myocardial infarction (MI) and stroke (haemorrhagic and ischaemic) were documented as potential confounders and modifiers. Post-hoc, congestive heart failure (CHF) was added to this list. All covariates were coded as "present" from time of first occurrence within the GP's EPD onwards.

Statistical Analysis

Associations between AHM-classes and incident dementia were calculated using Cox regression with time-dependent covariates.[22,23] To account for possible dependencies between datasets, we included random terms for them. Additionally, we explored the inclusion of fixed terms for datasets, and random terms for the individual general practices within datasets to assess the robustness our results. Time since first registered AHM prescription was used as timescale, with incident dementia as outcome. Changes to AHM-classes were handled dynamically. If a person would change within a class (e.g. Lisinopril to Perindopril, both ACEi), exposure status would remain unchanged. If a person was prescribed a new class, either by adding a drug from another class to the existing class, or replacing it, exposure would change from the exact timepoint the new class was added (e.g. adding Amlodipine to Perindopril after three years would change exposure from ACEi to ACEi and CCB from that moment onwards). All confounders were handled in a similar fashion. For example, if someone was diagnosed with diabetes after three years of follow-up, exposure to diabetes would start at time of diagnosis, leaving the person unexposed to diabetes for the first three years. Only active AHM-users were included. To facilitate comparison between the five AHM-classes, we decided to use one class as reference category. The choice fell on ACEi because, compared to the four other AHM-classes, they showed the highest dementia incidence, and were consistently associated with the highest dementia risk in our Cox regression models, consistent with previous studies.[7,13] Use of ARBs, BBs, CCBs, and diuretics were the main predictors, adjusted for the total number of AHM-classes used including ACEi, thereby resulting in hazard ratios (HR) for use of these AHM types compared to ACEi-use (*Supplementary Methods 3*). Model 1 included baseline age and sex as covariates (detailed effects in *Supplementary Methods 5*). Model 2 additionally included diabetes, MI and stroke. Model 3 corrected for all available covariates, including CHF. Proportional hazards assumptions were assessed using visual inspection of Schoenfeld residuals.

In Cox models, the exposure at the time of event determines the HR. However, prescription stop-dates in the GPRN may not always precisely reflect end-of-use. This may systematically differ per AHM-class and indication. To recompense, we set the end date of all AHM-classes prescribed during the last recorded year to the end of the last prescription in that year. Second, individuals with incipient dementia may withdraw from care or stop medication, resulting in longstanding AHM-users not having prescriptions at the actual dementia diagnosis date. To address this, the last recorded AHM-regimen was extended up to two years until censoring (*Supplementary Figure 1*). We assessed how these two adjustments influenced results in two sensitivity analyses, leaving out each modification respectively. Thirdly, we performed a

sensitivity analysis in which AHM-class exposure was determined relative to the total AHM exposure time, because AHM may exert their effects on dementia risk over a prolonged period, prior to the date of diagnosis. To account for reverse causation, we tested for AHM exposure cut-off at ≥25%, ≥50% and ≥75% of cumulative exposure time. We conducted two additional post-hoc analyses. One excluding individuals who developed dementia within one year of the last AHM regimen change, and another excluding those who developed dementia within one year of starting AHM treatment in our dataset. Lastly, to approach the association with dementia with and without a vascular component, we repeated the main analysis in participants with major cardiovascular disease (CVD), including myocardial infarction (MI) and stroke, and in those without this CVD comorbidity.

Subgroup analyses were performed, stratifying analyses according to 1.) sex, as studies have suggested that the influence of the renin-angiotensin system differs between men and women;[24] 2.) baseline age (<70 years, 70-80 and >80 years) as the major predictor of dementia risk; 3.) history of CVD (MI and/or stroke) and 4.) diabetes, as both these disease histories influence dementia risk as well as the preferential AHM-class for treatment. Furthermore, we stratified analyses according to the total number of AHM-classes used simultaneously, since this may be related to hypertension severity and comorbidity (and thereby dementia risk) and some AHM-classes may more often be prescribed at later stages and/or in combination. Finally, during the early years of this cohort (1988-2012), Dutch primary care guidelines recommended both ARBs and CCBs as later steps in hypertension treatment, whereas ACEi and diuretics were first line of choice. Due to this recommendation, ARBs and CCBs may have been reserved for patients with more severe hypertension during these early years of observation. In the latter years of this study (2012-2022), according to the updated guideline on CVD prevention in clinical practice, all AHM-classes were regarded as equivalent therapeutic options for treatment of uncomplicated hypertension.[25] To assess the consequence of this guideline-change, both time periods were studied separately, using 2015 as cut-off to ensure that the 2012 guideline change was adopted by all GPs.

We assessed the competing risk of death using a cause-specific hazard approach, repeating the main analysis for the outcomes of mortality and dementia/mortality combined. We chose this approach over a sub-distribution hazard (e.g. Fine-Gray analyses) for several reasons: 1) our research question is an etiological one, for which the cause-specific hazard approach is most appropriate,[26,27] 2) we were not aiming to create a prediction model, able to predict the expected number of dementia cases for different AHM groups over a projected period, for which the sub distribution hazard approach is appropriate[26], and 3.) analysis of time-varying covariates in Fine-Gray

models is problematic because it requires making assumptions about the exposure post-censoring for the competing event.[28] Nevertheless, we did explore the potential impact of the sub-distribution hazard approach on our results. Additionally, to explore how subgroups might influence our mortality findings, we repeated all subgroup analyses with mortality as endpoint.

Data were analysed using R 4.1.2 package 'survival'.[22,29]

RESULTS

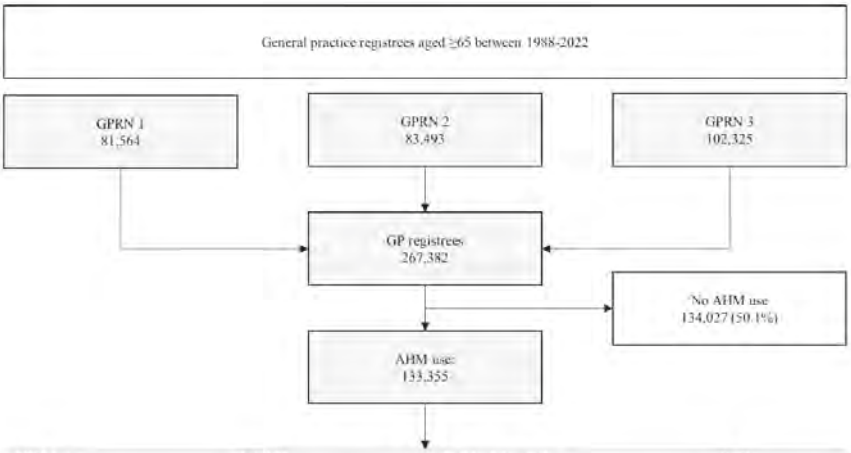
Out of 267,382 registrants aged ≥65 between 1988-2022, 133,355 (49·9%) used AHM and were included (**Figure 2**). Median age of entry into the cohort was 68 years (**Table 1**), 54·7% were women, and median follow-up was 7·6 years (IQR=4·1-11·0), yielding 1,004,775 person years (PY). During the observed period, 5,877 (4·4%) participants developed dementia and 14,079 (10·6%) died. Diabetes occurred in 36,613 (27·5%), MI in 19,139 (14·4%) stroke in 12,096 (9·1%), and congestive heart failure in 14,798 (11·1%) participants. Population characteristics were similar between GPRNs (*Supplementary Table 1*). Common AHM-class combinations at baseline and during the last year of observation are depicted in *Supplementary Table 2*.

Main outcomes

During a total of 357,122 PY of ACEi-use, 2,251 individuals developed dementia (**Table 2**), yielding an incidence rate of 6·3‰. This was 5·5‰ for ARB-use (1,346/246,006) and 5·9‰ for BBs (2989/509,093), CCBs (1759/300,174), and Diuretics (3167/533,719).

Described below are Cox regression analyses results for the fully adjusted Model 2. Compared to ACEi (**Table 2**), dementia risk was lower for ARBs (HR=0·86;95%-CI=0·80-0·92), BBs (HR=0·80;95%CI=0·73-0·87), CCBs (HR=0·77;95%CI=0·71-0·84), and diuretics (HR=0·65;95%CI=0·61-0·70). Furthermore, dementia risk was lower for Ang-II-stimulating (HR=0·88;95%CI=0·82-0·95) versus Ang-II-inhibiting AHM. Dementia risk was similar within CCB subclasses (dihydropyridine/non-dihydropyridine), and within diuretic subclasses (thiazide/loop/K-sparing) versus ACEi (*Supplementary Table 3*).

Figure 2. Flowchart data-extraction from the three General Practice Registration Networks (GPRN).



AHM-type	Total PY	Incident dementia	Death
Any	1,004,775	5,877 (0.58%)	14,079 (1.40%)
ACE	357,122	2,251 (0.63%)	5,140 (1.42%)
ARB	246,006	1,346 (0.55%)	2,946 (1.11%)
Beta blocker	509,093	2,989 (0.59%)	7,852 (1.52%)
CCB	300,174	1,759 (0.59%)	4,357 (1.43%)
Diuretic	533,719	3,167 (0.59%)	9,526 (1.76%)

Only patients aged 65 or above at any point between 1988 and 2022 were extracted. Abbreviations: GP: general practice, AHM: antihypertensive medication, ACE: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, BB: beta blocker, CCB: calcium channel blocker, Diu: diuretic

Table 1. Population characteristics at baseline, and after follow-up.

Baseline	Total population	ACEi	ARB	Beta blocker	CCB	Diuretic	Ang-II-stimulating AHM	Ang-II-inhibiting AHM
	N=133,355	**N=34,545**	**N=17,669**	**N=50,285**	**N=23,860**	**N=51,076**	**N=63,026**	**N=80,305**
Women, n(%)	72,884 (54·7)	15,770 (45·7)	9665 (54·7)	27,271 (54·2)	12,324 (51·7)	30,74 (60·2)	35,944 (57·0)	41,531 (51·7)
Baseline age in years, median [IQR]	68·2	68·2	68·7	67·9	69·2	69·7	68·3	67·9
	[62·0-75·8]	[62·3-75·4]	[62·6-76·1]	[61·5-75·6]	[63·4-76·5]	[63·0-77·8]	[62·4-75·6]	[61·7-75·4]
< 65, n(%)	49,279 (61·4)	12,491(36·2)	6177 (35·0)	19,333 (38·4)	7632 (32·5)	16,607 (32·5)	22,763 (36·1)	30,592 (38·1)
65-75, n(%)	47,765 (59·5)	13,038 (37·7)	6491 (36·7)	17,557 (34·9)	9178 (38·5)	17,806 (34·9)	23,440 (37·2)	28,807 (35·9)
75-85, n(%)	27,465 (34·2)	6944 (20·1)	3868 (21·9)	10,170 (20·2)	5418 (22·7)	11,856 (23·2)	13,064 (20·7)	16,044 (29·0)
≥ 85, n(%)	8846 (11·0)	2072 (6·0)	1133 (6·4)	3225 (6·4)	1632 (6·8)	4807 (9·4)	3759 (6·0)	4862 (6·1)
History of type 2 diabetes, n(%)	26,655 (20·0)	10,207 (29·5)	4611 (27·0)	8809 (17·5)	5218 (21·9)	10,831 (21·2)	13,643 (21·6)	17,194 (21·4)
History of myocardial infarction, n(%)	13,793 (10·3)	4989 (14·4)	1817 (10·3)	8110 (16·1)	2658(11·1)	3767(7·4)	4544 (7·2)	10,942 (13·6)
History of stroke, n(%)	9075 (6·8)	2169 (6·3)	1142 (6·5)	3624 (7·2)	1761 (7·4)	3282 (6·4)	4183 (6·6)	5551 (6·9)
History of congestive heart failure, n(%)	5846 (4·4)	1854 (5·4)	803 (4·5)	2641 (5·3)	917 (3·8)	3681 (7·2)	1784 (2·8)	3756 (4·7)
At time of censoring	**N=133,355**	**N=46,362**	**N=30,466**	**N=63,213**	**N=42,339**	**N=67,611**	**N=78,356**	**N=93,020**
	PY=1,004,775	**PY=357,122**	**PY=246,006**	**PY=509,093**	**PY=300,174**	**PY=533,719**	**PY=631,650**	**PY=727,829**
Censoring age in years, median	76·5	76·1	76·2	76·9	76·0	77·9	76·5	76·4
[IQR]	[70·7-83·6]	[70·6-83·0]	[70·8-83·0]	[71·1-84·0]	[70·6-82·9]	[71·6-85·1]	[70·7-83·6]	[70·8-83·5]
<65, n(%)	497 (0·4)	152 (0·3)	120 (0·4)	204 (0·3)	140 (0·3)	240 (0·4)	305 (0·4)	323 (0·3)
65-75, n(%)	58,190 (43·6)	17,162 (37·0)	13,421 (44·1)	26,455 (41·9)	19,100 (45·1)	26,061 (38·5)	35,307 (45·1)	40,537 (43·6)
75-85, n(%)	46,601 (34·9)	16,500 (35·6)	11,279 (37·0)	22,845 (36·1)	15,202 (35·9)	24,144 (35·7)	28,007 (35·7)	33,025 (35·5)
≥ 85, n(%)	28,049 (21·0)	8852 (19·1)	5646 (18·5)	13,709 (21·7)	7897 (18·7)	17,166 (25·4)	14,737 (18·8)	19,135 (20·6)
Type 2 diabetes, n(%)	36,613 (27·5)	16,151 (34·8)	10,034 (32·9)	18,134 (28·7)	13,275 (31·4)	20,833 (30·8)	23,712 (30·3)	27,476 (29·5)
Myocardial infarction, n(%)	19,139 (14·4)	8428 (18·2)	4664 (15·3)	13,400 (21·2)	6066 (14·3)	9225 (13·6)	9600 (12·3)	16,435 (17·7)
Stroke, n(%)	12,096 (9·1)	3945 (8·5)	2817 (9·2)	5966 (9·4)	4155 (9·8)	5806 (8·6)	7119 (9·1)	8534 (9·2)
Congestive heart failure, n(%)	14,798 (11·1)	5876 (12·7)	3627 (11·9)	9551 (15·1)	3801 (9·0)	12,380 (18·3)	6667 (8·5)	11,739 (12·6)
Incident dementia, n(%)	5877 (4·4)	2251 (4·9)	1346 (4·4)	2989 (4·7)	1759 (4·2)	3167 (4·7)	3491(4·5)	4312 (4·6)
Incident mortality, n(%)	14,079 (10·6)	5140 (11·1)	2946(9·7)	7852 (12·4)	4357(10·3)	9526 (14·1)	7330 (9·4)	10,409(11·2)

Baseline is the moment a participant enters a GPRN. Due to combination therapy, a participant may represented in multiple AHM-groups. Ang-II-stimulating/inhibiting AHM were analysed separately from individual AHM-classes. AHM= antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; Ang-II = angiotensin-II = angiotensin II type 2 receptor.

Table 2. Associations of AHM-use with dementia and mortality.

	Dementia			Mortality			Dementia/Mortality		
AHM-class	**Cases/PY n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY n (‰)**	**HR (95%CI)**	**P-value**	**Cases/PY n (‰)**	**HR (95%CI)**	**P-value**
ACEi	2,251/357,122 (6·3)	*Reference*		5,140/361,994 (14·2)	*Reference*		7662/357,122 (21·5)	*Reference*	
ARB	1,346/246,006 (5·5)	0·86 (0·80-0·92)	<0·001	2,946/248,697 (11·9)	0·83 (0·80-0·87)	<0·001	4443/246,006 (18·1)	0·85 (0·81-0·88)	<0·001
Beta blocker	2,989/509,093 (5·9)	0·81 (0·75-0·87)	<0·001	7,852/515,410 (15·2)	1·21 (1·15-1·27)	<0·001	11,225/509,093 (22·1)	1·06 (1·02-1·11)	<0·001
CCB	1,759/300,174 (5·9)	0·77 (0·71-0·84)	<0·001	4,357/304,486 (14·3)	1·04 (0·99-1·10)	0·15	6272/300,174 (20·9)	0·96 (0·92-1·00)	0·04
Diuretic	3,167/533,719 (5·9)	0·65 (0·61-0·70)	<0·001	9,526/541,233 (17·6)	1·69 (1·60-1·78)	<0·001	13,157/533,719 (24·7)	1·26 (1·21-1·31)	<0·001
Ang-II-inhibiting	4312/727,829 (5.9)	*Reference*		10,409/738,051 (14.1)	*Reference*		14,290/727,691 (19.6)	*Reference*	
Ang-II-stimulating	3491/631,650 (5.5)	0.88 (0.82-0.95)	<0·001	7330/639,836 (11.5)	0.86 (0.82-0.91)	<0·001	10,511/631,568 (16.6)	0.87 (0.84-0.91)	<0·001

Hazard ratio's (HR) for incident outcomes according Cox regression with time varying covariates. HRs present model 2, adjusting for age and sex at baseline, and number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction, and stroke as time dependent variables. Analyses for Ang-II inhibiting versus stimulating AHM were additionally adjusted for K-sparing & Loop diuretics as both subclasses are not represented in either Ang-II-stimulating or Ang-II-inhibiting AHM. Ang-II-inhibiting AHM include: ACEi, Beta blocker & non-dihydropyridine CCB ; AngII-stimulating AHM: ARB, dihydropyridine CCB & Thiazide(like) diuretics. We found no evidence for non-proportionality in our Cox models according to the distribution of the Schoenfeld residuals. Cases/PY represent the total number of incident cases (Cases) that occurred during the total person years (PY) of exposure observed for each class of interest. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker; Ang-II = angiotensin II type 2 receptor

Regarding the competing risk of death, BBs (HR=1·21;95%CI=1·15-1·27) and diuretics (HR=1·69;95%CI=1·60-1·78) were associated with significantly higher, CCBs with similar (HR=1·04;95%CI=0·99-1·10) and ARBs with significantly lower (HR=0·83; 95%CI=0·80-0·87) mortality risk versus ACEi. For the combined outcome of 'dementia/mortality', only ARBs (HR=0·85;95%CI=0·81-0·88), and CCBs (HR=0·96;95%CI=0·92-1·00), had a lower dementia/mortality risk than ACEi. For Ang-II-stimulating AHM, mortality risk (HR=0·84;95%CI=0·79-0·89) and dementia/mortality risk (HR=0·86;95%CI=0·82-0·91) was lower compared to Ang-II-inhibiting AHM (**Table 2**). Within diuretic subclasses, mortality risk was lower for thiazides (HR=0·87;95%CI=0·84-0·91) and higher for loop (HR=3·05;95%CI=2·89-3·22) and K-sparing (HR=1·50;95%CI=1·42-1·59) diuretics versus ACEi (*Supplementary Table 3*). Additionally adjusting for CHF did not change results for dementia and yielded slightly lower point estimates for mortality for diuretics compared to model 2 (*Supplementary Table 4*).

Sensitivity and subgroup analyses

Extending AHM final year prescriptions (*Supplementary Table 5*) and censoring at last prescription's end date (*Supplementary Table 6*) gave similar results. Different methods of adjusting for clustering did not change results (*Supplementary Table 7*). Defining AHM exposure as ≥25%, ≥50% and ≥75% of cumulative exposure time slightly attenuated HRs (*Supplementary Table 8*). Results were similar when excluding individuals who developed dementia within one year of either the last change in AHM regimen, or initiation of AHM treatment (*Supplementary Table 9*). Associations between AHM-classes and dementia were stronger in participants with- compared to participants without major CVD, except for BB (*Supplementary table 10*).

Results for dementia were similar for subgroups stratified by sex, diabetes, CVD, and total number of AHM-classes used simultaneously (*Supplementary Tables 11-12*), except for slightly lower dementia HRs for BBs with CVD (HR=0·72;95%CI=0·64-0·81) versus without CVD (HR=0·80;95%CI=0·73-0·87) (p-interaction=0·03). In individuals with CHF, dementia risk for ARBs (HR=1·02;95%CI=0·87-1·20) and BBs (HR=1·02;95%-CI=0·87-1·19) was comparable with ACEi. Stratified by baseline age (*Supplementary Table 13*), dementia HRs for ARBs and BBs versus ACEi attenuated with higher age (p-trend ≤0·02). Results were similar for individuals initiating AHM treatment before versus after 2015 (three years post guideline change), except for dementia HRs for BBs being neutral if prescribed after 2015 (*Supplementary Table 14*). *Supplementary Tables 15-18* present results for subgroup analyses for mortality, and for competing risk according to sub-distribution hazards (i.e. Fine- Gray).

DISCUSSION

In this observational cohort study, using continuous real-world AHM-exposure data from 133,355 AHM-using primary care patients with 5877 incident dementia cases during one million person-years, use of ARBs (HR=0·86), BBs (HR=0·81), CCBs (HR=0·77) and diuretics (HR=0·65), was associated with 14-35% lower dementia risk, compared to ACEi. These associations did not coincide with significantly increased mortality risks for ARBs (HR=0·83) and CCBs (HR=1·04), meaning that the lower dementia rates for these AHM-classes cannot be attributed to excess mortality. For BBs, excess mortality (HR=1·21) counterbalanced lower dementia risk. For diuretics, excess mortality (HR=1·69) exceeded lower dementia risk. This is substantiated when looking at the composite outcome dementia/mortality, where only ARBs (HR 0·85) and CCBs (HR 0·96) perform better than ACEi. Fine-Gray analysis yielded largely similar results to those of our main analysis. Dementia risks were similar for thiazides, K-sparing, and loop diuretics. However, only for thiazides, lower dementia risk (HR=0·75) coincided with lower mortality risk (HR=0·87). Ang-II-stimulating AHM were associated with 12% lower dementia risk (HR=0·80) compared to Ang-II-inhibiting AHM, without excess mortality (HR=0·86, HR 0·87 for dementia/mortality combined).

Results were stable when adjusting for additional covariates, across sensitivity analyses, and in subgroups of sex, diabetes, CVD, and number of AHM-classes used simultaneously. In individuals with CHF, dementia risk for ARBs and BBs was comparable to ACEi, but mortality risk remained lower for ARBs. The lower dementia risks associated with ARBs and beta-blockers compared to ACEi slightly attenuated with increasing age. This may be a chance finding. Alternative explanations are speculative. Possibly, some classes, such as ARBs, rely more on neuroprotective properties that are particularly exerted before extensive neuropathological changes associated with late life dementia develop, thereby potentially extending their therapeutic benefits, especially in younger age groups. Alternatively, ARBs might particularly reduce the risk of dementia with (micro-)vascular origin, which could represent a larger proportion of dementia cases in younger patients.[30] This hypothesis is supported by our analyses focusing on dementia in participants with major CVD. For beta-blockers, their predominant role in CVD, accompanied by subsequent increased mortality estimates, complicates interpretation. These age-related disparities may merit further investigation in future longitudinal studies.

Literature comparison

Similar to these results, a recent systematic review (n≈649,000 AHM-users, 19,600 dementia cases, 27 studies) that used network meta-analysis to compare AHM classes

directly, found 12-14% lower dementia risks for ARBs (RR=0·88) and CCBs (RR=0·86) versus ACEi.[7] The difference for diuretics (RR=0·95) versus ACEi was less clear.[7] Two recent smaller IPD meta-analyses found no clear differences in dementia risk between AHM-classes but did not compare these directly to each other. One (n≈7500 AHM-users, 650-750 dementia cases) found no significant differences for individual AHM-classes versus non-users or placebo.[12] However, compared to the point estimate for ACEi (OR=1·14), those for ARBs (OR=0·95), CCBs (OR=0·92) and diuretics (OR=0·84) yielded15-25% lower risk of dementia, comparable to our findings, but not for BBs (OR=1·17). The second IPD (n≈7800 AHM-users, up to 1250 dementia cases) found no significant differences in dementia risk between individual AHM-classes versus all other AHM-classes combined, using propensity scores to adjust for potential indication bias.[13] Nevertheless, the reported point estimates for ARBs (HR=0·88) diuretics (HR=0·95) and BBs (HR=0·95) yielded 15-20% lower dementia risk than ACEi (HR=1·11), consistent with our findings, although less so for CCBs (HR=1·04: 7% lower). Point estimates remained largely the same for Alzheimer's dementia compared to those of all-cause dementia.[13] Class-differences in these IPDs may have been significant had AHM-classes been compared directly to each other, rather than to any- or non-users. Two other recent meta-analyses that compared ACEi and ARBs with any other AHM-classes reported the lowest risk of dementia and AD for ARBs.[31,32] In a similar primary care setting in Germany, an observational study among individuals with hypertension, which matched participants with and without dementia, observed that users of ARBs had a 6% lower risk of dementia compared to those using ACEi.[33] None of these studies provided estimates of associated mortality for these AHM-classes, so the potential influence of excess mortality in these meta-analyses cannot be evaluated.

More recent studies specifically focused on Ang-II-stimulating vs Ang-II-inhibiting medication. In the first three,[17-19] Ang-II-stimulating AHM-use was associated with a 24-40% lower risk of incident dementia[17,19] or MCI/probable dementia[18] compared to Ang-II-inhibiting AHM, without excess mortality. Most recently and comprehensively, a study in approximately 58,000 Medicare beneficiaries with newly discovered hypertension with 2,000 incident dementia cases during 12 years of follow-up, found 16% lower AD and related dementias risk associated with Ang-II-stimulating versus Ang-II-inhibiting AHM-use.[19] Notably, this study used Cox regression with time-dependent exposure, similar to our study. It did not report on mortality risk.

Altogether, AHM-classes appear to have differential associations with dementia risk. Lower risks for ARBs versus ACEi are among the most consistently reported, which

is particularly noteworthy because these classes have identical indications, such as BP treatment in diabetes.

Mechanisms

Although concurrent mortality data are relatively sparsely reported, associations for ARBs, CCBs and thiazide(like) diuretics with lower dementia risk do not seem attributable to excess mortality, while those for BBs and other diuretics do. This is understandable because BBs, loop- and K-sparing diuretics are often prescribed for life-limiting conditions including MI, CHF, and renal insufficiency.[34] Conversely, the lower mortality risk observed among Ang-II-stimulating users could also be attributed to unknown patient characteristics, such as ethnicity and socioeconomic status, with potentially healthier participants more often prescribed specific classes (e.g. ARBs), leading to lower mortality rates in those groups.[35,36]

Several hypotheses suggest how individual AHM-classes might reduce dementia risk beyond BP lowering effects. For example, dihydropyridine CCBs may prevent neuronal cell death and AD neuropathology by regulating cellular calcium influx,[37-39] and ARBs may reduce inflammation, oxidative stress, and AD neuropathology by improving cerebral blood flow.[39,40] The more recent "angiotensin hypothesis" suggests that several AHM-classes lower dementia risk by stimulating the angiotensin-II-receptors type (ATR) 2 and 4, involved in cerebral ischemia and memory function (**Figure 1**).[17] ARBs directly block ATR1, increasing ATR2 and ATR4 stimulation and upregulating angiotensin-II production. Thiazide diuretics and dihydropyridine CCBs stimulate ATR2 and ATR4 by increasing renin and thereby angiotensin-II production. BBs and non-dihydropyridine CCBs decrease renin and thereby angiotensin-II production. Finally, ACEis inhibit angiotensin-II production, inhibiting ATR2 and ATR4, and may also decrease cerebral Amyloid-Beta degradation wherein ACE is involved. This would fit with ACEi generally being associated with the highest dementia risk, ARBs versus ACEi most consistently with lower dementia risk, and the consistent results of studies evaluating Ang-II-stimulating versus inhibiting medication, discussed above. Our results do not fully support the angiotensin hypothesis. This could be attributed to residual confounding within the observational data or to other, as-yet-unknown mechanisms that might also influence the differential associations between antihypertensive medication classes and the risk of dementia.

Strengths and limitations

This study has several strengths. First, we used a very large sample of community-dwelling older AHM-users, allowing for comprehensive subgroup and sensitivity analyses. Second, we studied exposures continuously rather than only at baseline

yielding more accurate associations, especially with the protracted follow-up required for studying incident dementia. Third, we compared individuals who used different types of AHM directly to each other. Therefore, all included subjects had hypertension, and used antihypertensive drugs. Consequently, our analyses were not affected by differences in dementia risks attributable to hypertension status (i.e. non-hypertensive individuals likely have lower dementia risk), health seeking behaviour (i.e. higher dementia risks in untreated hypertensive individuals), or access to anti-hypertensive drugs. Fourth, because Dutch GPs actively gather and maintain their patients' health data in the GPRNs used in our study, we have relatively accurate real-world data with very low drop-out, minimizing the risk of observational biases. Fifth, because nearly all community-dwelling individuals in the Netherlands are registered with an GP, our sample is generally representative of the Dutch community-dwelling population,[20] with the limitation that our participating GPRNs were located in the urbanised areas of Amsterdam and Utrecht. Dutch GP's EHRs also contain diagnoses provided by other physicians, including hospital specialists, resulting in excellent specificity (6 studies, median 100%, range 78-100) for mild, and moderate to severe dementia. Sensitivity, however, is limited (up to 60%).[41,42] Last, we extensively investigated individual AHM-classes, subclasses, and Ang-II categorizations, including concurrent associations for mortality. Thereby, this paper provides the most elaborate, comprehensive, and adequately powered evidence on differential associations for AHM-classes with dementia risk to date.

Unfortunately, we were unable to explore dementia subtypes due to data limitations. However, the likelihood of diagnostic imprecision varying with the class of AHM used is considered low, since the large majority of late-life dementia diagnoses concerns AD. This is supported by a large meta-analysis, which revealed similar hazards for both all-cause dementia and AD for different subclasses of AHM.[13] From a clinical perspective, many patients diagnosed with AD also have some form of cerebrovascular comorbidity, hence could probably also be considered to harbour to a varying degree a vascular factor in addition to the neurodegenerative component. A further limitation is potential confounding by indication, which may have affected AHM prescription patterns in several ways. In the present Dutch GP guidelines, all antihypertensive medication (AHM) classes are considered equivalent treatments for uncomplicated hypertension. In cases of insufficiently controlled hypertension, it is recommended to add another AHM-class, instead of increasing dosages of the current regimen, to avoid adverse drug reactions (ADR). Under certain conditions, including diabetes, CVD, and CHF, specific AHMs are preferred. These preferences do not seem to have affected our main findings, as adjusting and stratifying for age, diabetes, CVD, and CHF hardly changed results. Inclusion of additional covariates,

such as ethnicity and socioeconomic status could have further mitigated confounding by indication, although we believe the comorbidities incorporated in our analyses were the most relevant for the study objective. Our study relied on prescription data. Unknown patient characteristics, including treatment adherence and ADR may have influenced our results. Adherence can be adversely affected by ADR, which are common among users of AHMs. Older adults, in particular, are vulnerable to experiencing ADR due to polypharmacy. Consequently, they may experience decreased treatment adherence. For instance, ACE inhibitors (ACEi) and ARBs may cause kidney failure, especially when paired with diuretics or each other. BBs can induce fatigue and bradycardia, particularly when used alongside other negative chronotropic drugs, such as non-dihydropyridine CCBs. Non-dihydropyridine CCBs are associated with constipation, while dihydropyridines often lead to lower limb oedema, sometimes misinterpreted and mistakenly treated as heart failure. Diuretic-use may result in electrolyte imbalances, increased risk of diabetes when combined with BBs, or urinary incontinence. If more prevalent in specific classes, ADR may have resulted in increased inter-class switching and decreased adherence, which may have influenced results. Despite acknowledging the importance of considering ADR in older adults, most international hypertension guidelines, such as the American and Dutch guidelines, recommend the same five AHM classes for both younger and older individuals (aged >60), with British guidelines excluding BBs. This suggests that there is insufficient evidence for significant differences in ADR incidences among AHM-classes. Although current guidelines do not explicitly endorse a preference for specific classes with increasing hypertension severity or treatment resistance, GPs may prefer prescribing AHM classes in a specific order. Nevertheless, this appears to have had minimal impact, as the results were similar when stratified by the number of AHM used concurrently. Dihydropyridine CCBs and non-selective BBs are preferred for hypertensive emergencies, however, these treatments are generally short lasting and administered in hospitalised settings, limiting their influence in primary care data. Dutch GP guidelines before 2012 recommended initiating primary hypertension treatment with thiazides or CCBs.[25] Thus, these medications may have been particularly used in longstanding, relatively uncomplicated cases. However, associations were not attenuated for first-time users after 2015 except for BBs, suggesting that pre-existing AHM-class prescription preferences from before 2015 did not influence our results for ARBs, CCBs and thiazides. In the first half of our observational study, some classes, for instance ARBs, were still under patent resulting in higher prices, potentially limiting access to individuals with lower (social-) economic status. Nevertheless, results were similar when comparing prescription data before and after 2015. More importantly, in Dutch healthcare, all standard care including medication, is covered by mandatory health insurance, suggesting that overall impact of socioeconomic background on

outcomes may have been limited. Reverse causation, for instance through switching antihypertensive regimens shortly before dementia diagnosis, may have occurred due to factors such as ease of use, adherence concerns, or ADR. However, it is unlikely that physicians systematically changed AHM regimens to a specific class before dementia diagnosis. Moreover, results for different proportions of AHM exposure were similar. Therefore, if reverse causation were a major factor, substantial differences would have been expected between the results of these exposure time analyses and those of the main analyses, as participants would have switched medications relatively shortly before dementia diagnosis. However, these exposure analyses are less informative regarding reverse causation if individuals with a greater dementia risk are also more susceptible to ADR, and are therefore more likely to use AHM-classes with fewer ADR or to be less adherent to these classes. Despite the assurances above, we cannot fully exclude residual confounding by, for example, unknown GP preferences or patient characteristics differentially affecting dementia risk. Another limitation may come from using regular care data. Although actively maintained by GPs, these may have relative inaccuracies compared to data from purpose-designed longitudinal studies with protocolised measurements by research personnel. Moreover, potential underestimation of dementia diagnoses may have played a role in our analyses, given the low level of sensitivity in GP-data (up to 60%), especially in mild dementia cases.[42] It is unlikely that these inaccuracies systematically differed between AHM classes, biasing results towards neutral rather than exaggerated differences. Diagnoses made prior to entering a GPRN were available, however, medication were not. Therefore, some individuals that used and permanently stopped AHM prior to registering at a GPRN were not included in our dataset. Finally, the absence of blood pressure data in our model may be considered a potential limitation. However, significant proportions of missing data and potential bias in existing measurements towards higher risk would have hindered imputation of adequate time-dependent modelling necessary to account for the multitude of medication changes over time.[43] Furthermore, BP lowering effects are considered more or less equal between AHM-classes, and studies adjusting for BP levels reported similar results.[9,10,25,44] Moreover, a large meta-analysis reported that the association between blood pressure lowering with AHM and lower risk of dementia or cognitive decline was not affected by baseline blood pressure or cumulative systolic blood pressure change.[5] Finally, in a different cohort with similar characteristics where BP values were available, we found no apparent differences in BP values between AHM-classes.[14] Therefore, we expect that the differential associations in our study represent class-specific mechanisms affecting dementia risk beyond BP lowering effects.

Conclusion

ARBs, CCBs and thiazide diuretics were associated with lower dementia incidence rates compared to ACEi-use, without excess mortality. Combined with previous studies, our study makes a compelling case for differential associations between AHM-classes and dementia risk, particularly for lower risks associated with ARBs versus ACEi and Ang-II stimulating versus Ang-II-inhibiting AHM-classes. Given the inevitability of potential confounding by indication in observational settings, a large-scale RCT is warranted to confirm whether treatment with these classes lowers dementia risk without increasing the risk of any other poor outcomes. However, the need for prolonged follow-up with dementia as an outcome, coupled with the associated high study costs, suggests that results from such a trial may be over a decade away. In the meantime, developing a framework for designing and analysing observational studies aimed at estimating the causal effects of interventions, ideally incorporating BP values, therapy adherence, and additional prescription pattern-influencing covariates, could further enhance our understanding of the relationship between AHM-classes and dementia risk.

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SUPPLEMENTARY MATERIAL

Supplementary Methods 1. ICPC codes used for identifying incident dementia from the GPRN databases

Dementia was defined as P70 (senile dementia/Alzheimer disease), the only code within the ICPC for dementia. Another code slightly related is P20 (memory/concentration/orientation impairment), but it is nonspecific and was disregarded.

Supplementary Methods 2. A brief explanation of the role of the Dutch GP within Dutch health care

Referral to secondary care systems and diagnoses in GPs EHR: In Dutch Health Care, the GP is the gatekeeper of the system. All Dutch citizens need to be registered with a GP. The vast majority of health concerns, including management of hypertension and diabetes, are primarily handled by GPs. Patients cannot access secondary care systems (such as specialist clinics, hospitals, including emergency rooms) without a referral from their GP. Exceptions are emergencies, such as major accidents and life-threatening conditions (such as myocardial infarction and stroke). In these occasions, the patient is directly transported to a hospital, without need of prior need consultation with a GP. However, in all instances (i.e. after GPs referral, and after emergency hospital consultation/admission) the patients GP receives correspondence of this hospital consultation/admission, including made diagnoses, and changes to medication regiments.

Nursing homes: In the past decades, the number of nursing homes has drastically decreased in the Netherlands. Most older adults keep living at home for much longer aided by home care nurses and informal care by family members, friends, and neighbours. In these cases patients will still be under the care of a GP, along with hospital specialists and other health care workers, who all report to the GP. In some instances, for instance when suffering from invalidating comorbidities such as dementia or stroke, patients will be admitted to nursing homes. In some cases, a GP will remains the treating physician, in other cases care will be transferred to a dedicated nursing home physicians. In case of permanent admission to a nursing home away from a GPs care, the participant will be censored at that time, as they deregistered from the participating GPRN. It is unlikely that this affected dementia estimates, as the vast majority of dementia diagnoses will have been made prior to admission.

Supplementary Methods 3. Description of analytic models

Our analyses only included individuals who were actively using one or more of the compared antihypertensive categories. We aimed to compare associations for ARBs, beta blockers, CCBs, and diuretics to those for ACE-inhibitors as reference category, in order to have a stable reference point (i.e. the dementia risk for same antihypertensive type as reference for each analysis). In analyses wherein individuals could only use one of these medications at a time, this could be done using four dummy variables (0/1 coded variables) for each of these medication types. The resulting cox regression formula in R would be comparable to:

coxph(Surv(Start_Time,Stop_Time,Outcome_Status)~ARB_use+BB_use+CCB_use+Diuretic_use+covariates+frailty(GPRNs)).

Individuals with 0 for all of these dummy variables would then necessarily be ACE-inhibitor users, and therefore ACE-inhibitors would be the reference category. However, in our analyses, individuals can use multiple medications at a time, therefore, individuals with 1 on one or more of the dummy variables may still use ACE-inhibitors. Adding another dummy variable for ACE-inhibitor use would not solve this problem, because the reference category would then change to individuals with 0 for all of the dummy variables, resulting in a calculated 'floating average dementia risk' as reference, which would be different for each of the analyses. To reinstate ACE-inhibitor use as the stable reference category for these analyses, we included a second categorical variable, which comprised the total number of antihypertensive medications taken, with 1 (the minimum) as reference category. This resulted in an R formula comparable to:

coxph(Surv(Start_Time,Stop_Time,Outcome_Status)~ARB_use+BB_use+CCB_use+Diuretic_use+Total_nr_of_AHM_categorical+covariates+frailty(GPRNs)).

Thereby, individuals with 0 for ARBs, BBs, CCBs, and Diuretics, must take ACEi, and have the reference 1 value in the total AHM used variable. However, individuals using -for example- both diuretics and ACEi, would present the HR for diuretic use, adjusted for another medication that was concurrently taken, which was not ARB, BB, or CCBs, since these variables would all be 0, and thereby must be ACEi use. Thereby, the resulting HRs for ARBs, BBs, CCBs and diuretics effectively translate to the HRs for these medications compared to ACE inhibitors

Supplementary Methods 4. AHM-classes and corresponding ATC codes

AHM-class[a]	ATC codes[b]
ACEi	C09A; C09B
ARB	C09C; C09D
Beta blocker	C07; C09BX02; C09BX04; C09DX05
CCB	C07FB; C08; C09BB; C09BX01; C09BX03; C09BX04; C09DB; C09DX01; C09DX03; C09DX06; C09DX07; C09XA53
Dihydropyridine	C07FB; C08CA; C08G; C09BB02; C09BB03; C09BB04; C09BB05; C09BB06; C09BB07; C09BB12; C09BB13; C09BX01; C09BX03; C09BX04; C09DB; C09DX01; C09DX03; C09DX06; C09DX07; C09XA53
Non-dihydropyridine	C08DA; C08DB; C08E; C09BB10;
Diuretic	C02L; C03; C07B; C07C; C07D; C08G; C09BA; C09BX01; C09BX03; C09DA; C09DX01; C09DX03; C09DX06; C09DX07; C09XA52; C09XA54
Thiazide(like)	C03A; C03BA; C03EA; C07B; C07C; C07D; C08G; C09BA; C09BX-1; C09BX04; C09DA; C09DX01; C09DX03; C09DX06; C09DX07; C09XA52; C09XA54
Loop	C03CA; C03CB; C03EB
Potassium sparing	C03AB; C03BB; C03D; C03E

[a] Ang-II-stimulating AHM include all codes associated with ARB, dihydropyridine CCB, and Thiazide(like) diuretics. Ang-II-inhibiting AHM include all codes associated with ACEi, beta blocker, and non-dihydropyridine CCB [b] Includes all underlying codes (e.g. C09A includes, C09AA01- C09AA16). AHM = antihypertensive medication; ATC = anatomical therapeutic chemical; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

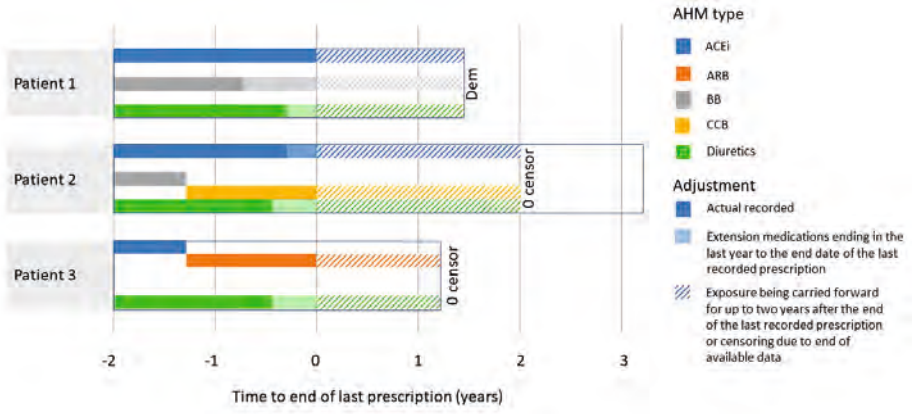
Supplementary Methods 5. Results of crude models, and separate models adjusted only for sex and age, to evaluate the separate effects of adjusting for these factors on the results of model 1

AHM-class	Dementia cases/total person years[a] n(‰)	HR crude model (95%CI)	P-value	HR crude model + baseline age (95%CI)	P-value	HR crude model + sex (95%CI)	P-sex	HR Model 1 [b] (95%CI)	P-value
ACEi	2251/357,122 (6·3)	*Reference*							
ARB	1346/246,006 (5·5)	0·84 (0·79-0·90)	<0·001	0·85 (0·79-0·91)	<0·001	0·82 (0·76-0·88)	<0·001	0·85 (0·79-0·91)	<0·001
Beta blocker	2989/509,093 (5·9)	0·91 (0·85-0·98)	0·01	0·79 (0·73-0·85)	<0·001	0·88 (0·82-0·94)	<0·001	0·79 (0·73-0·85)	<0·001
CCB	1759/300,174 (5·9)	0·90 (0·83-0·98)	0·01	0·76 (0·70-0·82)	<0·001	0·87 (0·80-0·94)	<0·001	0·76 (0·70-0·82)	<0·001
Diuretic	3167/533,719 (5·9)	0·94 (0·87-1·02)	0·11	0·64 (0·59-0·69)	<0·001	0·87 (0·80-0·94)	<0·001	0·64 (0·59-0·69)	<0·001

[a] Within class of interest [b] Adjusted for baseline age, sex & AHM-classes used simultaneously. Individual participants can be represented in multiple AHM-classes in case of combination therapy and medication switching over time.

AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Figure 1. Examples for alterations done in sensitivity analysis 1 and 2



Dem = dementia; 0 censor = censored without dementia diagnosis during the observed period. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, BB = beta blockers CCB = calcium channel blocker.

Reading example: For patient 1, ACEi (blue) was the last ending prescription. BB (grey) and Diuretics (green) ended within one year before, so their use was extended to the end of ACEi (light shaded grey and green). These three prescription exposures were then carried forward for up to 2 years (dashed shade), in this case to 1.4 years when the patient was censored with dementia. For patient 2, CCB (yellow) was the last ending prescription. ACEi (blue) and Diuretics (green) ended within one year before, and were therefore extended up to the end of CCBs (light shaded blue and green). BB (grey) ended more than a year before CCBs (yellow), and was therefore not extended. For ACEi, CCBs and Diuretics, prescription exposures were carried forward for 2 years (dashed blue, yellow and green), at which time no event had occurred, so the patient was censored as no dementia. For patient 3, ARB (orange) was the last ending prescription. Only diuretics (green) ended in the last year before that, so was extended up to ARB's end (light shaded green). The last prescriptions were then carried forward for up to 2 years (dashed orange and green). In this case, the patient was censored without an event after 1.2 years, because that was the time up until which information was available for this patient.

Supplementary Table 1. Population characteristics and medication use for the combined population split per GPRN

	AMC	UMCU	VUMC	Combined
Baseline	N=40,207	N=49,167	N=43,981	N=133,355
Women, n(%)	20,890 (52·0)	27,413 (55·8)	24,581 (55·9)	72,884 (54·7)
Baseline age, median[IQR]	68·2 [62·9-75·5]	68·0 [61·1-75·6]	68·6 [61·9-76·3]	68·2 [62·0-75·8]
History of type 2 diabetes, n(%)	10,869 (27·0)	7866 (16·0)	7920 (18·0)	26,655 (20·0)
History of coronary heart disease, n(%)	5141 (12·8)	4419 (9·0)	4233 (9·6)	13,793 (10·3)
History of stroke, n(%)	3783 (9·3)	2419 (6·0)	2873 (6·5)	9075 (6·8)
ACEi users at baseline	11,822 (29·4)	11,821 (29·4)	10,902 (24·8)	34,545 (25·9)
ARB users at baseline, n(%)	6251 (15·5)	5020 (12·5)	6398 (14·5)	17,669 (13·2)
Beta blocker users at baseline, n(%)	16,121 (40·0)	16,929 (42·0)	17,235 (39·2)	50,285 (37·7)
CCB users at baseline, n(%)	9785 (24·3)	6089 (15·1)	7986 (18·2)	23,860 (17·9)
Diuretic users at baseline, n(%)	16,813 (41·8)	17,852 (44·3)	16,411 (37·3)	51,076 (38·3)
Follow-up				
Median observed years [IQR]	7·6 [5·2-10·4]	11·8 [7·0-17·0]	9·4 [5·9-15·7]	7·6 [4·1-11·0]
Total observed person years	248,973	407,877	347,926	1,004,775
Median censoring age [IQR]	74·9 [69·6-81·8]	78·7 [71·5-84·6]	78·0 [71·1-84·1]	76·5 [70·7-83·6]
Incident type 2 diabetes, n(%)	1534 (3·8)	4967 (9·6)	3727 (8·5)	9,958 (7·5)
Incident coronary heart disease, n(%)	1029 (2·6)	2290 (4·7)	2027 (4·6)	5346 (4·0)
Incident stroke, n(%)	516 (1·3)	1237 (2·5)	1268 (2·9)	3021 (2·3)
Incident dementia, n(%)	1527 (3·8)	2179 (5·4)	2171 (4·9)	5877 (4·4)
Mortality, n(%)	4588 (11·4)	5076 (12·6)	4413 (10·0)	14,079 (10·6)
ACEi users at censoring, n(%)*	14,663 (36·4)	16,618 (41·3)	15,081 (34·3)	46,362 (34·8)
ARB users at censoring, n(%)*	9291 (23·1)	10,142 (25·2)	11,033 (25·1)	30,466 (22·8)
Beta blocker users at censoring, n(%)*	19,930 (49·5)	21,328 (53·0)	21,955 (49·9)	63,213 (47·4)
CCB users at censoring, n(%)*	15,236 (37·9)	12,986 (32·2)	14,117 (32·1)	42,339 (31·7)
Diuretic users at censoring, n(%)*	20,324 (50·5)	24,636 (61·2)	22,651 (51·5)	67,611 (50·7)

* AHM use at censoring was defined as used during the last year of observation before reaching an endpoint. GPRN = General Practice Registration Network; AMC = Academic Medical Center; UMCU = University Medical Center Utrecht; VUMC = Vrije Universiteit Medical Center; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; AHM = antihypertensive medication

Supplementary Table 2. Common AHM-class combinations at baseline and during last year of follow-up

AHM-class combinations at baseline	**N (%)** n=133,355
Beta blocker monotherapy	31694 (23·8)
Diuretic monotherapy	28,524 (21·4)
ACEi monotherapy	19,174 (14·4)
CCB monotherapy	13,133 (9·8)
ARB monotherapy	8039 (6·0)
ACEi+diuretic	4824 (3·6)
Beta blocker+diuretic	4462 (3·3)
ARB+diuretic	3742 (2·8)
ACEi+beta blocker	3576 (2·7)
ACEi+beta blocker+diuretic	2541 (1·9)
AHM-class combinations at during last year of follow-up	**N (%)** n=133,355
Beta blocker monotherapy	17,300 (13·0)
Diuretic monotherapy	15,210 (11·4)
ACEi monotherapy	11,219 (8·4)
CCB monotherapy	9010 (6·8)
Beta blocker+diuretic	7814 (5·9)
ACEi+diuretic	7354 (5·5)
ACEi+beta blocker+diuretic	7195 (5·4)
ARB monotherapy	5611 (4·2)
ACEi+beta blocker	5542 (4·2)
ARB+diuretic	5268 (4·0)

This table depicts the most common combinations of simultaneously used AHM-classes, including monotherapy. The top section depicts combinations at baseline (i.e. when participants enter the GPRN). The bottom depicts combinations during the last year of observation (which was the exposure for our main analyses). AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

Supplementary Table 3. Associations between use of AHM-(sub)classes and dementia and mortality, compared with use of ACEi

AHM-(sub)class	Dementia cases/ total person years[a] n(‰)	HR Dementia[b] (95%CI)	P-value Dementia	Mortality cases/ total person years[a] n(‰)	HR Mortality[b] (95%CI)	P-value Mortality
ACEi	2251/357,122 (6·3)	*Reference*		5140/361,994 (14·2)	*Reference*	
ARB	1346/246,006 (5·5)	0·85 (0·79-0·91)	<0·001	2946/248,697 (11·9)	0·88 (0·84-0·92)	<0·001
Beta blocker	2989/509,093 (5·9)	0·81 (0·76-0·88)	<0·001	7852/515,410 (15·2)	1·06 (1·01-1·12)	0·015
CCB						
Dihydropyridine	1511/257,851 (5·9)	0·79 (0·72-0·86)	<0·001	3681/261,284 (14·1)	1·07 (1·02-1·14)	0·009
Non-dihydropyridine	257/40,308 (6·4)	0·80 (0·70-0·91)	0·001	741/40,954 (18·1)	1·13 (1·04-1·23)	0·004
Diuretic						
Thiazide(like)	1908/389,315 (4·9)	0·75 (0·69-0·82)	<0·001	3420/393,295 (8·7)	0·87 (0·83-0·93)	<0·001
Loop	1374/129,170 (10·6)	0·78 (0·71-0·85)	<0·001	6670/132,748 (50·3)	3·05 (2·89-3·22)	<0·001
Potassium sparing	572/78,464 (7·3)	0·77 (0·69-0·86)	<0·001	2631/79,687 (33·0)	1·50 (1·42-1·59)	<0·001

[a] Within class of interest [b] Model 2, adjusted for baseline age, sex, number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker. Note: point estimates for ACEi, ARBs, and beta blockers are slightly different from Table 2 in the main text because the models here include all the subtypes of CCBs and diuretics separately, instead of for CCBs and Diuretics combined as in the main analyses. The slightly different predictors in the models resulted in slightly different results for ACEi, ARBs and beta blockers.

Supplementary Table 4. Comparing Model 2 and 3 for dementia, mortality, and dementia or mortality

	Dementia			Mortality			Dementia or Mortality		
AHM-class	**Cases/PY n (‰)**	**HR model 2 (95%CI)**	**HR model 3 (95%CI)**	**Cases/PY n (‰)**	**HR model 2 (95%CI)**	**HR model 3 (95%CI)**	**Cases/PY n (‰)**	**HR model 2 (95%CI)**	**HR model 3 (95%CI)**
ACEi	2,251/357,122 (6·3)	*Reference*		5,140/361,994 (14·2)	*Reference*		7662/357,123 (21·5)	*Reference*	
ARB	1,346/246,006 (5·5)	0·86 (0·80-0·92)	0·86 (0·80-0·92)	2,946/248,697 (11·9)	0·83 (0·80-0·87)	0·85 (0·81-0·89)	4443/246,006 (18·1)	0·85 (0·81-0·88)	0·86 (0·83-0·90)
Beta blocker	2,989/509,093 (5·9)	0·81 (0·75-0·87)	0·81 (0·75-0·87)	7,852/515,410 (15·2)	1·21 (1·15-1·27)	1·16 (1·11-1·22)	11,225/509,093 (22·1)	1·06 (1·02-1·11)	1·04 (0·99-1·08)
CCB	1,759/300,174 (5·9)	0·77 (0·71-0·84)	0·77 (0·71-0·84)	4,357/304,486 (14·3)	1·04 (0·99-1·10)	1·10 (1·04-1·16)	6272/300,174 (20·9)	0·96 (0·92-1·00)	0·99 (0·95-1·04)
Diuretic	3,167/533,719 (5·9)	0·65 (0·61-0·70)	0·65 (0·60-0·70)	9,526/541,233 (17·6)	1·69 (1·60-1·78)	1·47 (1·30-1·55)	13,157/533,719 (24·7)	1·26 (1·21-1·31)	1·16 (1·11-1·21)
Ang-II-inhibiting	4312/727,829 (5·9)	*Reference*		10,409/738,051 (14·1)	*Reference*		14,290/727,691 (19·6)	*Reference*	
Ang-II-stimulating	3491/631,650 (5·5)	0·88 (0·82-0·95)	0·88 (0·82-0·95)	7330/639,836 (11·5)	0·86 (0·82-0·91)	0·89 (0·85-0·93)	10,511/631,568 (16·6)	0·87 (0·84-0·91)	0·89 (0·85-0·93)

Hazard ratio's (HR) for incident outcomes according Cox regression with time varying covariates· HRs present model 2, adjusting for age and sex at baseline, and number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction, and stroke as time dependent variables. Model 3 is additionally adjusted for congestive heart failure. Analyses for Ang-II inhibiting versus stimulating AHM were additionally adjusted for K-sparing & Loop diuretics as both subclasses are not represented in either Ang-II-stimulating or Ang-II-inhibiting AHM. Ang-II-inhibiting AHM include: ACEi, Beta blocker & non-dihydropyridine CCB ; AngII-stimulating AHM: ARB, dihydropyridine CCB & Thiazide(like) diuretics. We found no evidence for non-proportionality in our Cox models according to the distribution of the Schoenfeld residuals. Cases/PY represent the total number of incident cases (Cases) that occurred during the total person years (PY) of exposure observed for each class of interest. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time.

Abbreviations: AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker; Ang-II = angiotensin II type 2 receptor

Supplementary Table 5-I. Sensitivity analysis with prescriptions at censoring. Association between AHM-classes and dementia, compared to use of ACEi

AHM-class	Dementia cases/total person years[a] n(‰)	HR[b] (95%CI)	P-value
ACEi	1867/350,717 (5·3)	*Reference*	
ARB	1098/502,026 (4·5)	0·89 (0·82-0·96)	<0·002
Beta blocker	2476/502,026 (4·9)	0·80 (0·75-0·86)	<0·001
CCB	1417/293,396 (4·8)	0·84 (0·78-0·91)	<0·001
Diuretic	2530/524,831 (4·8)	0·66 (0·61-0·71)	<0·001

Supplementary Table 5-II. Main analysis with prescriptions used during the final year of observation for comparison. Association between AHM-classes and dementia, compared to use of ACEi.

AHM-class	Dementia cases/total person years[a] n(‰)	HR[b] (95%CI)	P-value
ACEi	2251/357,122 (6·3)	*Reference*	
ARB	1346/246,006 (5·5)	0·87 (0·81-0·93)	<0·001
Beta blocker	2989/509,093 (5·9)	0·81 (0·76-0·88)	<0·001
CCB	1759/300,174 (5·9)	0·78 (0·72-0·85)	<0·001
Diuretic	3167/533,719 (5·9)	0·67 (0·62-0·72)	<0·001

[a] Within class of interest [b] Model 2, adjusted for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM= antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker

Supplementary Table 6-I. Sensitivity analysis with observations not carried forward. Association between AHM-classes and dementia, compared to use of ACEi

AHM-class	Dementia cases/total person years[a] n(‰)	HR[b] (95%CI)	P-value
ACEi 1468/347,487 (4·2) *Reference*			
ARB	915/240,795 (3·8)	0·88 (0·81-0·96)	0·006
Beta blocker	2015/492,799 (4·1)	0·84 (0·76-0·92)	<0·001
CCB	1156/292,527 (4·0)	0·73 (0·66-0·81)	<0·001
Diuretic	2059/517,569 (4·0)	0·64 (0·58-0·71)	<0·001

Supplementary Table 6-II. Main analysis with observations carried forward up to two years for comparison. Association between AHM-classes and dementia, compared to use of ACEi.

AHM-class	Dementia cases/total person years[a] n(‰)	HR[b] (95%CI)	P-value
ACEi	2251/357,122 (6·3)	*Reference*	
ARB	1346/246,006 (5·5)	0·87 (0·81-0·93)	<0·001
Beta blocker	2989/509,093 (5·9)	0·81 (0·76-0·88)	<0·001
CCB	1759/300,174 (5·9)	0·78 (0·72-0·85)	<0·001
Diuretic	3167/533,719 (5·9)	0·67 (0·62-0·72)	<0·001

[a] Within class of interest [b] Model 2, adjusted for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM= antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker

Supplementary Table 7. Comparison of three methods of adjusting for clustering. Associations between AHM-classes and dementia

		Random terms for general practices	Fixed terms for datasets	Main model (random terms for datasets)
AHM-class	**Cases/PY n (‰)**	**HR[a]**	**HR[a]**	**HR[a]**
ACEi	2,251/357,122 (6·3)	*Reference*	*Reference*	*Reference*
ARB	1,346/246,006 (5·5)	0·86 (0·80-0·92)	0·86 (0·80-0·92)	0·86 (0·80-0·87)
Beta blocker	2,989/509,093 (5·9)	0·78 (0·72-0·84)	0·81 (0·75-0·87)	0·71 (0·75-0·87)
CCB	1,759/300,174 (5·9)	0·79 (0·73-0·86)	0·77 (0·71-0·84)	0·77 (0·71-0·84)
Diuretic	3,167/533,719 (5·9)	0·64 (0·59-0·69)	0·65 (0·60-0·70)	0·65 (0·60-0·70)

This study includes data from 79 individual general practices spread over 3 general practice registration networks. Hazard ratio's (HR) for incident dementia according Cox regression with time varying covariates. [a] Model 2, adjusting for age and sex at baseline, and number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction, and stroke as time dependent variables. Abbreviations: AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Table 8. Sensitivity analysis with AHM-class exposure as a proportion of total AHM time use

			Model 1[c]		Model 2[d]	
Proportion cut-off[a]	***AHM-class***	***Dementia cases/total person years[b] n(‰)***	***HR (95%CI)***	***P-value***	***HR (95%CI)***	***P-value***
>25%	ACEi	2403/380,859 (6·3)	*Reference*		*Reference*	
	ARB	1489/255,152 (5·8)	0·88 (0·82-0·95)	<0·001	0·90 (0·84-0·97)	0·003
	Beta blocker	3295/533,674 (6·2)	0·86 (0·80-0·92)	<0·001	0·89 (0·83-0·96)	0·003
	CCB	1919/308,169 (6·2)	0·79 (0·73-0·85)	<0·001	0·82 (0·76-0·89)	<0·001
	Diuretic	3513/561,935 (6·3)	0·69 (0·64-0·75)	<0·001	0·73 (0·67-0·79)	<0·001
>50%	ACEi	2051/339,164 (6·1)	*Reference*		*Reference*	
	ARB	1268/224,698 (5·6)	0·90 (0·83-0·96)	0·003	0·92 (0·85-0·98)	0·02
	Beta blocker	2970/494,116 (6·0)	0·87 (0·81-0·93)	<0·001	0·90 (0·84-0·97)	0·006
	CCB	1567/264,334 (5·9)	0·80 (0·73-0·86)	<0·001	0·83 (0·76-0·90)	<0·001
	Diuretic	3103/514,171(6·0)	0·71 (0·65-0·76)	<0·001	0·74 (0·68-0·80)	<0·001
>75%	ACEi	1755/294,456 (6·0)	*Reference*		*Reference*	
	ARB	1028/187,498 (5·5)	0·89 (0·82-0·96)	0·002	0·90 (0·83-0·98)	0·01
	Beta blocker	2580/447,649 (5·8)	0·84 (0·78-0·90)	<0·001	0·87 (0·81-0·94)	<0·001
	CCB	1238/216,397 (5·7)	0·78 (0·72-0·85)	<0·001	0·81 (0·75-0·89)	<0·001
	Diuretic	2638/451,444 (5·8)	0·69 (0·64-0·75)	<0·001	0·72 (0·67-0·78)	<0·001

[a] Proportion of time class of interest was used divided by total time any AHM was used. [b] Within class of interest [c] Adjusted for baseline age, sex and number of AHM-classes used simultaneously [d] and type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Table 9-I. Sensitivity analysis excluding dementia cases within 1 year of the last regimen change

AHM-class	Cases/PY n (‰)	HR[a] (95%CI)	P-value
ACEi	2020/356,971 (5·7)	*Reference*	
ARB	1240/245,917 (5·0)	0·87 (0·81-0·93)	<0·001
Beta blocker	2698/508,831 (5·3)	0·81 (0·75-0·87)	<0·001
CCB	1605/300,087 (5·5)	0·77 (0·71-0·84)	<0·001
Diuretic	2828/53,495 (5·3)	0·64 (0.59-0·69)	<0·001

[a] Model 2 , adjusting for age and sex at baseline, and number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction, and stroke as time-dependent variables. Abbreviations: AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Table 9-II. Sensitivity analysis excluding dementia cases within 1 year of initiating AHM

AHM-class	Cases/PY n (‰)	HR[a] (95%CI)	P-value
ACEi	1645/356,274 (4·6)	*Reference*	
ARB	1014/245,515 (4·1)	0·86 (0·80-0·93)	<0·001
Beta blocker	2150/507,904 (4·2)	0·80 (0·74-0·87)	<0·001
CCB	1317/299,546 (4·4)	0·79 (0·72-0·85)	<0·001
Diuretic	2245/532,464 (4·2)	0·63 (0·59-0·69)	<0·001

[a] Model 2 , adjusting for age and sex at baseline, and number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction, and stroke as time-dependent variables. Abbreviations: AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Table 10. Dementia in participants with- or without history of major cardiovascular disease

	Dementia in participants with history of major CVD N=1387		Dementia in participants without history of major CVD N=4490		Dementia in all participants N=5877	
AHM-class	**Cases/total PY, n(‰)**	**HR[a] (95%CI)**	**Cases/total PY, n(‰)**	**HR[a] (95%CI)**	**Cases/total PY, n(‰)**	**HR[a] (95%CI)**
ACEi	592/857,053 (0·68)	*Reference*	1659/857,053 (1·90)	*Reference*	2251/857,053 (2·57)	*Reference*
ARB	306/589,285 (0·52)	0·76 (0·66-0·88)	1040/589,285 (1·76)	0·89 (0·83-0·97)	1346/589,285 (2·28)	0·86 (0·80-0·92)
Beta blocker	861/1,248,816 (0·69)	1·05 (0·90-1·23)	2128/1,248,816 (1·70)	0·75 (0·69-0·82)	2989/1,248,816 (2·39)	0·81 (0·75-0·87)
CCB	413/731,855 (0·56)	0·66 (0·56-0·78)	1346/731,855 (1·84)	0·82 (0·75-0·90)	1758/731,855 (2·40)	0·77 (0·72-0·84)
Diuretic	861/1,285,692 (0·55)	0·49 (0·42-0·58)	2463/1,285,692 (1·92)	0·70 (0·64-0·77)	3167/1,285,692 (2·92)	0·65 (0·60-0·70)

Dementia in participants with/without history of major CVD (i.e. stroke or myocardial infarction), and dementia in all participants, regardless history of CVD. Hazard ratio's (HR) for incident outcomes according Cox regression with time varying covariates. [a] adjusted for baseline age and sex, and number of AHM-classes simultaneously used, type 2 diabetes, and congestive heart failure as time dependent variables. Abbreviations: CVD = cardiovascular disease; AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Table 11-I. Subgroup analyses stratified for sex, and diabetes; associations between use of AHM-classes and dementia, compared to use of ACEi

Subgroup	**AHM-class**	**Dementia cases/ total person years[a] n(‰)**	**HR[b] (95%CI)**	**P-value interaction (men vs women)**
Women	ACEi	1246/168,312 (7·4)	*Ref*	
	ARB	889/139,116 (6·4)	0·87 (0·80-0·95)	*Ref*
	Beta blocker	1864/280,454 (6·6)	0·81 (0·74-0·88)	*Ref*
	CCB	1139/159,725 (7·1)	0·80 (0·73-0·87)	*Ref*
	Diuretic	2111/321,857 (6·6)	0·64 (0·68-0·69)	*Ref*
Men	ACEi	1005/188,811 (5·3)	*Ref*	
	ARB	457/106,890 (4·3)	0·83 (0·75-0·93)	0·46
	Beta blocker	1125/228,639 (4·9)	0·80 (0·73-0·89)	0·94
	CCB	620/140,449 (4·4)	0·73 (0·65-0·81)	0·13
	Diuretic	1056/211,862 (5·0)	0·69 (0·62-0·76)	0·17
Subgroup	***AHM-class***	***Dementia cases/total person years[a] n(‰)***	***HR[b] (95%CI)***	***P-value interaction (diabetes vs no diabetes)***
No diabetes	ACEi	1426/227,505 (6·3)	*Ref*	
	ARB	890/165,268 (5·4)	0·81 (0·73-0·91)	*Ref*
	Beta blocker	2058/366,613 (5·6)	0·80 (0·73-0·92)	*Ref*
	CCB	1165/203,860 (5·7)	0·76 (0·68-0·86)	*Ref*
	Diuretic	2141/366,761 (5·8)	0·66 (0·59-0·74)	*Ref*
Diabetes	ACEi	825/129,618 (6·4)	*Ref*	
	ARB	456/80,738 (5·7)	0·89 (0·81-0·96)	0·22
	Beta blocker	913/142,480 (6·5)	0·81 (0·75-0·88)	0·84
	CCB	594/96,314 (6·2)	0·78 (0·71-0·85)	0·71
	Diuretic	1026/166,958 (6·2)	0·65 (0·60-0·71)	0·75

[a] Within class of interest [b] Model 2, adjusted for baseline age, sex, number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. Similarly, patients may switch subgroup after developing diabetes, CVD or congestive heart failure over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; P-int = p for interaction between the two subgroups; CVD = cardiovascular disease; CHF = congestive heart failure; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 11-II. Subgroup analyses stratified for cardiovascular disease [a] and congestive heart failure; association between use of AHM-classes and dementia, compared to use of ACEi

Subgroup	**AHM-class**	**Dementia cases/ total person years[b] n(‰)**	**HR[c] (95%CI)**	**P-value interaction (CVD vs no CVD)**
No CVD	ACEi	1659/272,630 (6·1)	*Reference*	
	ARB	1040/196,202 (5·3)	0·87 (0·80-0·94)	*Ref*
	Beta blocker	2128/373,265 (5·7)	0·82 (0·76-0·89)	*Ref*
	CCB	1346/231,960 (5·8)	0·80 (0·73-0·87)	*Ref*
	Diuretic	2463/435,515 (5·7)	0·65 (0·64-0·82)	*Ref*
CVD	ACEi	592/84,493 (7·0)	*Reference*	
	ARB	306/49,805 (6·1)	0·85 (0·74-0·97)	0·98
	Beta blocker	861/135,829 (6·3)	0·72 (0·64-0·81)	0·03
	CCB	413/68,214 (6·0)	0·71 (0·62-0·81)	0·09
	Diuretic	6704/98,204 (7·2)	0·69 (0·61-0·78)	0·27
Subgroup	***AHM-class***	***Dementia cases/ total person years[b] n(‰)***	***HR[c] (95%CI)***	***P-value interaction (CHF vs no CHF)***
No CHF	ACEi	1911/326,624 (5·9)	*Reference*	
	ARB	1134/226,812 (5·0)	0·83 (0·77-0·89)	*Ref*
	Beta blocker	2429/460,035 (5·3)	0·77 (0·72-0·83)	*Ref*
	CCB	1544/279,477 (5·5)	0·77 (0·71-0·84)	*Ref*
	Diuretic	2486/475,382 (5·2)	0·66 (0·61-0·71)	*Ref*
CHF	ACEi	340/30,499 (11·2)	*Reference*	
	ARB	212/19,195 (11·0)	1·02 (0·87-1·20)	0·02
	Beta blocker	560/49,058 (11·4)	1·02 (0·87-1·19)	<0·001
	CCB	215/20,697 (10·4)	0·77 (0·65-0·92)	0·93
	Diuretic	681/58,337 (11·7)	0·62 (0·52-0·75)	0·57

[a] Cardiovascular disease is a composite of history of heart attack and/or stroke [b] Within class of interest [c] Model 2, adjusted for baseline age, sex, number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. Similarly, patients may switch subgroup after developing diabetes, CVD or congestive heart failure over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; P-int = p for interaction between the two subgroups; CVD = cardiovascular disease; CHF = congestive heart failure; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 12. Subgroup analysis stratified for number of simultaneously used AHM-classes; association between AHM classes and dementia, compared to use of ACEi

Number of AHM classes used simultaneously	AHM-class	Dementia cases/ total person years[a] n(‰)	HR[b] (95%CI)	P-value interaction[c] (versus "One" AHM users)
One	ACEi	477/79,466 (6·0)	*Ref*	
	ARB	225/42,686 (5·3)	0·83 (0·71–0·98)	*Ref*
	Beta blocker	622/136,309 (4·6)	0·76 (0·68–0·86)	*Ref*
	CCB	304/51,327 (5·9)	0·84 (0·73–0·97)	*Ref*
	Diuretic	615/98,218 (6·3)	0·68 (0·60–0·77)	*Ref*
Two	ACEi	853/130,345 (6·5)	*Ref*	
	ARB	465/84,186 (5·5)	0·85 (0·76–0·95)	0·86
	Beta blocker	1042/157,875 (6·6)	0·84 (0·75–0·94)	0·26
	CCB	530/83,019 (6·4)	0·75 (0·67–0·86)	0·27
	Diuretic	1160/198,724 (5·8)	0·62 (0·55–0·70)	0·98
Three	ACEi	686/105,454 (6·5)	*Ref*	
	ARB	456/79,351 (5·8)	0·88 (0·78–1·00)	0·57
	Beta blocker	962/146,701 (6·6)	0·84 (0·69–1·03)	0·41
	CCB	576/99,030 (5·8)	0·76 (0·63–0·91)	0·37
	Diuretic	1028/167,212 (6·2)	0·68 (0·55–0·84)	0·98
Four	ACEi	216/37,431 (5·8)	*Ref*	
	ARB	181/35,356 (5·1)	0·87 (0·69–1·08)	0·99
	Beta blocker	344/63,781 (5·4)	0·74 (0·39–1·41)	0·94
	CCB	330/62,370 (5·3)	0·61 (0·39–0·94)	0·17
	Diuretic	345/65,139 (5·3)	0·37 (0·19–0·73)	0·09

[a] Within class of interest [b] Model 2 adjusted (for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke) [c] Compared to simultaneous use of one AHM class. AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; HR = hazard ratio; CI = confidence interval; P-int = p for interaction compared to simultaneous use of one AHM class. ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 13. Subgroup analysis stratified for baseline age-group; association between AHM-classes and dementia, compared to use of ACEi

Age category	AHM-class	Dementia cases/total person years[b] n(‰)	HR (95%CI)	P-value interaction (versus <60 years)	P-interaction-trend[c] (age category as ordinal)
<60 years	ACEi	273/211,430 (1.3)	*Reference*		
	ARB	135/142,783 (1·0)	0·71 (0·58-0·86)	*Ref*	
	Beta blocker	292/296475 (1·0)	0·67 (0·57-0·79)	*Ref*	
	CCB	187/166,722 (1·1)	0·82 (0·68-0·98)	*Ref*	
	Diuretic	302/293,740 (1·0)	0·71 (0·61-0·84)	*Ref*	
60 – 70 years	ACEi	876/102,431 (8·6)	*Reference*		
	ARB	512/73,131 (7·0)	0·80 (0·72-0·88)	0·28	0·02
	Beta blocker	1083/144,618 (7·5)	0·76 (0·69-0·84)	0·15	0·01
	CCB	687/92,077 (7·5)	0·79 (0·71-0·88)	0·75	0·12
	Diuretic	1096/158,026 (6·9)	0·66 (0·60-0·73)	0·39	0·12
> 70 years	ACEi	1102/43,262 (25·5)	*Reference*		
	ARB	699/30,092 (23·2)	0·94 (0·86-1·03)	0·07	
	Beta blocker	1614/68,000 (23·7)	0·89 (0·82-0·98)	0·01	
	CCB	885/41,375 (21·4)	0·75 (0·68-0·82)	0·33	
	Diuretic	1769/81,954 (21·6)	0·67 (0·62-0·74)	0·42	

[a] Within class of interest [b] Model 2, adjusted for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time [c] P-trend for interaction term with the three categories as an ordinal variable from <60, to 60-70, to >70 years. AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; HR = hazard ratio; P-int = p for interaction between individual strata; CI = confidence interval; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 14-I. Analysis for individuals with their first AHM prescription starting 2015 or later: association between AHM-classes and dementia, compared to use of ACEi

AHM-class	Dementia cases/ total person years[a] n(‰)	HR[b] Dementia (95%CI)	P-value Dementia	Mortality cases/ total person years[b] n(‰)	HR[b,c] Mortality (95%CI)	P-value Mortality
ACEi	273/30,758 (8·9)	*Reference*		549/28,547 (19·2)	*Reference*	
ARB	132/17,272 (7·6)	0·78 (0·63-0·97)	0·025	240/16,268 (14·8)	0·73 (0·62-0·85)	0·0001
Beta blocker	352/35,996 (9·8)	0·94 (0·76-1·15)	0·34	863/32,363 (26·7)	1·56 (1·36-1·76)	<0·001
CCB	204/28,247 (7·2)	0·71 (0·57-0·89)	0·003	448/26,205 (17·1)	1·07 (0·91-1·24)	0·38
Diuretic	347/36,917 (9·4)	0·77 (0·62-0·95)	0·02	1173/33,655 (34·9)	2·75 (2·40-3·16)	<0·001

[a] Within class of interest [b] Model 2 adjusted (for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke). Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; HR = hazard ratio; P-int = p for interaction between individual strata; CI = confidence interval; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 14-II. Analysis for individuals with their first AHM prescription before 2015: association between AHM-classes and dementia, compared to use of ACEi

AHM-class	Dementia cases/ total person years[a] n(‰)	HR[b] Dementia (95%CI)	P-value Dementia	Mortality cases/ total person years[b] n(‰)	HR[b,c] Mortality (95%CI)	P-value Mortality
ACEi	1,978/326,365 (6·1)	*Reference*		4,417/299,599 (14·7)	*Reference*	
ARB	1,214/228,735 (5·3)	0·87 (0·81-0·93)	0·001	2,582/207,830 (12·4)	0·84 (0·80-0·89)	<0·001
Beta blocker	2,637/473,097 (5·6)	0·79 (0·73-0·86)	<0·001	6,800/426,309 (16·0)	1·21 (1·15-1·28)	<0·001
CCB	1,555/271,927 (5·7)	0·78 (0·71-0·85)	<0·002	3,781/251,147 (15·1)	1·06 (1·00-1·12)	0·06
Diuretic	2,820/496,802 (5·7)	0·64 (0·59-0·70)	<0·003	8,256/449,857 (18·4)	1·67 (1·59-1·79)	<0·001

[a] Within class of interest [b] Model 2 adjusted (for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke). Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; HR = hazard ratio; P-int = p for interaction between individual strata; CI = confidence interval; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 15-I. Subgroup analyses stratified for sex, and diabetes; associations between use of AHM-classes and mortality, compared to use of ACEi

Subgroup	**AHM-class**	**Mortality cases/total person years[a] n(‰)**	**HR[b] (95%CI)**	**P-value interaction (men vs women)**
Women	ACEi	2373/164,123 (14·5)	*Reference*	
	ARB	1573/136,483 (11·5)	0·85 (0·80-0·90)	*Ref*
	Beta blocker	3890/272,040 (14·3)	1·17 (1·11-1·25)	*Ref*
	CCB	2220/155,933 (14·2)	1·05 (0·99-1·12)	*Ref*
	Diuretic	5110/313,049 (16·3)	1·60 (1·50-1·70)	*Ref*
Men	ACEi	2767/184,173 (15·0)	*Reference*	
	ARB	1373/104,771 (13·1)	0·81 (0·76-0·87)	0·37
	Beta blocker	3962/222,297 (17·8)	1·23 (1·16-1·31)	0·17
	CCB	2137/137,164 (15·6)	1·06 (0·97-1·11)	0·72
	Diuretic	4416/206,238 (21·4)	1·80 (1·69-1·92)	0·001
Subgroup	***AHM-class***	***Dementia cases/total person years[b] n(‰)***	***HR[c] (95%CI)***	***P-value interaction (CHF vs no CHF)***
No CHF	ACEi	1911/326,624 (5·9)	*Reference*	
	ARB	1134/226,812 (5·0)	0·83 (0·77-0·89)	*Ref*
	Beta blocker	2429/460,035 (5·3)	0·77 (0·72-0·83)	*Ref*
	CCB	1544/279,477 (5·5)	0·77 (0·71-0·84)	*Ref*
	Diuretic	2486/475,382 (5·2)	0·66 (0·61-0·71)	*Ref*
CHF	ACEi	340/30,499 (11·2)	*Reference*	
	ARB	212/19,195 (11·0)	1·02 (0·87-1·20)	0·02
	Beta blocker	560/49,058 (11·4)	1·02 (0·87-1·19)	<0·001
	CCB	215/20,697 (10·4)	0·77 (0·65-0·92)	0·93
	Diuretic	681/58,337 (11·7)	0·62 (0·52-0·75)	0·57

[a] Within class of interest [b] Model 2, adjusted for baseline age, sex, number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. Similarly, patients may switch subgroup after developing diabetes, CVD or congestive heart failure over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; P-int = p for interaction between the two subgroups; CVD = cardiovascular disease; CHF = congestive heart failure; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 15-II. Subgroup analyses stratified for cardiovascular disease [a] and congestive heart failure; association between use of AHM-classes and mortality, compared to use of ACEi

Subgroup	**AHM-class**	**Mortality cases/ total person years[b] n(‰)**	**HR[c] (95%CI)**	**P-value interaction (CVD vs no CVD)**
No CVD	ACEi	1650/82,828 (19·9)	*Reference*	
	ARB	906/49,045 (18·5)	0·86 (0·80-0·93)	*Ref*
	Beta blocker	2831/132,859 (19·3)	1·19 (1·12-1·31)	*Ref*
	CCB	1294/67,056 (19·3)	0·98 (0·92-1·07)	*Ref*
	Diuretic	2805/96,317 (29·1)	1·99 (1·85-2·15)	*Ref*
CVD	ACEi	3490/265,467 (13·2)	*Reference*	
	ARB	2040/192,209 (10·6)	0·81 (0·78-0·86)	0·26
	Beta blocker	5021/361,482(13·9)	1·20 (1·14-1·27)	0·77
	CCB	3063/226,041 (13·6)	1·07 (1·01-1·14)	0·03
	Diuretic	6721/422,970 (15·9)	1·59 (1·50-1·68)	<0·001
Subgroup	***AHM-class***	***Mortality cases/total person years[b] n(‰)***	***HR[c] (95%CI)***	***P-value interaction (CHF vs no CHF)***
No CHF	ACEi	3504/318,295 (11·0)	*Reference*	
	ARB	2050/222,271 (9·2)	0·82 (0·78-0·87)	*Ref*
	Beta blocker	5195/445,930 (11·7)	1·15 (1·09-1·21)	*Ref*
	CCB	3374/272,718 (12·4)	1·16 (1·09-1·23)	*Ref*
	Diuretic	5793/461,983 (12·5)	1·41 (1·33-1·49)	*Ref*
CHF	ACEi	1636/30,001 (54·5)	*Reference*	
	ARB	896/18,982 (47·2)	0·92 (0·85-1·00)	0·01
	Beta blocker	2657/48,411 (54·9)	1·15 (1·06-1·24)	0·91
	CCB	983/20,380 (48·2)	0·93 (0·85-1·01)	<0·001
	Diuretic	3733/57,304 (65·1)	1·96 (1·76-2·19)	<0·001

[a] Cardiovascular disease is a composite of history of heart attack and/or stroke [b] Within class of interest [c] Model 2, adjusted for baseline age, sex, number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction and stroke as time dependent variables. Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. Similarly, patients may switch subgroup after developing diabetes, CVD or congestive heart failure over time. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; P-int = p for interaction between the two subgroups; CVD = cardiovascular disease; CHF = congestive heart failure; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 16. Subgroup analysis stratified for number of simultaneously used AHM-classes; association between AHM classes and mortality, compared to use of ACEi

Number of AHM classes used simultaneously	AHM-class	Mortality cases/ total person years[a] n(‰)	HR[b] (95%CI)	P-value interaction[c] (versus "One" AHM users)
One	ACEi	667/75,247 (8·9)	*Ref*	
	ARB	307/40,788 (7·5)	0·87 (0·76-0·99)	*Ref*
	Beta blocker	1158/126,674 (9·1)	1·06 (0·97-1·17)	*Ref*
	CCB	574/47,842 (12,0)	1·24 (1·11-1·38)	*Ref*
	Diuretic	1779/90,497 (19·7)	1·80 (1·65-1·97)	*Ref*
Two	ACEi	1609/127,464 (12·6)	*Ref*	
	ARB	842/824,445 (10·2)	0·85 (0·78-0·93)	0·85
	Beta blocker	2543 (154,880 (16·4)	1·34 (1·25-1·45)	<0·001
	CCB	1130/81,090 (13·9)	1·21 (1·11-1·32)	0·75
	Diuretic	3332/194,477 (17·1)	1·82 (1·68-1·97)	0·90
Three	ACEi	2062/104,093 (19·8)	*Ref*	
	ARB	1184/78,564 (15·1)	0·82 (0·76-0·88)	0·49
	Beta blocker	2946/145,092 (20·3)	1·22 (1·08-1·37)	0·076
	CCB	1509/97,880 (15·4)	0·87 (0·79-0·97)	<0·001
	Diuretic	3198/165278 (19·4)	1·33 (1·16-1·51)	<0·001
Four	ACEi	745/37,107 (20·1)	*Ref*	
	ARB	556/35,071 (15·9)	0·77 (0·68-0·87)	0·23
	Beta blocker	1148/63,310 (18·3)	0·85 (0·57-1·26)	0·27
	CCB	1087/61,899 (17·6)	0·51 (0·40-0·64)	<0·001
	Diuretic	1160/64,649 (17·9)	0·70 (0·41-1·19)	<0·001

[a] Within class of interest [b] Model 2 adjusted (for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke) [c] Compared to simultaneous use of one AHM class.
AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; HR = hazard ratio; CI = confidence interval; ARB = angiotensin receptor blocker; CCB = calcium channel blocker

Supplementary Table 17. Subgroup analysis stratified for baseline age; association between AHM classes and mortality, compared to use of ACEi

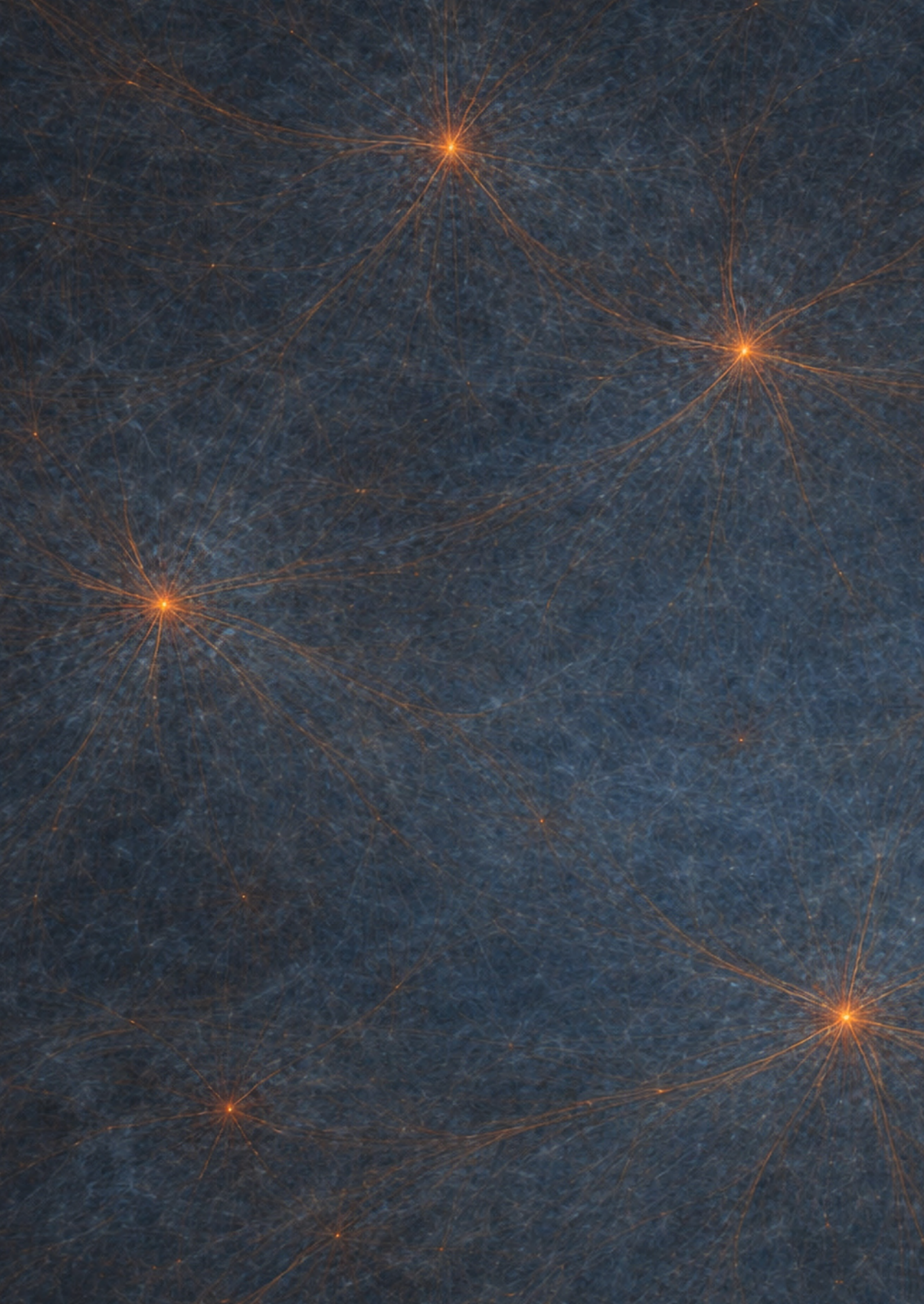
Age category	AHM-class	Dementia cases/total person years[b] n(‰)	HR (95%CI)	P-value interaction (versus <60 years)	P-interaction-trend[c] (age category as ordinal)
<60 years	ACEi	942/207,077 (4·6)	*Reference*		
	ARB	489/140,493 (3·5)	0·74 (0·67-0·82)	*Ref*	
	Beta blocker	1235/287,808 (4·3)	1·02 (0·94-1·12)	*Ref*	
	CCB	760/163,209 (4·7)	1·11 (1·01-1·222)	*Ref*	
	Diuretic	1386/287,170 (4·8)	1·52 (1·39-1·66)	*Ref*	
60 – 70 years	ACEi	1751/99,649 (17·6)	*Reference*		
	ARB	1041/71,622 (14·5)	0·81 (0·76-0·88)	0·12	0·002
	Beta blocker	2629/140,793 (18·7)	1·24 (1·16-1·33)	<0·001	<0·001
	CCB	1496/89,835 (16·7)	1·04 (0·97-1·12)	0·23	0·10
	Diuretic	2958/153,663 (19·3)	1·65 (1·53-1·77)	0·11	<0·001
> 70 years	ACEi	2447/41,570 (58·9)	*Reference*		
	ARB	1416/29,139 (48·6)	0·88 (0·83-0·94)	0·003	
	Beta blocker	3988/65,740 (60·7)	1·24 (1·17-1·32)	<0·001	
	CCB	2101/40,053 (52·5)	1·02 (0·96-1·09)	0·09	
	Diuretic	5182/78,454 (66·1)	1·81 1·70-1·94)	<0·001	

[a] Within the class of interest when used during final year of observation [b] Model 2 adjusted (for baseline age, sex, number of AHM-classes used simultaneously, type 2 diabetes, myocardial infarction and stroke). Individual participants may be represented in multiple AHM-classes in case of combination therapy and medication switching over time. AHM = antihypertensive medication; ACEi = angiotensin-converting enzyme inhibitor; HR = hazard ratio; P-int = p for interaction between individual strata; P-trend = P for trend between the three strata; CI = confidence interval; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

Supplementary Table 18. Competing risk according sub-distribution hazards (Fine & Gray)

AHM-class	Cases/PY n (‰)	HR[a] (95%CI)	P-value
ACEi	2251/463,154 (4·9)	*Reference*	
ARB	1346/305,062 (4·4)	0·90 (0·85-0·97)	0·007
Beta blocker	2989/673,934 (4·4)	0·80 (0·74-0·86)	<0·001
CCB	1759/389,583 (4·5)	0·80 (0·74-0·87)	<0·001
Diuretic	3167/728,310 (4·4)	0·60 (0·56-0·65)	<0·001

[a] Model 2 , adjusting for age and sex at baseline, and number of AHM-classes simultaneously used, type 2 diabetes, myocardial infarction, and stroke as time-dependent variables. Abbreviations: AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.



Chapter IV

The Risk of Major Cardiovascular Events, Dementia, and Mortality Differs Between Antihypertensive Medication Classes: A Longitudinal Cohort Study in the Netherlands

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RESEARCH IN CONTEXT

Evidence before this study: Hypertension is a major risk factor for dementia, stroke, and mortality. Observational studies suggest that specific antihypertensive medication (AHM) classes including angiotensin-receptor blockers (ARBs), dihydropyridine-calcium channel blockers (dCCB), and thiazide diuretics may reduce dementia risk 10-35% more than other AHM classes. Long-term associations with other adverse outcomes, including acute myocardial infarction (MI) and stroke are unclear, but essential to weigh potential gains of dementia risk reduction against risks of cardiovascular events. We searched PubMed for longitudinal cohort studies comparing real-world use of multiple AHM classes to each other published in any language up to February 2025, using the terms "cohort" AND "antihypertensive classes", AND ("Stroke" OR "Myocardial Infarction"). We identified several (reviews and meta-analyses) of randomized controlled trials only comparing single medication pairs in selected trial populations. We identified one large-scale observational study comparing multiple AHM classes simultaneously, based on electronic health records. This study found significant 11-22% lower risks of stroke and MI with thiazides, ACE-inhibitors (ACEi), ARBs and dCCB vs non-dihydropyridine CCBs (ndCCB). These differences were most pronounced for thiazides and ARBs, findings showing significantly lower risks for thiazides vs ACEi (MI HR=0·84, 95%CI=0·75-95; stroke HR=0·83, 95%CI=0·74-0·95); thiazides vs ndCCB (MI HR=0·70, 95%CI=0·59-0·84; stroke HR=0·78, 95%CI=0·71-0·87); ARB vs ndCCB for (MI HR=0·78; 95%CI=0·69-0·91; stroke HR=0·84; 95%CI=0·73-0·97); for dCCB vs ndCCB (MI HR=0·84; 95%CI=0·76-0·93; stroke HR=0·87; 95%CI=0·79-0·96); and ACEi vs ndCCB (MI HR=0·87, 95%CI=0·77-1·00; stroke HR=0·89; 95%CI=0·82-0·98). However, this study only assessed single medication users for the duration of their initial AHM treatment, resulting in an average follow-up time of less than a year and diminishing generalizability to clinical practise where AHM classes are often switched and combined.

Added value of this study: We endeavoured to address limitations encountered by previous studies by assessing the risk of major adverse events (dementia, stroke, myocardial infarction and mortality), simultaneously evaluating all main AHM classes, in a continuous time-dependent framework, allowing multiple concurrent AHM-classes and incorporating changes in AHM regimen during follow-up, in a large population of community-dwelling older people with primary hypertension without comorbidity indicating specific AHM-classes, minimizing the risk of confounding by indication. In addition, we thoroughly assessed potential biases and moderators in extensive sensitivity and subgroup analyses. We found that compared to ACEi, major adverse events risk was lower for thiazides (HR=0·71; 95%CI=0·67-0·75), ARBs (HR=0·86; 95%CI=0·82-

0·91), and dCCBs (HR=0·93; 95%CI=0·90-0·97). The lower risks for thiazide diuretics and ARBs were robust across extensive subgroup and sensitivity analyses.

Implications of all the available evidence: Older individuals using thiazides, ARBs, and–to lesser extent– dCCBs had a consistent, significantly lower major adverse event risk compared to users of ACEi. These findings support the growing evidence that preferentially prescribing these widely available antihypertensive medication classes may provide a safe, cost-effective strategy to reduce the risk of dementia and possibly cardiovascular events. The consistently lower risk of ARBs versus ACEi is particularly noteworthy given their nearly identical indications, minimizing the risk of confounding by indication. In light of all the evidence, a long-term pragmatic RCT assessing both dementia and cardiovascular outcomes seems warranted.

ABSTRACT

Background: Angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (DiCCBs) and thiazide diuretics have been associated with lower dementia risk compared to other antihypertensive medication (AHM) classes. However, the long-term associations with other poor outcomes -the primary reasons for AHM treatment- are unclear. We aimed to comprehensively study the associations between AHM (sub)classes and stroke, myocardial infarction (MI), dementia and mortality, in community-dwelling primary care patients in the Netherlands.

Methods: We studied 84,254 AHM-users aged ≥65 years with primary hypertension without major comorbidities from three Dutch general practitioner registration networks from 1998 to 2020. Exposures were prescription of angiotensin-converting enzyme inhibitors (ACEi), ARBs, BBs, DiCCBs, and thiazide(-like) diuretics. Outcomes were the first recorded major adverse event (MAE, including stroke, MI, all-cause dementia, mortality), assessed using time-dependent Cox regression analyses.

Results: During a median follow-up of 5·6 years (524,482 person-years), 11,380 individuals (13·5%) experienced an MAE: 3316 (29·1%) a stroke, 2129 (18·7%) an MI, 2615 (23·0%) dementia, and 3479 (30·6%) death. Compared to ACEi, MAE risk was lower for thiazides (HR=0·71;95%CI=0·67-0·75), ARBs (HR=0·86;95%CI=0·82-0·91), and DiCCBs (HR=0·93;95%CI=0·90-0·97). The lower risks for thiazide diuretics and ARBs were robust across extensive subgroup and sensitivity analyses.

Conclusions and relevance: Older individuals using thiazide diuretics and ARBs have a lower MAE risk than ACEi-users. These findings suggest that preferentially prescribing these cheap and widely available antihypertensive medication classes may provide a safe, cost-effective strategy to improve antihypertensive treatment outcomes and reduce dementia globally. The consistently lower risk with ARBs versus ACE inhibitors is particularly noteworthy given their identical indications. An RCT confirming these findings is warranted.

INTRODUCTION

Hypertension is an important risk factor for cardiovascular disease (CVD) and dementia.[1,2] Antihypertensive treatment with angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (dCCBs), and thiazide diuretics (thiazides) has been associated with a 10-35% lower dementia risk than treatment with other antihypertensive medication (AHM) classes, including angiotensin-converting enzyme inhibitors (ACEi) and beta blockers (BBs), independent of blood pressure (BP) control, and without excess mortality.[3-5] However, these studies did not examine CVD outcomes, including acute myocardial infarction (AMI) and stroke. Investigating long-term associations with these CVD outcomes is essential, as their prevention is one of the key reasons for initiating AHM treatment.

While generally considered equally effective for reducing cardiovascular risk, there is a dearth of RCT evidence directly comparing AHM-classes.[6] Two observational studies associated thiazides, ARBs, and dCCBs with a 5-15% lower risk of AMI, stroke, and mortality, compared to ACEi and BBs.[6,7] However, results were heterogeneous, and studies only assessed new-users using one single AHM-class, followed-up until the first AHM regimen change. This led to short follow-up, low event-rates, and limited generalizability to clinical practice where regimens often change and involve multiple AHM-classes. Moreover, studies simultaneously assessing CVD, dementia, and mortality are lacking, impeding risk comparisons for these important outcomes.

This study aims to investigate how specific AHM (sub-)classes are associated with major adverse events (MAEs), including first documented AMI, stroke, all-cause dementia, and mortality in older individuals using large-scale real-world data from primary care patients in the Netherlands.

METHODS

Population

We used routine care data from three Dutch General Practice Registration Networks (GPRNs), from January 1988 to December 2022. GPRNs collect patient data from general practitioners (GP) offices' electronic health records (EHRs), containing medical histories, demographics, and prescriptions (>97% of Dutch citizens have a GP). EHRs also include diagnoses from hospital specialists (e.g. cardiologists, neurologists), making GPRN data highly representative of the Dutch population.[8] *Supplementary Methods 1* summarizes the GP's role in Dutch healthcare. The study was approved by all three GPRNs, with no ethical approval required as the data were anonymous and non-identifiable.

Diagnoses were coded using International Classification of Primary Care (ICPC) codes (*Supplementary Methods 2*) and prescriptions using ATC codes (*Supplementary Methods 3*).

We included individuals aged ≥65 years using AHM during the extracted period. Since we were interested in incident events in primary hypertension, we excluded individuals with a history of AMI, stroke, and dementia, as well as with non-acute coronary heart disease (CHD), congestive heart failure (CHF), and atrial fibrillation (AF), as these conditions may influence the choice of AHM-class prescribed. Additionally, we excluded individuals with prior prescription of loop diuretics and non-dihydropyridine CCBs (ndCCBs) as these AHM are often specifically indicated for kidney disease, CHF, and cardiac arrhythmia.

Exposure

For our main analysis, we compared the five AHM (sub)classes generally used for primary hypertension treatment: ACEi, ARBs, BBs, dCCBs, and thiazide(-like) diuretics. Loop diuretics and ndCCBs were not included because they are typically prescribed for specific comorbidities and rarely exclusively to treat hypertension. Because potassium-sparing agents are not regarded as stand-alone primary treatment options (only as add-on for treatment-resistant hypertension or electrolyte imbalances) we only included them as covariate.[9]

We created a continuous medication overview for all individuals, using over 8 million prescriptions. For chronic conditions, interruptions between repeat prescriptions may occur, e.g. due to pharmacy agreements allowing multiple dispensations from a single prescription. Therefore, for patients with three or more consecutive prescriptions of

the same AHM-class, we assumed continuous use of that AHM-class from the first to last prescription.

Endpoints and covariates

Primary outcome was first occurrence of AMI, stroke (ischaemic or haemorrhagic), all-cause dementia, or mortality. Secondary outcomes were the individual MAEs. Age (continuous), sex (man/woman), diabetes (yes/no), and dyslipidaemia (yes/no) were collected as covariates.

Statistical Analysis

We estimated associations between AHM-classes and the first occurring endpoint using Cox regressions with time-dependent exposures and covariates and time since first AHM prescription as timescale (*Supplementary Methods 4*).[10,11] Only individuals with active AHM prescriptions were included.

Exposures were use of ARBs, BBs, dCCBs, and/or thiazides, and the total number of concurrently used AHM-classes (maximum 5 including ACEi) as categorical variable, resulting in HRs relative to ACEi-use (*Supplementary Methods 4*). We used ACEi as reference category, because ACEi-use was consistently associated with the highest dementia/mortality risk in our previous studies.[4,5] Furthermore, it facilitates direct comparison between ACEi and ARBs, which have identical indications, minimizing the risk of confounding by indication for this comparison. Model 1 additionally adjusted for age, sex, potassium-sparing agents, and random intercepts per GPRN to account for clustering; model 2 also for diabetes, and dyslipidaemia. Individuals diagnosed with non-acute CHD, CHF, and AF were censored at diagnosis, as these conditions may indicate AHM for reasons other than hypertension. Similarly, individuals being prescribed loop diuretics or ndCCBs were censored at their prescription, because these are generally prescribed for comorbidities potentially influencing prescription patterns. We assessed proportional hazards assumptions by visually inspecting Schoenfeld residuals.

In time-dependent Cox models, exposure at the time-of-event determines the HR. However, stop dates for prescriptions in GPRNs may not always accurately reflect medication cessation. This discrepancy may vary systematically across AHM-classes and indications. To address this, we adapted the end date for all AHM-classes prescribed during the last exposure year to match that year's last recorded AHM prescription, thereby ensuring that HRs accounted for all medication used in the last year. Additionally, before dementia or death, certain medications, including antihypertensives, may be ceased, potentially resulting in longstanding AHM users not having

prescriptions at these endpoints. To compensate, we extended the last AHM regimen up to two years until censoring or outcome (*Supplementary Figure 1*).

We conducted sensitivity analyses to compare the impact of defining exposure by the last year of AHM prescriptions and of extending the last recorded regimen. Second, we conducted a sensitivity analysis including CHF as a primary endpoint to enhance comparability with previous studies.[9,10] Third, instead of censoring individuals with non-acute CHD, CHF, AF, or prescription of loop diuretics or ndCCBs, we additionally adjusted for these variables. Finally, to address potential cumulative AHM effects and/or reverse causation, we conducted two analyses: 1.) categorizing AHM exposure at thresholds of ≥25%, ≥50%, and ≥75% of the total exposure duration; 2.) excluding individuals with an outcome within three years of their last change in AHM regimen.[5]

We performed subgroup analyses, stratifying by sex, age, diabetes, dyslipidaemia, and number of AHM-classes concurrently used (rationale: *Supplementary Methods 5*). Furthermore, we investigated the impact of the 2012 Dutch guideline update (recommending all AHM-classes as equivalent first-line options, instead of only thiazides, BBs, and ACEi) by stratifying exposure before/after 2015, allowing a 3-year lag-time for guideline adoption.

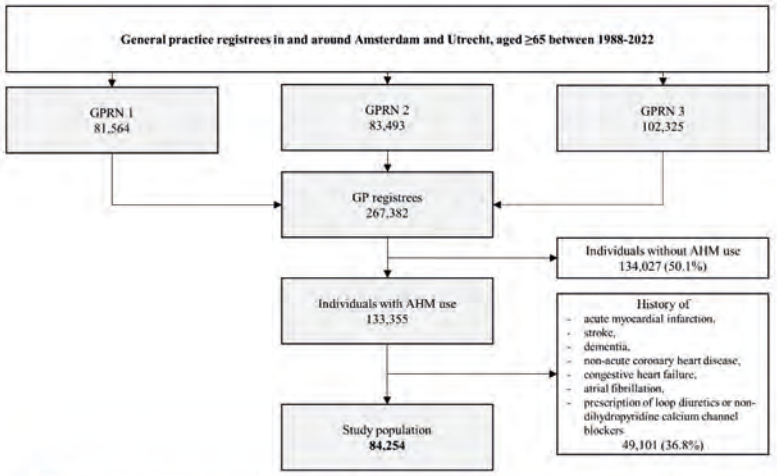
We used the 'survival' package in R 4·1.2 for all analyses.[10,12]

RESULTS

We included 84,254 individuals (58·3% women) aged ≥65 years with any AHM prescription between 1988 and 2022 (**Figure 1, Table 1**). Median follow-up duration was 5·6 years (IQR 2·8-9·2), yielding 524,482 person-years (PY) in total. Median cohort-entry age was 68·2 (IQR 65·0-74·8) and median censoring age 76·2 (IQR 71·2-82·3). During follow-up, 11,380 individuals experienced an MAE. Among these, 2129 (18·7%) had AMI as their first recorded MAE, 3316 (29·1%) stroke, 2615 (23·0%) dementia, and 3479 (30·6%) mortality (**Table 1**).

During 186,476 PY of ACEi-use, 4437 individuals were diagnosed with an MAE (**Table 2**), yielding an incident rate of 23·8‰. For ARBs this was 20·1‰ (2772/137,676), for BBs 24·5‰ (5412/220,811), for dCCBs 23·7‰ (3727/157,312), and for thiazides 19·2‰ (4790/248,801).

Figure 1. Flow chart of study population and event rates.



AHM type	Person Years	Incident Major adverse events	AMI	Stroke	Dementia	Mortality
Any	524,482	11,380	2129	3316	2615	3479
ACEi	186,476	4437	956	1258	991	1315
ARB	137,676	2772	496	866	642	809
Beta blocker	220,811	5421	1360	1524	1088	1517
dCCB	157,312	3727	648	1153	764	1213
Thiazide diuretic	248,801	4790	722	1527	1192	1420

Abbreviations: GPRN = general practitioner registration network, AHM = antihypertensive medication, MAE = major adverse events, AMI=acute myocardial infarction, ACEi = angiotensin-converting-enzyme inhibitor, ARB=angiotensin receptor blocker, dCCB = dihydroperidine calcium channel blocker.

Table 1. Population characteristics and antihypertensive medication use at baseline and time of censoring.

Baseline (first AHM use):	**Participants N=84,254**
Participant characteristics	
Women, n (%)	49,149 (58·3)
Baseline age, median [IQR]	68·2 [65·0-74·8]
Covariates	
History of type 2 diabetes, n (%)	17,234 (20·5)
History of dyslipidaemia, n (%)	12,887 (15·3)
AHM at baseline	
ACE inhibitor, n(%)	24,970 (29·6)
ARB, n (%)	15,364 (18·2)
Beta blocker, n (%)	29,938 (35·5)

Table 1. Population characteristics and antihypertensive medication use at baseline and time of censoring. *(Continued)*

Baseline (first AHM use):	**Participants N=84,254**
Dihydropyridine CCB, n(%)	17,756 (21·1)
Thiazide diuretic, n (%)	32,602 (38·7)
Potassium-sparing agent, n (%)	3904 (4·6)
Follow-up (time of censoring):	**Observed PY=524,482**
Participant characteristics	
Median observed years [IQR]	5·6 [2·8-9·2]
Censoring age, median [IQR]	76·2 [71·2-82·3]
AHM at censoring	
ACE inhibitor, n (%)	30,375 (36·1)
ARB, n (%)	21,277 (25·3)
Beta blocker, n (%)	35,879 (42·6)
Dihydropyridine CCB, n (%)	26,894 (31·9)
Thiazide diuretic, n (%)	32,654 (38·8)
Potassium-sparing agent, n (%)	5950 (7·1)
Covariates	
Incident diabetes, n (%)	5842 (6·5)
Incident dyslipidaemia, n(%)	5182 (6·2)
Censoring events	
Incident non-acute Coronary Heart Disease, n (%)	132 (0·2)
Incident Congestive Heart Failure, n (%)	458 (0·5)
Incident Atrial Fibrillation, n (%)	861 (1·0)
Incident Loop diuretic-use, n(%)	8927 (10·6)
Incident non-dihydropyridine CCB-use, n(%)	1662 (2·0)
Outcomes	
Incident Major Adverse Event, n (%)	11,380 (13·5)
Acute myocardial infarction, n (%)	2129 (18·7)
Stroke, n (%)	3316 (29·1)
Incident dementia, n (%)	2615 (23·0)
Mortality, n (%)	3479 (30·6)

Incident cases are defined as newly developed during the study observation after baseline. AHM use at censoring defined as used during the last year of observation before censoring. AHM = antihypertensive medication; IQR = interquartile range; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker, CCB = calcium channel blocker; PY = person years

Table 2. Associations between AHM-use and first occurring major adverse event.

	Major Adverse Events		
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
ACE inhibitor	4437/186,476 (23·8)	Reference	
ARB	2772/137,676 (20·1)	0·86 (0·82-0·91)	<0·001
Beta blocker	5412/220,811 (24·5)	1·07 (1·02-1·12)	0·015
Dihydropyridine CCB	3727/157,312 (23·7)	0·93 (0·87-0·98)	0·009
Thiazide diuretic	4790/248,801 (19·2)	0·71 (0·67-0·75)	<0·001
	Acute myocardial infarction		
ACE inhibitor	956/186,476 (5·1)	Reference	
ARB	496/137676 (3·6)	0·74 (0·66-0·83)	<0·001
Beta blocker	1360/220811 (6·2)	1·50 (1·33-1·69)	<0·001
Dihydropyridine CCB	648/157312 (4·1)	0·57 (0·50-0·65)	<0·001
Thiazide diuretic	722/248801 (2·9)	0·33 (0·29-0·38)	<0·001
	Stroke		
ACE inhibitor	1258/186,476 (6·8)	Reference	
ARB	866/137,676 (6·3)	0·93 (0·85-1·01)	0·095
Beta blocker	1524/220,811 (6·9)	1·02 (0·93-1·13)	0·624
Dihydropyridine CCB	1153/157,312 (7·3)	1·05 (0·94-1·16)	0·408
Thiazide diuretic	1527/248,801 (6·1)	0·86 (0·77-0·95)	0·005
	Dementia		
ACE inhibitor	991/186,5476 (5·3)	Reference	
ARB	642/137,676 (4·7)	0·86 (0·78-0·95)	0·004
Beta blocker	1088/220,811 (4·9)	0·84 (0·75-0·93)	0·001
Dihydropyridine CCB	764/157,312 (4·9)	0·81 (0·72-0·91)	<0·001
Thiazide diuretic	1192/248,801 (4·8)	0·84 (0·75-0·95)	0·004
	Mortality		
ACE inhibitor	1315/186,476 (7·0)	Reference	
ARB	809/137,676 (5·9)	0·88 (0·81-0·96)	0·007
Beta blocker	1517/220,811 (6·9)	1·05 (0·96-1·16)	0·286
Dihydropyridine CCB	1213/157,312 (7·7)	1·14 (1·03-1·26)	0·010
Thiazide diuretic	1420/248,801 (5·7)	0·79 (0·71-0·88)	<0·001

The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. HRs represent model 2, adjusting for age and sex, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according. Cox regression with time varying covariates. Major adverse events include acute myocardial infarction, stroke (ischaemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACE = angiotensin-converting enzyme, ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

Main analyses

HRs and 95% confidence intervals (CI) below are from model 2. Compared to ACEi, overall risk of MAEs was lower for thiazides (HR=0·71;95%CI=0·67-0·75); ARBs (HR=0·86;95%CI:0·82-0·91) and dCCBs (HR=0·93;95%CI=0·90-0·97), and higher for BBs (HR=1·07;95%CI:1·02-1·12).

Considering individual MAEs, the lower risk for thiazides versus ACEi was most pronounced for AMI (HR=0·33;95%CI=0·29-0·38), and also significant for stroke (HR=0·86;95CI=0·77-0·95), dementia (HR=0·84;95%CI=0·75-0·95), and mortality (HR=0·79;95%CI=0·71-0·88). For ARBs, lower risk versus ACEi was most pronounced for AMI (HR=0·74;95%CI=0·66-0·83), dementia (HR=0·86;95%CI=0·78-0·95) and mortality (HR=0·88;95%CI=0·81-0·96) and not significant for stroke (HR=0·93;-95CI=0·85-1·01).

For dCCBs, lower MAE risk compared to ACEi was mostly for AMI (HR=0·57;95%-CI=0·50-0·65), and dementia (HR=0·81;95%CI=0·72-0·91), did not significantly different for stroke (HR=1·05;95%CI=0·94-1·16), and was significantly higher for mortality (HR=1·14;95%CI=1·03-1·20). For BBs, the higher MAE risk was mostly for AMI (HR=1·50;95%CI=1·33-1·69); with neutral risks for stroke (HR=1·02;95%-CI=0·93-1·13) and mortality (HR=1·05;95%CI=0·96-1·16), and lower dementia risk (HR=0·84;95%CI=0·75-0·93), versus ACEi.

Results were similar for model 1 and model 2 (*Supplementary Table 1*).

Sensitivity analyses

Using the original end dates of the last years' prescriptions gave similar results, except that MAE risks for dCCBs versus ACEi were neutral (*Supplementary Table 2*). Not extending prescriptions gave similar results to the main analysis (*Supplementary Table 3*). Adding CHF as MAE gave additionally lower MAE risks for ARBs, dCCBs, and thiazides, versus ACEi (*Supplementary Table 4*). Adjusting for instead of censoring individuals with non-acute CHD, CHF, AF, loop diuretics or ndCCBs did not importantly change results, except that BBs had a neutral MAE risk versus ACEi (*Supplementary Table 5*). Categorizing AHM use at ≥25%, ≥50% and ≥75% of cumulative exposure time did not importantly change results, except that associations for dCCBs versus ACEi were not significant (*Supplementary Table 6*). Excluding individuals whose AHM regimen changed within three years of an endpoint did not importantly change results (*Supplementary Table 7*).

Subgroup analyses

Results were similar for women and men, except that BBs were associated with significantly higher MAE risk in men, particularly for AMI and mortality (*Supplementary Table 8*). Regarding baseline age, lower MAE risk for thiazides versus ACEi was most pronounced in individuals aged <75 years. MAE risk for BBs versus ACEi was higher in the <75 group, neutral in the 75-85 group, and lower in the >85 group (*Supplementary Table 9*). In individuals with diabetes, event rates for ACEi were relatively low, and only thiazides were significantly associated with lower MAE risk versus ACEi. HRs for ARBs and dCCBs were neutral. The HR for BB was higher than in the main analyses (*Supplementary Table 10*). Results were similar for individuals with and without dyslipidaemia (*Supplementary Table 11*), and for individuals using ≥3 versus <3 AHM classes concurrently (*Supplementary Table 12*). Results were similar before and after 2015, except that ARBs and thiazides were associated with additionally lower MAE risk versus ACEi after 2015 (*Supplementary Table 13*).

DISCUSSION

In this study, analyzing primary care data from 84,254 community-dwelling older persons during 524,482 person-years, we observed lower MAE risk for thiazides, ARBs and –less consistently– dCCBs compared to ACEi.

Compared to ACEi, MAE risk was 29% lower for thiazides (range: -67% for AMI to -14% for stroke) 14% lower for ARBs (range: -26% AMI to -7% stroke), and 7% lower for dCCBs (range: -43% AMI to +14% mortality). For BBs, MAE risk was 7% higher compared to ACEi (-16% dementia to +50% AMI).

Results were consistent between model 1 and 2 and across sensitivity analyses, although slightly less so for dCCBs. Findings were also similar when stratified by sex, dyslipidaemia status, time-period, number of classes and baseline age. However, in the diabetes subgroup, we observed lower event rates for ACEi compared to other AHM-classes, possibly due to their well-known benefits on kidney and cardiac function in patients with diabetes, aligning with their preferred status in hypertension management guidelines for this group.[9,13,14] Consistent results when dividing exposure between before/after 2015 suggest the results are not explained by older CVD guidelines, wherein ARBs and CCBs were typically reserved for treatment-resistant hypertension. BBs were associated with higher AMI risk, particularly in men. Possibly, men more often receive BBs for symptoms preceding AMI (e.g. angina) because these symptoms may be underdiagnosed in women.[15] The higher MAE risk for BBs

in younger age groups may be due to AMI being the main contributor, as AMIs make up a larger proportion of MAEs in younger individuals.

Our study is unique in assessing AMI, stroke, dementia, and mortality simultaneously, hindering comparison to previous studies. However, our findings appear largely consistent with previous studies directly comparing AHM-classes to each other with either CVD[6,7,16] or dementia[3,17,18] as outcome.

A Cochrane review of 23 RCTs (n>153,000) comparing CCBs with other AHM reported lower CVD risk (MI, stroke, CHF, and cardiovascular mortality) for thiazides, similar risks for ARBs and ACEi, and higher risk for BBs.[7] However, the review only compared two AHM at a time, not all five, limiting comparison to our study. Additionally, the trials were conducted in research settings with younger, healthier populations and shorter follow-up (range 2 to 5·3 years), potentially limiting their generalizability to older adults. One observational study based on 9 claims/EHR databases (n>4·9 million) reported a 15% lower CVD risk (AMI, stroke, and HF hospitalization) for thiazides versus ACEi; and a statistically not significant 5-10% lower cardiovascular risk for ARBs and CCBs versus ACEi.[6] This study only included new AHM users on monotherapy regimens without age restriction, and censored individuals when AHM regimens changed, resulting in short average follow-up time of less than a year. The relatively small effect sizes may be explained by the selection of younger healthier individuals with relatively mild hypertension and short follow-up reducing the contrast between AHM-classes. Another health-claims study (n>95,000) evaluating first-recorded monotherapy reported large erratic differences between AHM classes, likely due to insufficient statistical power from the very low number of total events.[16]

Regarding dementia, a large-scale network meta-analysis (22 studies, n>649,000) found 12-16% lower dementia risk for ARBs and CCBs versus ACEi and BBs, similar to our findings. The association for thiazides was smaller: a non-significant 5% lower dementia risk.[3] Two other recent, smaller IPD meta-analyses found no clear differences in dementia risk between AHM-classes, but did not compare these directly, reducing contrast and thereby power to detect differences.[17,18]

An explanation why ARBs and dCCBs, thiazides lower MAE risk more than other AHM-classes may relate to the renin-angiotensin system. According to the "angiotensin hypothesis", these classes stimulate angiotensin-II type 2 (ATR2) and 4 (ATR4) receptors, while BBs, ndCCBs, and ACEi inhibit them.[19-21] ATR2 stimulation may reduce oxidative stress, inflammation, and mucosal nitric oxide production (protecting endothelia from hypertensive and atherosclerotic damage), and ATR4 stimulation

may improve memory function.[22-25] ACEi may additionally increase dementia risk by blocking angiotensin-converting enzyme, which facilitates the degradation of amyloid-beta, a central protein Alzheimer's Disease pathology.[26]

Our study's main strengths are: 1.) the large dataset with numerous events and prolonged follow-up, enabling robust sensitivity and subgroup analyses; 2.) a representative population of community-dwelling older individuals with primary hypertension and no severe comorbidities, offering real-world evidence relevant for primary care physicians; and 3.) time-dependent, continuous prescription data and diagnoses, accounting for AHM changes and incident comorbidities, which are common in long-term follow-up of older people. This allowed for more accurate and comprehensive exposure assessment compared to studies relying on baseline data or only considering outcomes during the first monotherapy regimen.

Several factors need consideration when interpreting our results. First, medication use at the time of the event is decisive for the association, which may impede discerning cumulative effects over time, and increase sensitivity to reverse causation. However, our exposure-time and reverse causation sensitivity analyses corroborated our main results for all classes except dCCBs. Second, although guidelines recommend AHM-classes as equivalent treatments, some GPs may still prescribe classes in a particular order, leading to their more frequent use in cases of more severe hypertension. However, this does not explain our results, as our subgroup analysis on number of antihypertensives used showed consistent differences between classes, despite ≥3classes likely indicating more severe hypertension. We further minimized confounding by indication by censoring individuals with conditions indicating specific AHM-classes, and conducting extensive subgroup analyses evaluating factors potentially influencing AHM choice. Nevertheless, some confounding by indication may persist, particularly for BBs with AMI, as BBs may be prescribed for angina-like complaints, potentially explaining their strong association with elevated AMI risk. Confounding by indication is least likely to have influenced results for ARBs versus ACEi, because these classes have identical indications, making these results particularly interesting. Third, our dataset did not include BP data. We expect that this did not importantly influence our results because all AHM-classes have similar BP lowering effects,[9,14,27] BP values were similar across AHM-classes in another cohort comparable to ours,[4] and two large meta-analyses that found that differences between AHM-classes for dementia and cardiovascular outcomes were independent of baseline BP values and BP change.[28,29] However, residual confounding by other factors, including socioeconomic or ethnic background and differences in side-effects may exist. Fourth, comparing different AHM-classes directly to each other, instead of to non-users or each class to 'any other',

ensured that our results are not influenced by risk differences between hypertensive and non-hypertensive individuals, and preserved contrast between classes. However, a downside is that the difference with ACEi determines the effect sizes and their significance, as illustrated by the diabetes subgroup wherein differences in results might have been caused by ACEi performing relatively well, not by other classes performing worse. Finally, GP records are representative of the Dutch population with regard to demographics and primary care data.[8] These records also include diagnoses made by other physicians, including hospital specialists, with excellent specificity (6 studies, median 100%, range 78-100), but limited sensitivity (~60%).[30] Thus we are relatively certain of registered events but may have underestimated event rates and effect sizes due to non-differential misclassification.

Conclusion

Older individuals using thiazides, ARBs, and–to lesser extent–dihydropyridine CCBs had a consistent, significantly lower major adverse event risk compared to ACE inhibitor users. These findings support the growing evidence that preferentially prescribing these widely available antihypertensive medication classes may provide a safe, cost-effective strategy to reduce the risk of dementia and possibly CVD. The consistently lower risk of ARBs versus ACE inhibitors is particularly noteworthy given their nearly identical indications, minimizing the risk of confounding by indication. To definitively test the causality of these differential associations, an RCT assessing both dementia and cardiovascular outcomes seems warranted.

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SUPPLEMENTARY MATERIAL

Supplementary Methods 1. A brief explanation of the role of the Dutch GP within Dutch health care

Referral to secondary care systems and diagnoses in GPs EHR: In Dutch Health Care, the GP is the gatekeeper of the system. All Dutch citizens need to be registered with a GP. The vast majority of health concerns, including management of hypertension and diabetes, are primarily handled by GPs. Patients cannot access secondary care systems (such as specialist clinics, hospitals, including emergency rooms) without a referral from their GP. Exceptions are emergencies, such as major accidents and life-threatening conditions (such as acute myocardial infarction and stroke). In these occasions, the patient is directly transported to a hospital, without need of prior need consultation with a GP. However, in all instances (i.e. after GPs referral, and after emergency hospital consultation/admission) the patients GP receives correspondence of this hospital consultation/admission, including made diagnoses, and changes to medication regiments.

Nursing homes: In the past decades, the number of nursing homes has drastically decreased in the Netherlands. Most older adults keep living at home for much longer aided by home care nurses and informal care by family members, friends, and neighbours. In these cases patients will still be under the care of a GP, along with hospital specialists and other health care workers, who all report to the GP. In some instances, for instance when suffering from invalidating comorbidities such as dementia or stroke, patients will be admitted to nursing homes. In some cases, a GP will remains the treating physician, in other cases care will be transferred to a dedicated nursing home physicians. In case of permanent admission to a nursing home away from a GPs care, the participant will be censored at that time, as they deregistered from the participating GPRN. It is unlikely that this affected major adverse event estimates, as the vast majority of diagnoses will have been made prior to admission.

Supplementary Methods 2. ICPC codes used for identifying endpoints and covariates

Acute myocardial infarction was defined by international classification of primary care (ICPC) code K75, stroke as K90, dementia as P70, and mortality as A96. Other related codes K75 (other/ chronic ischaemic heart disease), K76 (coronary sclerosis), K89 (transient ischaemic attack), and P20 (memory/concentration/orientation impairment) were deemed as nonspecific and were disregarded. Covariates were defined

as follows: K76 (non-acute coronary heart disease), K77 (congestive heart failure); K78 (atrial fibrillation); T90 (diabetes), T93 (dyslipidaemia).

Supplementary Methods 3. AHM-classes and corresponding ATC codes

AHM-class	ATC codes[a]
ACEi	C09A; C09B
ARB	C09C; C09D
Beta blocker	C07; C09BX02; C09BX04; C09DX05
CCB	C07FB; C08; C09BB; C09BX01; C09BX03; C09BX04; C09DB; C09DX01; C09DX03; C09DX06; C09DX07; C09XA53
Dihydropyridine	C07FB; C08CA; C08G; C09BB02; C09BB03; C09BB04; C09BB05; C09BB06; C09BB07; C09BB12; C09BB13; C09BX01; C09BX03; C09BX04; C09DB; C09DX01; C09DX03; C09DX06; C09DX07; C09XA53
Non-dihydropyridine	C08DA; C08DB; C08E; C09BB10;
Diuretic	C02L; C03; C07B; C07C; C07D; C08G; C09BA; C09BX01; C09BX03; C09DA; C09DX01; C09DX03; C09DX06; C09DX07; C09XA52; C09XA54
Thiazide(like)	C03A; C03BA; C03EA; C07B; C07C; C07D; C08G; C09BA; C09BX-1; C09BX04; C09DA; C09DX01; C09DX03; C09DX06; C09DX07; C09XA52; C09XA54
Loop	C03CA; C03CB; C03EB
Potassium sparing agents	C03AB; C03BB; C03D; C03E

[a] Includes all underlying codes (e.g. C09A includes, C09AA01- C09AA16). AHM = antihypertensive medication; ATC = anatomical therapeutic chemical; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, CCB = calcium channel blocker.

Supplementary Methods 4. Description of analytic models

Diagnoses and changes in AHM regimens were managed dynamically. If individuals switched between medications within the same class, the exposure would remain identical. If individuals were prescribed a different AHM class, either in addition to or replacing the existing one, their exposure status would update starting from the date the new medication was prescribed. E.g., in patients initially prescribed an ARB with a dCCB added later, exposure status would shift from 'ARB' to 'ARB+dCCB' from the moment the dCCB was added. Covariates were handled similarly. E.g., a participant diagnosed with diabetes after their first AHM prescription would have diabetes exposure from the time of diagnosis.

Our analyses only included individuals who were actively using one or more of the compared antihypertensive categories. We aimed to compare associations for ARBs, beta blockers, CCBs, and diuretics to those for ACE-inhibitors as reference category, in order to have a stable reference point (i.e. the major adverse event (MAE) risk for same antihypertensive type as reference for each analysis). In analyses wherein individuals could only use one of these medications at a time, this could be done using four dummy variables (0/1 coded variables) for each of these medication types. The resulting cox regression formula in R would be comparable to:

coxph(Surv(Start_Time,Stop_Time,Outcome_Status)~ARB_use+BB_use+CCB_use+Diuretic_use+covariates+frailty(GPRNs)).

Individuals with 0 for all of these dummy variables would then necessarily be ACE-inhibitor users, and therefore ACE-inhibitors would be the reference category. However, in our analyses, individuals can use multiple medications at a time, therefore, individuals with 1 on one or more of the dummy variables may still use ACE-inhibitors. Adding another dummy variable for ACE-inhibitor use would not solve this problem, because the reference category would then change to individuals with 0 for all of the dummy variables, resulting in a calculated 'floating average MAE risk' as reference, which would be different for each of the analyses. To reinstate ACE-inhibitor use as the stable reference category for these analyses, we included a second categorical variable, which comprised the total number of antihypertensive medications taken, with 1 (the minimum) as reference category. This resulted in an R formula comparable to:

coxph(Surv(Start_Time,Stop_Time,Outcome_Status)~ARB_use+BB_use+CCB_use+Diuretic_use+Total_nr_of_AHM_categorical+covariates+frailty(GPRNs)).

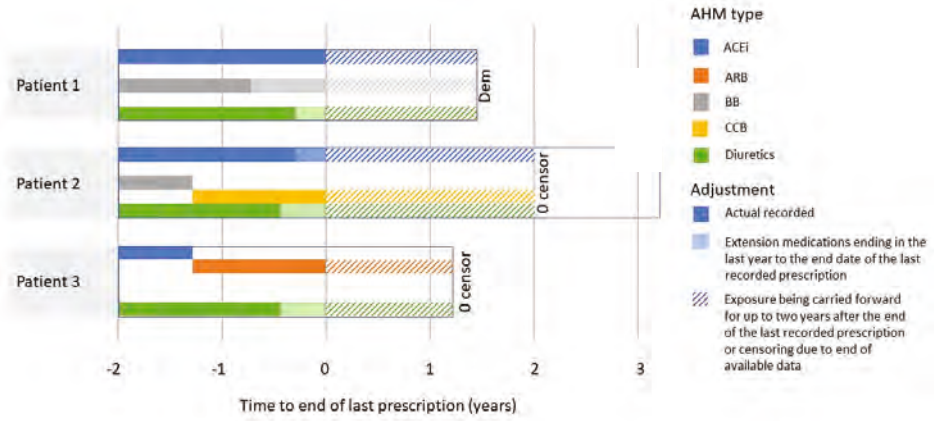
Thereby, individuals with 0 for ARBs, BBs, CCBs, and Diuretics, must take ACEi, and have the reference 1 value in the total AHM used variable. However, individuals using -for example- both diuretics and ACEi, would present the HR for diuretic use, adjusted for another medication that was concurrently taken, which was not ARB, BB, or CCBs, since these variables would all be 0, and thereby must be ACEi use. Thereby, the resulting HRs for ARBs, BBs, CCBs and diuretics effectively translate to the HRs for these medications compared to ACE inhibitors

Supplementary Methods 5. Subgroup analyses

We performed subgroup analyses, stratifying for sex, age, diabetes, dyslipidaemia, number of AHM classes used concurrently as potential moderators (rationale: *Supple-*

mentary Methods 5). 1.) Sex, as studies have reported differences in pharmacodynamics/pharmacokinetics, risk factors and treatment regimens between women and men;[13-17] 2.) Baseline age (<75 years, 75-85 years, and >85 years), as is a major predictor our primary endpoints. Consequently, in older age groups, the majority of preventable vascular damage may have already occurred, limiting the magnitude of class specific benefits; 3.) Diabetes, as ACEi and ARBs are more effective classes in diabetes, leading to different associations between participants with(out) diabetes;[18,19] 4.) Dyslipidaemia, as a significant risk factor for cardiovascular events in midlife, participants with dyslipidaemia may be treated more strictly;[20] 5). Number of AHM classes used simultaneously, as this may reflect hypertension severity, translating to higher cardiovascular risk. Class specific benefits may be more pronounced in participants with higher cardiovascular risk (i.e., participants using many classes); 6.) Time period: to investigate the impact of the updated Dutch guidelines, comparing pre-2012, when thiazides, BBs, and ACEi were first-line options, with post-2012, when all classes were considered equivalent according to these guidelines. We used 2015 as the cut-off, considering a 3-year period of lag-time for GPs to adapt to the updated guidelines.

Supplementary Figure 1. Examples for alterations done in sensitivity analysis 1 and 2



MAE = major adverse event; 0 censor = censored without MAE diagnosis during the observed period. AHM = antihypertensive medication; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker, BB = beta blockers CCB = calcium channel blocker.

Reading example: For patient 1, ACEi (blue) was the last ending prescription. BB (grey) and Diuretics (green) ended within one year before, so their use was extended to the end of ACEi (light shaded grey and green). These three prescription exposures were then carried forward for up to 2 years (dashed shade), in this case to 1·4 years when the patient was censored with an MAE. For patient 2, CCB (yellow) was the last ending prescription. ACEi (blue) and Diuretics (green) ended within one year before, and were therefore extended up to the end of CCBs (light shaded blue and green). BB (grey) ended more than a year before CCBs (yellow), and was therefore not extended. For ACEi, CCBs and Diuretics, prescription exposures were carried forward for 2 years (dashed blue, yellow and green), at which time no event had occurred, so the patient was censored as no MAE. For patient 3, ARB (orange) was the last ending prescription. Only diuretics (green) ended in the last year before that, so was extended up to ARB's end (light shaded green). The last prescriptions were then carried forward for up to 2 years (dashed orange and green). In this case, the patient was censored without an event after 1·2 years, because that was the time up until which information was available for this patient.

Supplementary Table 1. Comparing model 1 and 2

		Model 1		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**HR (95%CI)**	**P-value**
Major adverse events					
ACEi	4437/186,476 (23·8)	Reference		Reference	
ARB	2772/137,676 (20·1)	0·85 (0·72-1·01)	<0·01	0·86 (0·82-0·91)	<0·01
BB	5412/220,811 (24·5)	1·03 (0·89-1·20)	0·31	1·07 (1·02-1·12)	0·01
dCCB	3727/157,312 (23·7)	0·95 (0·82-1·12)	<0·01	0·93 (0·90-0·97)	<0·01
Thiazide diuretic	4790/248,801 (19·2)	0·73 (0·62-0·86)	<0·01	0·72 (0·67-0·75)	<0·01
Acute myocardial infarction					
ACEi	956/186,476 (5·1)	Reference		Reference	
ARB	496/137676 (3·6)	0·74 (0·56-0·98)	<0·01	0·74 (0·66-0·82)	<0·01
BB	1360/220811 (6·2)	1·50 (1·33-1·69)	<0·01	1·50 (1·33-1·69)	<0·01
dCCB	648/157312 (4·1)	1·02 (0·84-1·24)	<0·01	0·73 (0·65-0·81)	<0·01
Thiazide diuretic	722/248801 (2·9)	0·73 (0·52-1·01)	<0·01	0·33 (0·29-0·38)	<0·01
Stroke					
ACEi	1258/186,476 (6·8)	Reference		Reference	
ARB	866/137,676 (6·3)	0·85 (0·76-0·95)	0·06	0·93 (0·85-1·03)	0·18
BB	1524/220,811 (6·9)	0·83 (0·72-0·95)	0·94	1·02 (0·93-1·12)	0·62
dCCB	1153/157,312 (7·3)	0·88 (0·76-1·02)	0·67	0·92 (0·84-1·00)	0·04
Thiazide diuretic	1527/248,801 (6·1)	0·81 (0·71-0·93)	<0·01	0·86 (0·76-0·95)	<0·01
Dementia					
ACEi	991/186,5476 (5·3)	Reference		Reference	
ARB	642/137,676 (4·6)	0·85 (0·76-0·95)	<0·01	0·85 (0·76-0·95)	<0·01
BB	1088/220,811 (4·9)	0·83 (0·72-0·95)	<0·01	0·83 (0·74-0·93)	<0·01
dCCB	764/157,312 (4·9)	0·88 (0·76-1·02)	<0·01	0·79 (0·69-0·90)	<0·01
Thiazide diuretic	1192/248,801 (4·8)	0·81 (0·71-0·93)	<0·01	0·74 (0·67-0·82)	<0·01
Mortality					
ACEi	1315/186,476 (7·0)	Reference		Reference	
ARB	809/137,676 (5·9)	0·86 (0·76-0·97)	<0·01	0·86 (0·76-0·97)	0·01
BB	1517/220,811 (6·9)	0·99 (0·89-1·10)	0·80	0·99 (0·90-1·08)	0·69
dCCB	1213/157,312 (7·7)	1·02 (0·88-1·19)	0·13	1·08 (0·97-1·20)	0·13
Thiazide diuretic	1420/248,801 (5·7)	0·87 (0·78-0·98)	<0·01	0·74 (0·68-0·81)	<0·01

Cox regression with time varying covariates. The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. Model 1 adjusts for age, sex, potassium-sparing agents and number of AHM classes used simultaneously; model 2 additionally adjusts for diabetes, dyslipidaemia. Major adverse events include acute myocardial infarction, stroke (ischemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker; BB = beta blocker = dCCB = dihydropyridine calcium channel blocker.

Supplementary Table 2. Not extending prescriptions up to 2 years

		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Major adverse events			
ACEi	3320/144,277 (23·0)	Reference	
ARB	2086/107,918 (19·3)	0·85 (0·80-0·90)	<0·01
BB	4264/176,001 (24·2)	1·11 (1·05-1·18)	<0·01
dCCB	2764/118,704 (23·3)	0·88 (0·82-0·94)	<0·01
Thiazide diuretic	3554/199,294 (17·8)	0·63 (0·59-0·68)	<0·01
Acute myocardial infarction			
ACEi	909/144,277 (6·3)	Reference	
ARB	454/107,918 (4·2)	0·70 (0·62-0·79)	<0·01
BB	1299/176,001 (7·4)	1·48 (1·31-1·67)	<0·01
dCCB	601/118,704 (5·1)	0·56 (0·48-0·64)	<0·01
Thiazide diuretic	675/199,294 (3·4)	0·34 (0·27-0·35)	<0·01
Stroke			
ACEi	1093/144,277 (7·6)	Reference	
ARB	765/107,919 (7·1)	0·92 (0·84-1·02)	0·10
BB	1335/176,001 (7·6)	0·99 (0·89-1·10)	0·91
dCCB	1014/118,704 (8·5)	1·07 (0·95-1·20)	0·25
Thiazide diuretic	1320/199,294 (6·6)	0·79 (0·70-0·89)	<0·01
Dementia			
ACEi	608/144,277 (4·2)	Reference	
ARB	420/107,918 (3·9)	0·88 (0·78-1·00)	0·06
BB	710/176,001 (4·0)	0·86 (0·77-0·96)	0·03
dCCB	490/118,704 (4·1)	0·81 (0·69-0·94)	<0·01
Thiazide diuretic	772/199,294 (3·9)	0·83 (0·71-0·97)	0·02
Mortality			
ACEi	727/144,277 (5·0)	Reference	
ARB	455/107,919 (4·2)	0·87 (0·77-0·98)	0·02
BB	937/176,001 (5·3)	1·19 (1·05-1·37)	<0·01
dCCB	672/118,704 (5·7)	1·08 (0·95-1·25)	0·25
Thiazide diuretic	800/199,295 (4·0)	0·72 (0·67-0·84)	<0·01

Not extending prescriptions up to 2 years to an endpoint. Cox regression with time varying covariates. The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according. Major adverse events include acute myocardial infarction, stroke (ischemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker; BB = beta blocker = dCCB = dihydropyridine calcium channel blocker.

Supplementary Table 3. Last prescription (instead of last year's prescriptions)

		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Major adverse events			
ACEi	4113/181,097 (22·7)	Reference	
ARB	2571/134,411 (19·1)	0·89 (0·85-0·94)	<0·01
BB	5136/216,224 (23·8)	1·11 (1·06-1·17)	<0·01
dCCB	3387/150,565 (22·5)	1·01 (0·95-1·07)	0·74
Thiazide diuretic	4223/240,342 (17·6)	0·75 (0·71-0·80)	<0·01
Acute myocardial infarction			
ACEi	933/181,097 (5·2)	Reference	
ARB	493/134,411 (3·7)	0·76 (0·68-0·85)	<0·01
BB	1330/216,224 (6·2)	1·46 (1·30-1·64)	<0·01
dCCB	633/150,565 (4·2)	0·62 (0·54-0·70)	<0·01
Thiazide diuretic	715/240,342 (3·0)	0·36 (0·32-0·42)	<0·01
Stroke			
ACEi	1191/181,097 (6·6)	Reference	
ARB	825/134,411 (6·1)	0·95 (0·86-1·04)	0·23
BB	1455/216,224 (6·7)	1·03 (0·94-1·14)	0·51
dCCB	1078/150,565 (7·2)	1·08 (0·98-1·20)	0·14
Thiazide diuretic	1399/240,342 (5·8)	0·85 (0·76-0·94)	<0·01
Dementia			
ACEi	895/181,097 (4·9)	Reference	
ARB	575/134,411 (4·3)	0·89 (0·80-0·99)	0·03
BB	975/216,224 (4·5)	0·86 (0·78-0·96)	<0·01
dCCB	670/150,565 (4·5)	0·92 (0·82-1·03)	0·16
Thiazide diuretic	1004/240,342 (4·2)	0·89 (0·79-1·00)	0·06
Mortality			
ACEi	1171/181,097 (6·5)	Reference	
ARB	714/134,411 (5·3)	0·93 (0·85-1·03)	0·15
BB	1447/216,224 (6·7)	1·19 (1·08-1·30)	<0·01
dCCB	1050/150,565 (7·0)	1·27 (1·16-1·40)	<0·01
Thiazide diuretic	1167/240,342 (4·9)	0·87 (0·78-0·96)	<0·01

Using the last prescription instead of last year of prescriptions as exposure. Cox regression with time varying covariates. The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according. Major adverse events include acute myocardial infarction, stroke (ischemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker; BB = beta blocker = dCCB = dihydropyridine calcium channel blocker.

Supplementary Table 4. Congestive Heart Failure as additional endpoint

		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Major adverse events			
ACEi	8064/225,573 (35·8)	Reference	
ARB	4697/165,081 (30·3)	0·89 (0·85-0·92)	<0·01
BB	10,568/279,970 (37·8)	1·07 (1·03-1·11)	<0·01
dCCB	6211/185,688 (33·5)	0·80 (0·77-0·84)	<0·01
Thiazide diuretic	7148/279,197 (25·9)	0·54 (0·52-0·56)	<0·01
Acute myocardial infarction			
ACEi	1323/225,573 (5·9)	Reference	
ARB	709/165,081 (4·3)	0·77 (0·70-0·85)	<0·01
BB	1866/279,970 (6·7)	1·38(1·24-1·54)	<0·01
dCCB	876/185,688 (4·7)	0·55 (0·49-0·62)	<0·01
Thiazide diuretic	251/279,197 (3·1)	0·30 (0·27-0·34)	<0·01
Stroke			
ACEi	1661/225,573 (7·4)	Reference	
ARB	1158/165,081 (7·0)	0·96 (0·89-1·04)	0·29
BB	2124/279,970 (7·6)	1·01 (0·93-1·10)	0·75
dCCB	1492/185,688 (8·0)	1·06 (0·97-1·16)	0·22
Thiazide diuretic	1857/279,197 (6·8)	0·85 (0·78-0·94)	<0·01
Congestive heart failure			
ACEi	2186/225,573 (9·7)	Reference	
ARB	1320/165,081 (8·0)	0·91 (0·85-0·98)	0·02
BB	3005/279,970 (10·7)	0·90 (0·82-0·97)	0·01
dCCB	1412/185,688 (7·6)	0·64 (0·59-0·70)	<0·01
Thiazide diuretic	1484/279,197 (5·3)	0·55 (0·51-0·61)	<0·01
Dementia			
ACEi	1218/225,573 (5·4)	Reference	
ARB	781/165,081 (4·7)	0·88 (0·80-0·97)	<0·01
BB	1412/279,970 (5·0)	0·87 (0·79-0·96)	<0·01
dCCB	902/185,688 (4·9)	0·82 (0·74-0·92)	<0·01
Thiazide diuretic	1357/279,197 (4·9)	0·87 (0·79-0·97)	0·001

Supplementary Table 4. Congestive Heart Failure as additional endpoint *(Continued)*

		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Mortality			
ACEi	1838/225,573 (8·2)	Reference	
ARB	1110/165,081 (6·7)	0·90 (0·83-0·97)	<0·01
BB	2332/279,970 (8·3)	1·13 (1·05-1·23)	<0·01
dCCB	1626/185,688 (8·8)	1·14 (1·04-1·24)	<0·01
Thiazide diuretic	1766/279,197 (6·3)	0·73 (0·67-0·80)	<0·01

Including CHF as additional endpoint. Cox regression with time varying covariates. The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according. Major adverse events include acute myocardial infarction, stroke (ischemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker; BB = beta blocker = dCCB = dihydropyridine calcium channel blocker; CHF = congestive heart failure.

Supplementary Table 5. Adjusting (instead of censoring) for censoring variables

		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Major adverse events			
ACEi	6840/248,545 (27·5)	Reference	
ARB	4343/184,335 (23·6)	0·87 (0·84-0·9)	<0·01
BB	9651/336,554 (28·7)	1·04 (0·99-1·08)	0·10
dCCB	5482/202,728 (27·0)	0·89 (0·85-0·93)	<0·01
Thiazide diuretic	6479/299,429 (21·6)	0·67 (0·64-0·71)	<0·01
Acute myocardial infarction			
ACEi	1424/248,545 (5·7)	Reference	
ARB	796/184,335 (4·3)	0·75 (0·72-0·86)	<0·01
BB	2086/336,554 (6·2)	1·26 (1·14-1·39)	<0·01
dCCB	943/202,728 (4·7)	0·57 (0·50-0·63)	<0·01
Thiazide diuretic	958/299,429 (3·2)	0·33 (0·29-0·37)	<0·01
Stroke			
ACEi	1902/248,545 (7·7)	Reference	
ARB	1353/184,335 (7·3)	0·95 (0·88-1·02)	0·13
BB	2673/336,554 (7·9)	1·02 (0·94-1·11)	0·58
dCCB	1679/202,728 (8·3)	1·00 (0·91-1·09)	0·97
Thiazide diuretic	2056/299,429 (6·9)	0·81 (0·74-0·88)	<0·01
Dementia			
ACEi	1413/248,545 (5·7)	Reference	
ARB	890/184,335 (4·8)	0·83 (0·76-0·91)	<0·01
BB	1808/336,554 (5·4)	0·83 (0·76-0·91)	<0·01
dCCB	1037/202,728 (5·1)	0·80 (0·73-0·89)	<0·01
Thiazide diuretic	1492/299,429 (5·0)	0·83 (0·75-0·92)	<0·01
Mortality			
ACEi	2218/248,545 (8·9)	Reference	
ARB	1361/184,335 (7·4)	0·86 (0·81-0·93)	<0·01
BB	3211/336,554 (9·5)	1·09 (1·01-1·17)	0·02
dCCB	1986/202,728 (9·8)	1·04 (0·96-1·12)	0·33
Thiazide diuretic	2065/299,429 (6·9)	0·71 (0·65-0·77)	<0·01

Adjusting instead of censoring for censoring variables. Censoring variables are non-acute CHD, CHF, AF, and prescription of ndCCBs or loop diuretics. Cox regression with time varying covariates. The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according. Major adverse events include acute myocardial infarction, stroke (ischemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker; BB = beta blocker = dCCB = dihydropyridine calcium channel blocker; CHD = coronary heart disease; CHF = congestive heart failure; AF = atrial fibrillation; ndCCBs = non-dihydropyridine calcium channel blocker.

Supplementary Table 6. Proportional-use categorised at ≥25%, ≥50% and ≥75

	≥25			≥50			≥75		
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Major adverse events									
ACEi	4461/194,633 (22·9)	Reference		3996/177,440 (22·5)	Reference		1382/160,409 (22·3)	Reference	
ARB	2833/141,435 (20·0)	0·89 (0·85-0·94)	<0·01	2504/129,225 (19·4)	0·89 (0·84-0·94)	<0·01	2150/114,617 (18·8)	0·87 (0·83-0·92)	<0·01
BB	5465/230,242 (23·7)	1·09 (1·04-1·15)	<0·01	4980/215,094 (23·2)	1·07 (1·02-1·13)	0·01	4490/198,485 (22·6)	1·05 (1·00-1·11)	0·06
dCCB	3644/159,035 (22·9)	0·97 (0·91-1·02)	0·23	3102/139,642 (22·2)	0·96 (0·91-1·02)	0·21	2643/119,339 (22·2)	0·99 (0·93-1·05)	0·77
Thiazides	5363/270,289 (19·8)	0·78 (0·73-0·83)	<0·01	4767/248,146 (19·2)	0·79 (0·75-0·84)	<0·01	4141/222,221 (18·6)	0·80 (0·75-0·85)	<0·01
Acute myocardial infarction									
ACEi	887/194,633 (4·6)	Reference		807/177,440 (4·6)	Reference		740/160,409 (4·6)	Reference	
ARB	488/141,435 (3·5)	0·81 (0·72-0·91)	<0·01	439/129,225 (3·4)	0·82 (0·72-0·92)	<0·01	382/114,617 (3·3)	0·79 (0·70-0·90)	<0·01
BB	1228/230,242 (5·3)	1·45 (1·29-1·63)	<0·01	1150/215,094 (5·4)	1·43 (1·28-1·61)	<0·01	1082/198,485 (5·5)	1·44 (1·28-1·61)	<0·01
dCCB	610/159,035 (3·8)	0·72 (0·62-0·82)	<0·01	543/139,642 (3·9)	0·75 (0·66-0·86)	<0·01	471/119,339 (4·0)	0·77 (0·67-0·86)	<0·01
Thiazides	803/270,289 (3·0)	0·48 (0·42-0·56)	<0·01	719/248,146 (2·9)	0·50 (0·44-0·58)	<0·01	635/222,221 (2·9)	0·51 (0·44-0·59)	<0·01
Stroke									
ACEi	1274/194,633 (6·7)	Reference		1152/177,440 (6·5)	Reference		1040/160,409 (6·5)	Reference	
ARB	875/141,435 (6·2)	0·94 (0·86-1·03)	0·21	773/129,225 (6·0)	0·92 (0·84-1·02)	0·10	665/114,617 (5·8)	0·90 (0·81-0·99)	0·04
BB	1572/230,242 (6·8)	1·09 (0·99-1·20)	0·09	1449/215,094 (6·7)	1·07 (0·97-1·18)	0·18	1311/198,485 (6·6)	1·04 (0·95-1·15)	0·40
dCCB	1127/159,035 (7·1)	1·08 (0·97-1·20)	0·15	989/139,642 (7·1)	1·10 (0·99-1·23)	0·08	873/119,339 (7·3)	1·17 (1·03-1·31)	<0·01
Thiazides	1660/270,289 (6·1)	0·90 (0·81-1·01)	0·07	1500/248,146 (6·0)	0·91 (0·82-1·02)	0·10	1323/222,221 (6·0)	0·92 (0·82-1·02)	0·12
Dementia									
ACEi	1001/194,633 (5·1)	Reference		869/177,440 (4·9)	Reference		765/160,409 (4·8)	Reference	
ARB	668/141,435 (4·7)	0·90 (0·80-1·00)	0·04	582/129,225 (4·5)	0·91 (0·82-1·02)	0·10	488/114,617 (4·3)	0·89 (0·80-1·00)	0·06

Supplementary Table 6. Proportional-use categorised at ≥25%, ≥50% and ≥75 *(Continued)*

	≥25			≥50			≥75		
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
BB	1174/230,242 (5·1)	0·91 (0·82-1·02)	0·09	1046/215,094 (4·9)	0·90 (0·81-1·00)	0·07	904/198,485 (4·6)	0·86 (0·76-0·96)	<0·01
dCCB	747/159,035 (4·7)	0·81 (0·72-0·92)	<0·01	606/139,642 (4·3)	0·82 (0·72-0·93)	<0·01	487/119,339 (4·1)	0·81 (0·71-0·93)	<0·01
Thiazides	1328/270,289 (4·9)	0·86 (0·76-0·97)	<0·01	1150/248,146 (4·6)	0·87 (0·77-0·99)	0·03	985/222,221 (4·4)	0·88 (0·78-0·99)	0·04
Mortality									
ACEi	1382/194,633 (7·1)	Reference		1241/177,440 (7·0)	Reference		1090/160,409 (6·8)	Reference	
ARB	846/141,435 (6·0)	0·88 (0·80-0·96)	<0·01	740/129,225 (5·7)	0·87 (0·79-0·95)	<0·01	637/114,617 (5·6)	0·87 (0·79-0·96)	<0·01
BB	1568/230,242 (6·8)	1·03 (0·93-1·13)	0·59	1406/215,094 (6·5)	0·98 (0·89-1·08)	0·74	1253/198,485 (6·3)	0·98 (0·89-1·08)	0·62
dCCB	1212/159,035 (7·6)	1·12 (1·01-1·24)	0·04	1007/139,642 (7·2)	1·06 (0·96-1·18)	0·26	846/119,339 (7·1)	1·08 (0·96-1·21)	0·16
Thiazides	1652/270,289 (6·1)	0·81 (0·73-0·90)	<0·01	1465/248,146 (5·9)	0·83 (0·74-0·92)	<0·01	1252/222,221 (5·6)	0·82 (0·73-0·91)	<0·01

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.

Supplementary Table 7. Excluding events within 3 years of AHM regimen change

		Model 2	
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**
Major adverse events			
ACEi	2653/185,645 (14·3)	Reference	
ARB	1863/137,218 (13·6)	0·91 (0·86-0·97)	<0·01
BB	3286/219,811 (14·9)	1·05 (1·00-1·11)	0·14
dCCB	2366/156,648 (15·1)	0·92 (0·86-0·99)	0·03
Thiazide diuretic	3050/247,937 (12·3)	0·76 (0·70-0·82)	<0·01
Acute myocardial infarction			
ACEi	420/185,645 (2·3)	Reference	
ARB	251/137,218 (1·8)	0·77 (0·66-0·91)	<0·01
BB	603/219,811 (2·7)	1·47 (1·22-1·77)	<0·01
dCCB	331/156,648 (2·1)	0·62 (0·51-0·77)	<0·01
Thiazide diuretic	346/247,937 (1·4)	0·35 (0·29-0·35)	<0·01
Stroke			
ACEi	745/185,645 (4·0)	Reference	
ARB	581/137,218 (4·2)	0·99 (0·88-1·11)	0·085
BB	981/219,811 (4·5)	1·13 (0·99-1·28)	0·07
dCCB	704/156,648 (4·5)	0·96 (0·84-1·11)	0·58
Thiazide diuretic	942/247,937 (3·8)	0·85 (0·73-0·98)	0·02
Dementia			
ACEi	670/185,645 (3·6)	Reference	
ARB	472/137,218 (3·4)	0·88 (0·78-1·00)	0·04
BB	755/219,811 (3·4)	0·83 (0·73-0·95)	<0·01
dCCB	543/156,648 (3·5)	0·78 (0·68-0·91)	<0·01
Thiazide diuretic	822/247,937 (3·3)	0·81 (0·70-0·94)	<0·01
Mortality			
ACEi	878/185,645 (4·7)	Reference	
ARB	588/137,218 (4·3)	0·90 (0·81-1·01)	0·07
BB	1005/219,811 (4·6)	1·02 (0·90-1·15)	0·78
dCCB	823/156,648 (5·3)	1·08 (0·95-1·23)	0·21
Thiazide diuretic	994/247,937 (4·0)	0·84 (0·74-0·96)	0·01

Cox regression with time varying covariates. The upper section of the table depicts the overall associations between the classes and first occurring major adverse event. The lower section depicts associations between AHM classes and the individual first occurring major adverse events. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according. Major adverse events include acute myocardial infarction, stroke (ischemic or haemorrhagic), all-cause dementia, and mortality. Thiazide diuretics encompass both thiazide- and thiazide-like diuretics. Abbreviations: AHM = antihypertensive medication; PY = person years; HR = hazard ratio; CI = confidence interval; ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker; BB = beta blocker = dCCB = dihydropyridine calcium channel blocker.

Supplementary Table 8. Subgroup stratified for sex

		Women		Men			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Major adverse events							
ACEi	2196/97,400 (22·6)	Reference		2241/89,077 (25·1)	Reference		
ARB	576/83,553 (18·9)	0·83 (0·78-0·89)	<0·01	1196/54,122 (22·1)	0·89 (0·83-0·96)	<0·01	0·23
BB	3063/140,198 (21·8)	0·98 (0·92-1·05)	0·60	2349/80,613 (29·1)	1·18 (1·09-1·27)	<0·01	<0·01
dCCB	2025/89,686 (22·6)	0·91 (0·85-0·99)	0·02	1702/67,627 (25·2)	0·94 (0·86-1·02)	0·13	0·85
Thiazide diuretic	2876 /158,654 (18·1)	0·71 (0·66-0·77)	<0·01	1914/90,147 (21·2)	0·72 (0·66-0·78)	<0·01	0·73
Acute myocardial infarction							
ACEi	289/97,400 (4·0)	Reference		567/89,077 (6·4)	Reference		
ARB	243/83,553 (2·9)	0·72 (0·61-0·85)	<0·01	253/54,122 (4·7)	0·73 (0·63-0·86)	<0·01	0·88
BB	605/140,198 (4·3)	1·23 (1·03-1·47)	0·03	755/80,613 (9·4)	1·76 (1·50-2·06)	<0·01	<0·01
dCCB	285/89,686 (3·2)	0·54 (0·44-0·66)	<0·01	363/67,627 (5·4)	0·59 (0·49-0·71)	<0·01	0·53
Thiazide diuretic	36/158,654 (2·3)	0·31 (0·25-0·38)	<0·01	362/90,147 (4·0)	0·36 (0·30-0·43)	<0·01	0·27
Stroke							
ACEi	647/97,400 (6·6)	Reference		611/89,077 (6·9)	Reference		
ARB	490/83,553 (5·9)	0·87 (0·77-0·98)	0·02	376/54,122 (7·0)	1·00 (0·88-1·15)	0·97	0·12
BB	931/140,198 (6·6)	1·02 (0·90-1·16)	0·72	593/80,613 (7·4)	1·02 (0·88-1·18)	0·80	0·98
dCCB	644/89,686 (7·2)	1·04 (0·90-1·20)	0·60	509/67,627 (7·5)	1·04 (0·89-1·23)	0·60	0·98
Thiazide diuretic	930/158,654 (5·9)	0·85 (0·74-0·98)	0·03	597/90,147 (6·6)	0·86 (0·73-1·02)	0·08	0·83
Dementia							
ACEi	613/97,400 (6·3)	Reference		378/89,077 (4·2)	Reference		
ARB	444/83,553 (5·3)	0·84 (0·74-0·96)	<0·01	198/54,122 (3·7)	0·89 (0·74-1·06)	0·19	0·61

Supplementary Table 8. Subgroup stratified for sex *(Continued)*

		Women		Men			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
BB	769/140,198 (5·5)	0·83 (0·72-0·94)	<0·01	319/80,613 (4·0)	0·86 (0·71-1·03)	0·10	0·74
dCCB	532/89,686 (5·9)	0·85 (0·73-0·98)	0·02	232/67,627 (3·4)	0·75 (0·60-0·93)	<0·01	0·36
Thiazide diuretic	855/158,654 (5·4)	0·82 (0·71-0·95)	<0·01	337/90,147 (3·7)	0·89 (0·72-1·09)	0·25	0·52
Mortality							
ACEi	590/97,400 (6·1)	Reference		725/89,077 (8·1)	Reference		
ARB	424/83,553 (5·1)	0·85 (0·75-0·97)	0·01	385/54,122 (7·1)	0·90 (0·79-1·03)	0·12	0·54
BB	806/140,198 (5·8)	0·98 (0·86-1·11)	0·73	711/80,613 (8·8)	1·13 (0·99-1·29)	0·07	0·13
dCCB	594/89,686 (6·6)	1·07 (0·93-1·24)	0·33	619/67,627 (9·2)	1·21 (1·04-1·39)	0·01	0·29
Thiazide diuretic	775/158,654 (4·9)	0·74 (0·64-0·86)	<0·01	645/90,147 (7·2)	0·84 (0·73-0·98)	0·03	0·20

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agen,ts, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.

Supplementary Table 9. Subgroup stratified for baseline age

	≥75			≥50			≥75			P-int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Major adverse events										
ACEi		Reference			Reference			Reference		
ARB	1887/115,364 (16·4)	0·86 (0·81-0·92)	<0·01	710/19,560 (36·3)	0·88 (0·79-0·96)	<0·01	175/2751 (63·6)	0·83 (0·69-1·01)	0·06	0·91
BB	3559/179,028 (19·9)	1·11 (1·04-1·19)	<0·01	1491/36,028 (41·4)	1·04 (0·95-1·15)	0·40	362/5755 (62·9)	1·19 (1·01-1·39)	0·03	<0·01
dCCB	2532/129,804 (19·5)	0·96 (0·89-1·03)	0·26	958/23,994 (39·9)	0·89 (0·80-0·99)	0·03	237/3514 (67·4)	0·82 (0·66-1·01)	0·06	0·27
Thiazides	3147/205,097 (15·3)	0·69 (0·64-0·74)	<0·01	1279/37,971 (33·7)	0·75 (0·67-0·83)	<0·01	364/5733 (63·5)	0·81 (0·66-1·00)	0·05	<0·01
Acute myocardial infarction										
ACEi		Reference			Reference			Reference		
ARB	404/115,364 (3·5)	0·79 (0·69-0·90)	<0·01	79/19,560 (4·0)	0·56 (0·43-0·74)	<0·01	13/2751 (4·7)	0·71 (0·36-1·41)	0·33	0·30
BB	1051/179,028 (5·9)	1·62 (1·41-1·86)	<0·01	263/36,028 (7·3)	1·18 (0·91-1·53)	0·22	46/5755 (8·0)	1·42 (0·77-2·59)	0·26	0·34
dCCB	512/129,804 (3·9)	0·60 (0·51-0·70)	<0·01	119/23,994 (5·0)	0·47 (0·35-0·65)	<0·01	17/3514 (4·8)	0·59 (0·28-1·22)	0·15	0·90
Thiazides	558/205,097 (2·7)	0·34 (0·29-0·40)	<0·01	142/37,971 (3·7)	0·31 (0·23-0·42)	<0·01	22/5733 (3·8)	0·44 (0·21-0·91)	0·03	0·30
Stroke										
ACEi		Reference			Reference			Reference		
ARB	639/115,364 (5·5)	0·92 (0·83-1·02)	0·13	195/19,560 (10·0)	0·99 (0·82-1·20)	0·95	32/2751 (11·6)	0·74 (0·47-1·14)	0·17	0·64
BB	1077/179,028 (6·0)	1·03 (0·92-1·16)	0·63	378/36,028 (10·5)	1·11 (0·91-1·34)	0·31	69/5755 (12·0)	0·74 (0·49-1·12)	0·15	0·23
dCCB	842/129,804 (6·5)	1·04 (0·92-1·18)	0·51	259/23,994 (10·8)	1·08 (0·87-1·34)	0·50	52/3514 (14·8)	0·94 (0·60-1·46)	0·77	0·83
Thiazides	1083/205,097 (5·3)	0·81 (0·71-0·93)	<0·01	368/37,971 (9·7)	1·00 (0·81-1·24)	0·99	76/5733 (13·3)	0·85 (0·54-1·33)	0·47	0·24
Dementia										
ACEi		Reference			Reference			Reference		
ARB	328/115,364 (2·8)	0·84 (0·73-0·97)	0·02	243/19,560 (12·4)	0·88 (0·75-1·04)	0·14	71/2751 (25·8)	0·89 (0·66-1·21)	0·46	0·20
BB	535/179,028 (3·0)	0·90 (0·77-1·06)	0·20	433/36,028 (12·0)	0·82 (0·69-0·97)	0·02	120/5755 (20·9)	0·68 (0·50-0·94)	0·02	1·00
dCCB	410/129,804 (3·2)	0·95 (0·80-1·13)	0·56	282/23,994 (11·8)	0·75 (0·62-0·91)	<0·01	72/3514 (20·5)	0·62 (0·44-0·89)	0·01	0·24

Supplementary Table 9. Subgroup stratified for baseline age *(Continued)*

	≥75			≥50			≥75			P-int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Thiazides	611/205,097 (3·0)	0·94 (0·79-1·11)	0·45	439/37,971 (11·6)	0·77 (0·64-0·93)	<0·01	142/5733 (24·8)	0·86 (0·61-1·20)	0·37	0·08
Mortality										
ACEi		Reference			Reference			Reference		
ARB	547/115,364 (4·7)	0·88 (0·79-0·98)	0·02	202/19,560 (10·3)	0·92 (0·77-1·10)	0·36	60/2751 (21·8)	0·80 (0·58-1·13)	0·19	0·99
BB	947/179,028 (5·3)	1·03 (0·92-1·16)	0·61	437/36,028 (12·1)	1·17 (0·98-1·40)	0·08	83/5755 (23·1)	0·86 (0·64-1·42)	0·34	0·50
dCCB	798/129,804 (6·2)	1·15 (1·02-1·31)	0·03	315/23,994 (13·1)	1·15 (0·95-1·40)	0·15	70/3514 (28·5)	1·02 (0·73-1·42)	0·92	0·86
Thiazides	933/205,097 (4·6)	0·78 (0·68-0·89)	<0·01	356/37,971 (9·4)	0·81 (0·66-0·99)	0·04	131/5733 (22·9)	0·84 (0·60-1·17)	0·30	0·12

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.

Supplementary Table 10. Subgroup stratified for diabetes status

		No diabetes		Diabetes			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Major adverse events							
ACEi	2805/121,296 (23·1)	Reference		1632/65,180 (25·0)	Reference		
ARB	1792/96,359 (18·6)	0·81 (0·77-0·87)	<0·01	980/41,317 (23·7)	0·95 (0·88-1·03)	0·25	0·03
BB	3844/166,189 (23·1)	1·02 (0·96-1·09)	0·48	1568/54,622 (28·7)	1·19 (1·08-1·31)	<0·01	0·01
dCCB	2480/110,788 (22·4)	0·88 (0·83-0·95)	<0·01	1247/46,525 (26·8)	1·04 (0·94-1·16)	0·44	0·01
Thiazide diuretic	3217/177,743 (18·1)	0·68 (0·64-0·73)	<0·01	1573/71,058 (22·1)	0·79 (0·71-0·88)	<0·01	0·02
Acute myocardial infarction							
ACEi	669/121,296 (5·5)	Reference		287/65,180 (4·4)	Reference		
ARB	322/96,359 (3·3)	0·64 (0·56-0·74)	<0·01	174/41,317 (4·2)	0·98 (0·80-1·20)	0·84	<0·01
BB	1035/166,189 (6·2)	1·48 (1·29-1·69)	<0·01	325/54,622 (6·0)	1·58 (1·25-2·01)	<0·01	0·61
dCCB	438/110,788 (4·0)	0·51 (0·43-0·59)	<0·01	210/46,525 (4·5)	0·80 (0·62-1·04)	0·09	<0·01
Thiazide diuretic	493/177,743 (2·8)	0·30 (0·26-0·35)	<0·01	229/71,058 (3·2)	0·45 (0·35-0·59)	<0·01	0·01
Stroke							
ACEi	805/121,296 (6·6)	Reference		453/65,180 (7·0)	Reference		
ARB	557/96,359 (5·8)	0·86 (0·77-0·96)	<0·01	309/41,317 (7·5)	1·06 (0·91-1·23)	0·48	0·03
BB	1076/166,189 (6·5)	0·97 (0·86-1·08)	0·57	448/54,622 (8·2)	1·19 (0·99-1·42)	0·07	0·06
dCCB	780/110,788 (7·0)	1·02 (0·90-1·16)	0·75	373/46,525 (8·0)	1·10 (0·90-1·34)	0·34	0·55
Thiazide diuretic	1029/177,743 (5·8)	0·82 (0·72-0·93)	<0·01	498/71,058 (7·0)	0·95 (0·78-1·16)	0·64	0·21

Supplementary Table 10. Subgroup stratified for diabetes status *(Continued)*

		No diabetes		Diabetes			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Dementia							
ACEi	624/121,296 (5·1)	Reference		367/65,180 (5·6)	Reference		
ARB	440/96,359 (4·6)	0·87 (0·76-0·98)	0·03	202/41,317 (4·9)	0·85 (0·71-1·01)	0·07	0·86
BB	783/166,189 (4·7)	0·82 (0·72-0·94)	<0·01	305/54,622 (5·6)	0·90 (0·73-1·10)	0·31	0·50
dCCB	525/110,788 (4·7)	0·81 (0·70-0·93)	<0·01	239/46,525 (5·1)	0·84 (0·67-1·04)	0·11	0·86
Thiazide diuretic	825/177,743 (4·6)	0·84 (0·73-0·97)	0·01	367/71,058 (5·2)	0·88 (0·71-1·10)	0·27	0·63
Mortality							
ACEi	767/121,296 (6·3)	Reference		548/65,180 (8·4)	Reference		
ARB	500/96,359 (5·2)	0·86 (0·76-0·96)	0·01	309/41,317 (7·5)	0·92 (0·80-1·06)	0·26	0·45
BB	1007/166,189 (6·1)	1·00 (0·89-1·12)	0·95	510/54,622 (9·3)	1·21 (1·03-1·42)	0·02	0·06
dCCB	772/110,788 (7·0)	1·10 (0·97-1·25)	0·13	441/46,525 (9·5)	1·24 (1·04-1·47)	0·02	0·33
Thiazide diuretic	924/177,743 (5·2)	0·80 (0·70-0·90)	<0·01	496/71,058 (7·0)	0·79 (0·66-0·95)	0·01	0·97

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.

Supplementary Table 11. Subgroup stratified for dyslipidaemia status

		No dyslipidaemia		Dyslipidaemia			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Major adverse events							
ACEi	3493/145,938 (23·9)	Reference		944/40,538 (23·3)	Reference		
ARB	2164/106,623 (20·3)	0·87 (0·82-0·92)	<0·01	608/31,052 (19·6)	0·85 (0·76-0·94)	0·02	0·73
BB	4271/173,751 (24·6)	1·06 (1·00-1·13)	0·04	1141/47,061 (24·3)	1·07 (0·96-1·21)	0·22	0·87
dCCB	2946/122,856 (24·0)	0·94 (0·89-1·01)	0·08	781/34,457 (22·7)	0·86 (0·75-0·97)	0·02	0·18
Thiazide diuretic	3810/196,536 (19·4)	0·72 (0·67-0·77)	<0·01	980/52,265 (18·8)	0·69 (0·60-0·78)	<0·01	0·55
Acute myocardial infarction							
ACEi	738/145,938 (5·1)	Reference		218/40,538 (5·4)	Reference		
ARB	370/106,623 (3·5)	0·72 (0·63-0·82)	<0·01	126/31,052 (4·1)	0·77 (0·61-0·97)	0·03	0·64
BB	1059/173,751 (6·1)	1·50 (1·31-1·71)	<0·01	301/47,061 (6·4)	1·49 (1·14-1·94)	<0·01	0·99
dCCB	480/122,856 (3·9)	0·56 (0·48-0·65)	<0·01	168/34,457 (4·9)	0·61 (0·45-0·81)	<0·01	0·68
Thiazide diuretic	557/196,536 (2·8)	0·34 (0·29-0·40)	<0·01	165/52,265 (3·2)	0·32 (0·23-0·43)	<0·01	0·70
Stroke							
ACEi	983/145,938 (6·7)	Reference		275/40,538 (6·8)	Reference		
ARB	680/106,623 (6·4)	0·95 (0·86-1·05)	0·31	186/31,052 (6·0)	0·85 (0·70-1·03)	0·09	0·32
BB	1195/173,751 (6·9)	1·03 (0·92-1·15)	0·60	329/47,060 (7·0)	1·01 (0·81-1·25)	0·96	0·85
dCCB	921/122,856 (7·5)	1·10 (0·98-1·24)	0·10	232/34,457 (6·7)	0·83 (0·66-1·06)	0·14	0·06
Thiazide diuretic	1200/196,536 (6·1)	0·86 (0·76-0·97)	0·01	327/52,265 (6·3)	0·84 (0·66-1·07)	0·16	0·89

Supplementary Table 11. Subgroup stratified for dyslipidaemia status *(Continued)*

		No dyslipidaemia		Dyslipidaemia			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Dementia							
ACEi	790/145,938 (5·4)	Reference		201/40,538 (5·0)	Reference		
ARB	506/106,623 (4·8)	0·86 (0·77-0·97)	0·01	136/31,052 (4·4)	0·85 (0·68-1·07)	0·17	0·96
BB	870/173,751 (5·0)	0·84 (0·74-0·94)	<0·01	218/47,060 (4·6)	0·84 (0·66-1·07)	0·15	0·99
dCCB	595/122,856 (4·8)	0·78 (0·69-0·90)	<0·01	169/34,457 (4·9)	0·92 (0·70-1·19)	0·52	0·33
Thiazide diuretic	956/196,536 (4·9)	0·84 (0·73-0·96)	<0·01	236/52,265 (4·5)	0·88 (0·67-1·14)	0·32	0·78
Mortality							
ACEi	1055/145,938 (7·2)	Reference		260/40,538 (6·4)	Reference		
ARB	643/106,623 (6·0)	0·88 (0·79-0·97)	0·01	166/31,052 (5·4)	0·90 (0·74-1·10)	0·30	0·86
BB	1215/173,751 (7·0)	1·04 (0·94-1·15)	0·47	302/47,061 (6·4)	1·10 (0·89-1·37)	0·37	0·59
dCCB	996/122,856 (8·1)	1·18 (1·05-1·32)	<0·01	217/34,457 (6·3)	0·99 (0·78-1·25)	0·92	0·12
Thiazide diuretic	1160/196,536 (5·9)	0·80 (0·71-0·90)	<0·01	260/52,265 (5·0)	0·74 (0·58-0·94)	0·01	0·56

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.

Supplementary Table 12. Subgroup stratified by number of simultaneously used classes

	Two or less			Three or more			
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**P-int**
Major adverse events							
ACEi	2921/127126 (23·0)	Reference		1583/61,841 (25·6)	Reference		
ARB	1577/84184 (18·7)	0·83 (0·80-0·91)	<0·001	1195/53,492 (22·3)	0·88 (0·81-0·95)	<0·01	0·70
BB	3317/139086 (23·9)	1·06 (1·01-1·13)	0·03	2095/81,726 (25·6)	1·08 (0·94-1·25)	0·28	0·99
dCCB	1887/82298 (22·9)	0·94 (0·88-1·01)	0·07	1840/75,015 (24·5)	0·90 (0·78-1·02)	0·11	0·32
Thiazide diuretic	2701/154264 (17·5)	0·73 (0·68-0·78)	<0·001	2089/94,537 (22·1)	0·67 (0·58-0·77)	<0·01	0·21
Acute myocardial infarction							
ACEi	586/127126 (4·6)	Reference		389/61,8441 (6·3)	Reference		
ARB	235/84184 (2·8)	0·69 (0·60-0·81)	<0·001	162/37,979 (4·3)	0·78 (0·63-0·96)	0·02	0·37
BB	840/139086 (6·0)	1·53 (1·35-1·75)	<0·001	359/57,510 (6·2)	1·37 (0·94-2·02)	0·10	0·40
dCCB	259/82298 (3·2)	0·58 (0·49-0·68)	<0·001	240/50,836 (4·7)	0·55 (0·39-0·77)	<0·01	0·44
Thiazide diuretic	315/154264 (2·0)	0·35 (0·30-0·41)	<0·001	251/69,829 (3·6)	0·29 (0·21-0·41)	<0·01	0·19
Stroke							
ACEi	800/127126 (6·3)	Reference		473/61,841 (7·7)	Reference		
ARB	455/84184 (5·4)	0·89 (0·79-1·00)	0·04	259/37,979 (6·8)	1·03 (0·87-1·22)	075	0·24
BB	849/139086 (6·1)	0·98 (0·88-1·09)	0·65	437/57,510 (7·6)	1·40 (1·06-1·86)	0·02	0·10
dCCB	555/82298 (6·7)	1·07 (0·95-1·21)	0·27	360/50,836 (7·1)	1·16 (0·89-1·51)	0·29	0·75
Thiazide diuretic	832/154264 (5·4)	0·87 (0·77-0·98)	0·02	455/69,829 (6·5)	0·95 (0·72-1·26)	0·44	0·81

Supplementary Table 12. Subgroup stratified by number of simultaneously used classes *(Continued)*

	Two or less			Three or more			
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**P-int**
Dementia							
ACEi	697/127126 (5·5)	Reference		311/61,841 (5·0)	Reference		
ARB	415/84184 (4·9)	0·88 (0·78-0·99)	0·04	165/37,979 (4·3)	0·85 (0·69-1·04)	0·12	0·55
BB	710/139086 (5·1)	0·86 (0·76-0·97)	0·01	268/57,510 (4·6)	0·77 (0·55-1·09)	0·15	0·41
dCCB	408/82298 (5·0)	0·81 (0·70-0·92)	0·002	247/50,836 (4·9)	0·86 (0·62-1·21)	0·39	0·86
Thiazide diuretic	770/154264 (5·0)	0·87 (0·77-0·99)	0·03	314/69,829 (4·5)	0·81 (0·56-1·16)	0·25	0·43
Mortality							
ACEi	889/127126 (7·0)	Reference		443/61,841 (7·2)	Reference		
ARB	488/84184 (5·8)	0·89 (0·79-0·99)	0·03	244/37,979 (6·4)	0·93 (0·78-1·10)	0·39	0·84
BB	954/139086 (6·9)	1·05 (0·95-0·16)	0·36	414/57,510 (7·2)	1·13 (0·85-1·50)	0·41	0·65
dCCB	684/82298 (8·3)	1·17 (1·05-1·31)	0·01	376/50,836 (7·4)	1·08 (0·82-1·43)	0·57	0·59
Thiazide diuretic	816/154264 (5·3)	0·78 (0·70-0·88)	<0·001	451/69,829 (6·5)	0·91 (0·68-1·22)	0·52	0·30

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.

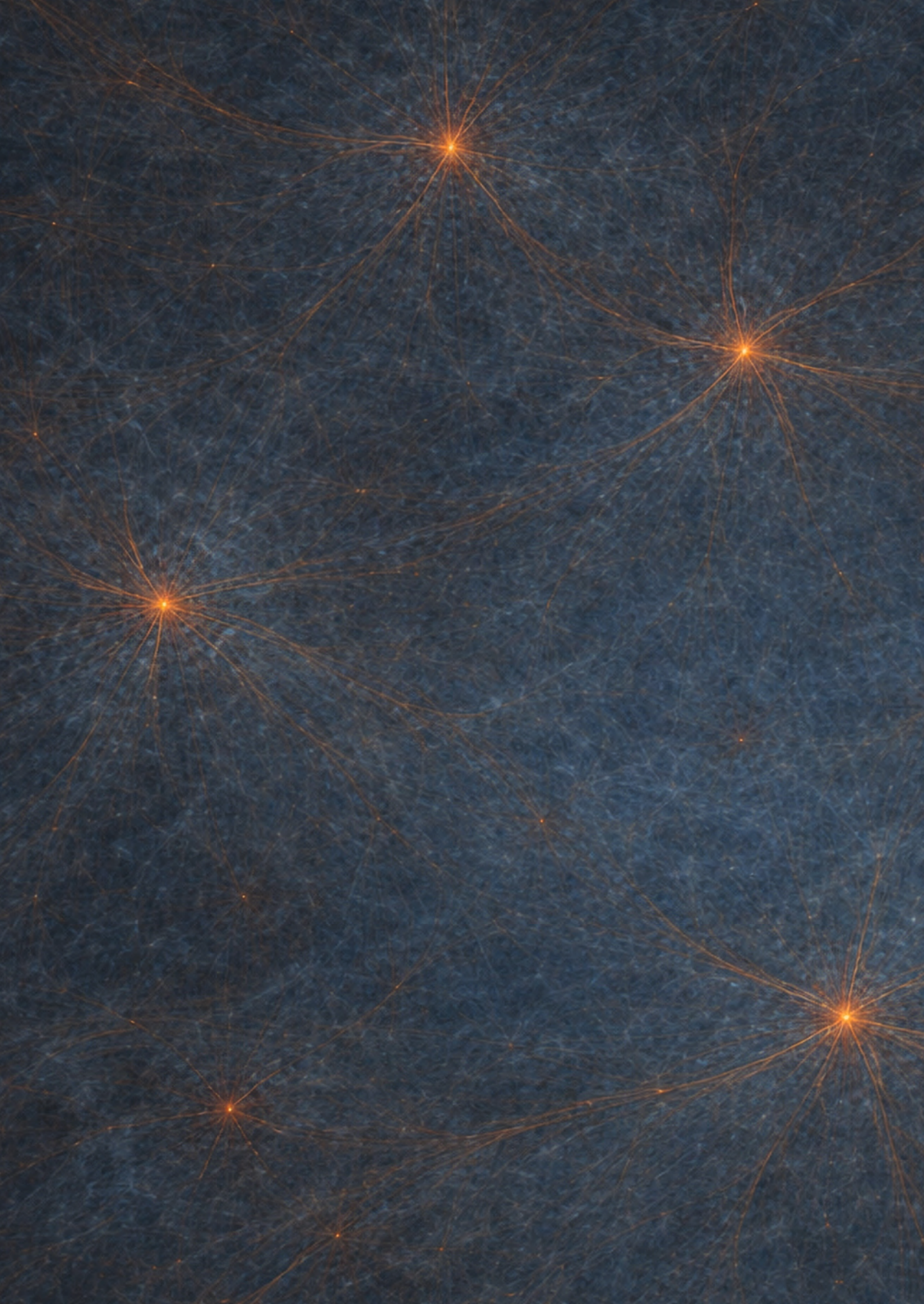
Supplementary Table 13. Subgroup stratified for period in time (<2015 versus ≥2015)

		<2015		≥2015			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Major adverse events							
ACEi	3565/138,695 (25·7)	Reference		872/47,781 (18·3)	Reference		
ARB	2338/105,359 (22·2)	0·88 (0·83-0·93)	<0·01	434/32,317 (13·4)	0·79 (0·70-0·89)	<0·01	0·05
BB	4567/177,247 (25·8)	1·05 (1·00-1·12)	0·07	845/43,565 (19·4)	1·09 (0·97-1·22)	0·16	0·60
dCCB	2949/111,718 (26·4)	0·95 (0·89-1·01)	0·10	778/45,595 (17·1)	0·89 (0·79-1·01)	0·07	0·26
Thiazide diuretic	4100/194,824 (21·0)	0·74 (0·69-0·79)	<0·01	690/53,977 (12·8)	0·61 (0·54-0·70)	<0·01	0·02
Acute myocardial infarction							
ACEi	733/138,695 (5·3)	Reference		223/47,781 (4·7)	Reference		
ARB	405/105,359 (3·8)	0·77 (0·68-0·88)	<0·01	91/32,317 (2·8)	0·60 (0·47-0·78)	<0·01	0·06
BB	1101/177,247 (6·2)	1·49 (1·30-1·70)	<0·01	269/43,565 (6·0)	1·40 (1·18-1·81)	<0·01	0·70
dCCB	499/111,718 (4·5)	0·62 (0·54-0·73)	<0·01	149/45,595 (3·3)	0·46 (0·34-0·61)	<0·01	0·05
Thiazide diuretic	592/194,824 (3·0)	0·35 (0·30-0·41)	<0·01	130/53,977 (2·4)	0·28 (0·21-0·38)	<0·01	0·26
Stroke							
ACEi	1004/138,695 (7·2)	Reference		254/47,781 (5·3)	Reference		
ARB	726/105,359 (6·9)	0·94 (0·85-1·04)	0·25	140/32,317 (4·3)	0·86 (0·70-1·07)	0·18	0·35
BB	1314/177,247 (7·4)	1·05 (0·94-1·17)	0·37	210/43,565 (4·8)	0·88 (0·70-1·10)	0·25	0·17
dCCB	884/111,718 (7·9)	1·02 (0·91-1·15)	0·72	269/45,595 (5·9)	1·17 (0·94-1·46)	0·16	0·34
Thiazide diuretic	1298/194,824 (6·7)	0·88 (0·78-0·99)	0·04	229/53,977 (4·2)	0·75 (0·59-0·96)	0·02	0·31

Supplementary Table 13. Subgroup stratified for period in time (<2015 versus ≥2015) *(Continued)*

		<2015		≥2015			P -int
AHM class	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	**Cases/PY, n(‰)**	**HR (95%CI)**	**P-value**	
Dementia							
ACEi	852/138,695 (6·1)	Reference		139/47,781 ()	Reference		0·99
ARB	564/105,359 (5·4)	0·86 (0·77-0·96)	<0·01	78/32,317 (2·4)	0·88 (0·66-1·18)	0·40	0·71
BB	963/177,247 (5·4)	0·82 (0·73-0·92)	<0·01	125/43,565 (2·9)	0·87 (0·68-1·16)	0·34	0·41
dCCB	649/111,718 (5·8)	0·84 (0·74-0·96)	<0·01	115/45,595 (2·5)	0·74 (0·55-1·01)	0·05	0·69
Thiazide diuretic	1065/194,824 (5·5)	0·85 (0·74-0·96)	0·01	127/53,977 (2·4)	0·79 (0·58-1·07)	0·13	
Mortality							
ACEi	1048/138,695 (7·6)	Reference		267/47,781 (5·6)	Reference		
ARB	680/105,359 (6·5)	0·90 (0·81-0·99)	0·04	129/32,317 (4·0)	0·81 (0·65-1·01)	0·06	0·29
BB	1260/177,247 (7·1)	1·03 (0·93-1·15)	0·57	257/43,565 (5·9)	1·17 (0·96-1·44)	0·13	0·25
dCCB	959/111,718 (8·6)	1·16 (1·03-1·31)	0·01	254/45,595 (5·6)	1·07 (0·87-1·33)	0·50	0·44
Thiazide diuretic	1209/194,824 (6·2)	0·83 (0·74-0·93)	<0·01	211/53,977 (3·9)	0·69 (0·55-0·86)	<0·01	0·19

Cox regression with time varying covariates. HRs represent model 2, adjusting for age, sex, potassium-sparing agents, diabetes, dyslipidaemia, and number of AHM classes used simultaneously and were calculated according.



Chapter V

General Practitioners' Perspectives, Preferences, and Practices in Prescribing Antihypertensive Medication in Primary, Uncomplicated Hypertension

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ABSTRACT

Background: International guidelines consider most antihypertensive medication (AHM) classes as equivalent options for treating primary hypertension. However, limited research has examined whether general practitioners (GPs) share this view or have specific prescribing preferences. Understanding GPs' perspectives is crucial for identifying how guidelines are implemented in daily practice. This study explores the perspectives, preferences, and prescribing practices of Dutch GPs regarding AHM classes in patients with primary hypertension who have no cardiovascular comorbidities or diabetes.

Methods: We conducted a qualitative study with semi-structured interviews among Dutch GPs. Interviews were audio-recorded, transcribed verbatim, and thematically analyzed.

Results: We interviewed 18 Dutch GPs (56% female) and identified three key themes: contextual factors when initiating treatment, preferences for AHM classes, and considerations on combination therapy. GPs consider lifestyle modifications, patient age, and initial blood pressure (BP) when deciding on treatment. Most GPs do not view all AHM classes as interchangeable, with their preferences shaped by perceived efficacy, side effects, and patient-specific factors, including ethnicity and patient preferences. GPs often favour a gradual titration approach, starting with one class before adjusting the dosage or adding another.

Conclusion: GPs adopt a multifaceted, patient-centred approach to hypertension, prioritising lifestyle interventions and weighing short-term risks against long-term benefits. We identified several discrepancies between guideline recommendations and everyday practice—particularly regarding the perceived non-equivalence of AHM classes and limited support for initiating combination therapy. Incorporating GPs' perspectives into guideline development may lead to more practical, tailored recommendations that improve adherence and patient outcomes in real-world care.

BACKGROUND

In the pharmacological treatment of (perceived) primary, uncomplicated hypertension, defined as hypertension without an identifiable secondary cause and without diabetes or cardiovascular comorbidity, most international guidelines consider several antihypertensive medication (AHM) classes to be equivalent first-line options. In this context, e*quivalence* refers to comparable average efficacy in lowering blood pressure and reducing cardiovascular risk at the population level. These classes include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), (dihydropyridine) calcium channel blockers (CCBs), (thiazide) diuretics, and, to a lesser extent, beta-blockers.[1-3] Historically, diuretics and beta-blockers were the most commonly used AHM classes[4], but more recently, CCBs and renin-angiotensin system (RAS)-inhibitors, particularly ACE-inhibitors, have gained popularity.[5-7]

Although guidelines recommend that general practitioners (GPs) select from these equivalent classes, there is a striking lack of research on whether GPs actually perceive these medications as interchangeable—that is, whether they feel free to select any class without a specific guideline-driven rationale—or whether they hold specific preferences when managing primary, uncomplicated hypertension. Variations in prescription patterns may arise based on factors such as patient age, blood pressure (BP) levels, or side effects associated with certain AHM classes.

Exploring clinical expertise—a cornerstone of evidence-based medicine[8]—could offer valuable insights into how GPs implement guidelines in practice, helping to explain observed prescription patterns, and potentially informing future guideline adaptations. In this study, we aimed to investigate the perspectives, preferences, and practices of Dutch GPs regarding the prescription of AHM classes for patients with primary, uncomplicated hypertension.

METHODS

Participants

We conducted semi-structured interviews with 18 Dutch GPs[9], recruited through personal networks, snowball sampling (where interviewees recommended colleagues with differing views), and random emails to GP practices. This approach ensured a purposive sample based on sex, years of experience, practice location (urban vs. rural), and practice size.

Initially, 41 GPs received an email with study details, followed by two reminders. Of these, 15 (37%) did not respond, and 8 (20%) declined, primarily due to time constraints. The sample size was guided by data saturation, reached when consecutive interviews yielded no new insights.

Data Collection, Coding, and Analysis

Between February 2021 and December 2023, two physician-PhD students (JLS and MPW, both male) conducted semi-structured interviews using an interview guide (*Supplementary Methods 1*). Interviewers and interviewees were aware of each other's profession. The interview guide focused on the perspectives, preferences and practices in treating newly diagnosed primary, uncomplicated hypertension, exploring specific preferences for AHM classes, and considerations on combination therapy (defined in this manuscript as the simultaneous use of two AHM classes, either as separate pills or as a fixed-dose combination tablet). At the time of the interviews, earlier versions of the hypertension guidelines—which are part of a broader Cardiovascular Risk Management Guideline—were still in effect.[1,3] By the time of manuscript preparation, the guidelines had been updated.[10,11] However, some of the forthcoming changes were already addressed during the interviews. The topics of AHM-preferences by ethnic background and decisions on discontinuing treatment were not explored, as they were previously investigated.[12,13]

JLS and MPW conducted the first two interviews together to standardise their interviewing techniques. During data collection, they refined the interview guide to improve question clarity and outcomes. Interviews lasted 40–75 minutes; no repeat interviews were deemed necessary. Due to COVID-19 restrictions, only six interviews were conducted in person; the remaining twelve were remote: eight via video conferencing, and four by phone. All interviews were audio-recorded with permission and transcribed verbatim; no field notes were taken. JLS, MPW, and senior researcher EPMvC periodically reviewed findings to identify key themes.

The authors coded the interviews and conducted a thematic analysis following Braun and Clarke's six-phase framework (*Supplementary Methods 2*)[14], using MaxQDA software.[15] The study was reported in accordance with COREQ-guidelines (*Supplementary Methods 3*).[16]

RESULTS

We interviewed 18 GPs (**Table 1**), of whom 10 (56%) were female. Their experience ranged from 1 to 37 years, with an average of 15.7 years and a median of 9.5 years. Eight (44%) worked in rural areas, and 7 (39%) operated solo practices. Individual characteristics of participating GPs are detailed in *Supplementary Table 1*.

Table 1. General Practitioners' Characteristics (n = 18).

Sex (women)	10 (56%)
Years of Experience as a GP	
0-15 years	11 (61%)
>15 years	7 (39%)
Median (IQR)	10 years (7-20)
Mean (range)	14 years (1-37)
Current Practice Setting	
Urban	10 (56%)
Rural	8 (44%)
Current Practice Size	
Small	7 (44%)
Large	11 (61%)

Small practices were defined as those with one or two GPs, while large practices consisted of three or more. Abbreviations: IQR = interquartile range; GP = general practitioner.

Our thematic analysis identified three main themes: 1. Contextual factors when initiating treatment, 2. AHM class preferences, and 3. Considerations on combination therapy.

1. Contextual Factors when Initiating Treatment

When managing newly diagnosed primary, uncomplicated hypertension, several contextual factors—including lifestyle behaviours, age, initial BP levels, and patient preferences—guide GPs in deciding how to initiate treatment.

Lifestyle Modifications

GPs emphasised the importance of lifestyle modifications, particularly for younger patients, as the first-line approach to managing hypertension. They prioritised changes like dietary improvements, increased physical activity, and weight management to postpone or potentially eliminate the need for medication.

> "Particularly with younger patients, I tend to prioritise lifestyle changes first, as I prefer not to over-medicalise people."**-GP9**

Even after initiating AHM, GPs continued to emphasise lifestyle modifications as a key component of hypertension management.

> "I believe lifestyle changes should always be prioritised. When blood pressure lowers, that's when lifestyle adjustments are crucial. With effort, you might be able to reduce or even stop blood pressure medication."**-GP11**

However, in older patients, maintaining lifestyle changes appeared more difficult due to the increased likelihood of physical limitations.

> "And the elderly, who already face reduced mobility due to osteoarthritis or other conditions, I think: yes, lifestyle interventions, at least in terms of exercise, offer fewer opportunities there."**-GP11**

Age

GPs were generally reluctant to initiate AHM in both older and younger patients, weighing the short-term risks of side effects and the lifelong commitment to medication against the less tangible long-term cardiovascular benefits. For older adults, GPs prioritised overall vitality and activity levels over chronological age, tailoring strategies for fit and active individuals compared to those who were frail.

> "It's very much a discussion with the patient, but if they're a lively individual, you might think: this person could still have another 15 years ahead. If they're more vulnerable, and you think lowering their blood pressure might just make them dizzy and cause a fall, then you're doing more harm than good."**-GP14**

GPs had differing views on starting AHM in younger patients. Some noted that younger individuals may lack vascular damage or comorbidities but emphasised the long-term risks of untreated hypertension.

> "But if someone is only 35 and has a systolic blood pressure of 165mmHg, I will treat them anyway (…) they're still putting strain on their blood vessels for another 30 years."**-GP8**

Others, however, felt that initiating AHM at a younger age requires strong justification due to the lifelong commitment to medication, stressing the need to carefully balance the potential benefits with the long-term implications.

> "Age is definitely important, because it's a big step to put someone who's, say, 40 years old on AHM—they'll have to take it for the rest of their life. I find that quite significant."**-GP9**

Initial BP Levels

GPs' decisions on hypertension management were strongly influenced by initial BP readings. Many viewed a systolic BP over 180 mmHg as a clear indication to start AHM immediately, bypassing lifestyle modifications.

> "If a young person has a systolic blood pressure consistently above 180mmHg, that's a clear indication for treatment, even if their overall 10-year risk isn't high."**-GP6**

For lower BP values, GPs weighed whether to start AHM or delay treatment to first assess the outcomes of lifestyle modification.

Patient Preferences

According to the interviewees, some patients preferred medication over lifestyle modifications due to concerns about cardiovascular risk, viewing it as a more immediate and reliable solution.

> "Yes. Some people are very clear: 'No, just give me the tablets, I really don't want to take this risk.' And that's perfectly fine."**-GP8**

Others found medication more convenient than the effort required for lifestyle changes to lower BP.

> "But I also have people who seem disengaged [when discussing lifestyle modifications], so I'll ask: 'Or would you prefer a tablet?' and they'll say, 'Yes, just give me that. I find it easier.' That's perfectly fine with me as well. It's about the end goal."**-GP7**

In some cases, rapid medication use was deemed necessary, such as before surgeries requiring controlled BP.

> "And sometimes it gets a bit more complicated. You hear, 'I need surgery in a month, and my BP is far too high. It needs to come down now! Otherwise, my surgery won't go ahead.' In such situations, it's sometimes necessary to prescribe medication straight away."**-GP18**

Conversely, patients opted to delay medication, focusing on lifestyle changes first, with GPs offering guidance or referrals to specialists like dietitians.

> "People tell me: 'I want to try it myself first.' And that's fine; I'll at least direct them to [the national GP-run patient information website] and say: 'Have a read through that and see what you can do about your lifestyle.' I also offer to involve a dietitian if they are overweight."**-GP13**

2. AHM class preferences

Only a few GPs agreed that the five main AHM classes were truly interchangeable options for initiating treatment in newly diagnosed primary, uncomplicated hypertension.

> "Yes, in principle. It varies from person to person, but that's true for nearly all medications, really."**-GP8**

However, most interviewed GPs had specific preferences or avoided certain classes in particular situations. Several GPs acknowledged that aspects of earlier guidelines—such as the previously prominent position of diuretics—still influenced their current prescribing practices.

> "I still have a tendency to prescribe diuretics"-**GP1**

Many preferred starting with ACE-inhibitors, especially for younger patients without comorbidities, mentioning their nephroprotective properties and manageable side effects. ARBs were generally reserved for patients who experienced side effects from ACE-inhibitors. CCBs were favoured for patients with higher initial BP readings, as they were perceived to be faster-acting and more potent. Additionally, GPs also preferred CCBs for patients of African descent. In other cases, CCBs were generally avoided as a first choice due to side effects like edema. Diuretics, once a go-to option, were typically added as a second-line treatment or reserved for milder hypertension. Their decline in popularity was tied to concerns about skin cancer and dehydration during hotter summers, particularly in older individuals. Beta-blockers, which were the second most popular class two decades ago, were no longer a first choice for any

of the interviewed GPs. Main reasons were their perceived limited antihypertensive effect and side effects, particularly in younger patients who experienced lower exercise tolerance. However, beta-blockers were still occasionally preferred when hypertension is accompanied by anxiety or palpitations.

Some GPs appreciated the guideline recommendations that offered greater flexibility in choosing an antihypertensive class for patients with primary, uncomplicated hypertension, while others expressed a desire for more explicit guidance.

> "I feel that if there's no clear-cut preference, it gives me the freedom to handle it in my own way—which I really appreciate."-**GP12**

> "I would actually welcome a bit more guidance, even though I used to regularly deviate from the old guidelines."-**GP11**

All other quotes related to this theme are presented in **Table 2**, categorised by AHM class

Table 2. General Practitioners Quotes on AHM class characteristics.

	AHM classes			
	RAS-inhibitors	**Calcium channel blockers**	**Diuretics**	**Beta-blockers**
Specific Beneficial Effects	"You increasingly hear that ACE inhibitors are better in the long run for additional benefits, such as protecting kidney function and improving cardiovascular outcomes."-**GP12**	"So, if you have very high blood pressure that needs to be lowered quickly, in my experience, a calcium channel blocker often works best."**-GP3**	"And if we're talking about someone who only needs a small amount, I might start with hydrochlorothiazide."**-GP7**	"Yes, but mainly a beta-blocker, and only occasionally for an 85-year-old woman who's extremely anxious, which is causing high blood pressure."**-GP6**
Side Effects	"Previously, I used ACE inhibitors more frequently, but I've noticed how often people experience coughing issues, so I end up switching to ARBs quite regularly."**-GP4**	"No, I think the reason for using calcium channel blockers later on is indeed because we often see peripheral oedema."**-GP2** "With amlodipine, the side effect profile is broader, which makes it less straightforward to advise patients and somewhat harder to manage."**-GP3**	"And especially now, with the changing climate and much warmer summers (…) diuretics used to be the first choice, but I find them less favourable for elderly patients, particularly with the risk of dehydration."**-GP16**	"It used to be the first choice, but many people actually experience issues with the reduced heart rate, particularly those who are still active—they struggle with physical activities. It's also not ideal for older adults due to the slow pulse and an increased risk of falling. So, unless a patient has arrhythmias, I generally wouldn't prescribe beta-blockers anymore."**-GP16**
Other Considerations	"ARBs, yes, I prescribe them to people—for instance, those with migraines or who experience side effects from other antihypertensive medication classes."**-GP16**	"And I prefer prescribing CCBs to Creole and African patients. They're generally more effective than diuretics, which are regarded as equivalent in the guidelines for these ethnic groups."**-GP10**	"There was that issue with hydrochlorothiazide and basal cell carcinomas a while back – that's something I keep in mind. These are medications people have to take for their entire lives."**-GP12**	"(…) it also causes more side effects, and I just want to encourage people to exercise, participate in sports, and so on."**-GP9** "Definitely not with the beta-blocker; they're less effective."**-GP16**

Abbreviations: AHM = antihypertensive medication; RAS = renin-angiotensin system; ACE = angiotensin-converting enzyme; GP = general practitioner; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.

3. Considerations on combination therapy

Most GPs found that, with some persuasion, patients were generally willing to accept adding a second AHM-class rather than increasing the dosage when hypertension was not yet adequately controlled.

> "I don't leave much room for discussion in that regard. A combination [of two classes] works much better for me than simply increasing the dosage of one. And if you explain to them that it's scientifically proven that multiple medications are more effective than increasing the dosage, they generally accept this approach."**-GP3**

However, some acknowledged that persuading patients to take an additional medication can sometimes be challenging.

> "But it is often harder to motivate people; they prefer to go from Lisinopril 10 to 20mg rather than take an additional tablet, and I can see why they feel that way."**-GP2**

When asked whether they routinely followed the guideline recommendation to add a second antihypertensive class—rather than increasing the dose of the initial drug—when blood pressure remained insufficiently controlled, GPs' gave mixed responses. Some preferred to increase dosages before introducing another class, either due to their own preference or that the patient. This was often because some GPs started with a marginally effective dosage to assess tolerance, opting to increase the dose before considering a second class.

> "Well, it depends a bit. Often, we start by increasing the dose and then add something. Monotherapy is often more acceptable to the patient than starting multiple medications at once. To be honest, I wouldn't want to take two tablets every day either if I could manage with just one."-**GP15**

One of the upcoming changes in the Dutch hypertension guideline at the time was the recommendation to initiate dual-class antihypertensive therapy in patients with elevated initial BP values (≥150 mmHg).[10] When discussing this proposed update, GPs generally acknowledged that a single AHM class would likely be insufficient in cases of very high initial blood pressure. However, only a few stated that they already initiated or intended to initiate treatment with two classes simultaneously. Most expressed a preference to start with one class and then, after a few weeks, evaluate the need for a second, aligning well with the continuity of care in primary care settings.

"I think few GPs are accustomed to initiating two classes at the same time; at least, I don't see this happening any time soon in my workplace."**-GP17**

> "No, I've never done that. If the blood pressure is very high and doesn't decrease with the first antihypertensive medication after a week to ten days, then I might quickly add a second one."**-GP8**

Concerns about a rapid BP decline causing more side effects, potentially negatively affecting adherence, also influenced this approach.

> "If you prescribe too many AHM, someone might collapse, and then treatment adherence is completely lost. I'll have them return a bit sooner."**-GP 16**

Additionally, starting with one class makes it easier to identify side effects.

> "No, I actually never do that. Because if there are side effects, you won't know exactly which medication is causing them."**-GP17**

Still, in some situations, some GPs did already initiate treatment with two classes at once.

> "Well, if I already have the impression that one AHM won't be enough, then very occasionally I do prescribe a fixed combination tablet and tell them to take half for the first two weeks. If all goes well, then they take the full tablet."**-GP10**

DISCUSSION

This study explored how Dutch GPs manage newly diagnosed primary, uncomplicated hypertension, identifying three key themes: contextual factors when initiating treatment, AHM class preferences, and considerations on combination therapy.

Contextual factors when initiating treatment included lifestyle modifications, patient age, initial BP, and patient preferences. GPs prioritised lifestyle changes, particularly for younger patients, to avoid early medicalisation, balancing short-term side effects with long-term benefits. Contrary to the guideline's stance that AHM classes are largely equivalent for treating primary hypertension, most GPs in our study did not consider them interchangeable. Their preferences were shaped by perceived efficacy, side effects, patient-specific characteristics, and earlier guideline recommendations.

Likewise, the proposed recommendation to initiate treatment with two AHM classes simultaneously, a pending guideline change at the time of the interviews, was met with limited enthusiasm. This raises questions about how easily such recommendations will be adopted in practice, although attitudes may shift over time. Interviewed GPs often preferred a stepped approach, starting with monotherapy to better identify side effects and promote shared decision-making. They also voiced concerns that a sudden BP drop initiating dual therapy could undermine patient adherence. These findings are consistent with a 2007 phone survey among GPs, that found a similar preference for monotherapy as initial treatment.[17] Rather than dismissing these concerns, acknowledging them in the guideline, with room for initial monotherapy followed by timely escalation, may support more effective uptake of recommendations while still promoting evidence-based care.

Interviewed GPs generally preferred ACE inhibitors for younger patients. Although this was not explicitly confirmed in the data, their choices may reflect the influence of earlier guidelines, particularly the AB/CD rule, which recommended ACE inhibitors or beta-blockers for younger, non-black patients, and calcium channel blockers or diuretics for older or black patients. ARBs were mainly prescribed for patients intolerant to ACE inhibitors, likely due to their more recent introduction and less established role in practice.[18] We expected to find other prescribing patterns, such as increased use of thiazide diuretics and beta-blockers among GPs trained under earlier guidelines, but no consistent trends were observed. Consistent with guidelines, CCBs were preferred for patients of African ancestry. They were also commonly used in patients with higher initial blood pressure, which is not supported by current guidelines. Meanwhile, thiazide diuretics and beta-blockers have declined in popularity as first-line options.

This decreased popularity aligns with data confirming a decline in the use of diuretics and beta-blockers.[5-7,19] Several GPs attributed their shift away from thiazide diuretics to concerns about the link between these drugs, particularly hydrochlorothiazide, and an increased risk of skin cancer,[20,21] prompting regulatory agencies, including the FDA, to issue warnings.[22-24] In response, the Netherlands saw a 45% reduction in hydrochlorothiazide prescriptions the following year.[25] Meanwhile, beta-blockers were almost entirely avoided due to perceived limited effectiveness and negative impact on exercise tolerance. Although beta-blockers were still a first-line option in prevailing guidelines,[1,3] concerns have recently emerged about their clinical inferiority and burdensome side effects,[11,26] concerns echoed by the GPs in this study. RAS-inhibitors have gained popularity over the last decades, reflected by increasing prevalence.[27] However, GPs did not provide a clear rationale for preferring ACE-inhibitors over ARBs;

factors like longer availability, stronger evidence, and, until recently, lower cost likely influenced this preference.[28] Regarding CCBs, several interviewees perceived them as more effective, achieving greater or faster BP reductions compared to other classes. Although CCBs are commonly used in hypertensive emergencies, there is no clear evidence that they outperform other classes in the treatment of primary hypertension.[1-3]

Physicians' views and experiences are important for understanding the challenges GPs face in everyday hypertension management. Evidence indicates that adherence to updated hypertension guidelines remains suboptimal, highlighting the need for qualitative studies to uncover the underlying reasons.[29-31] Recently, the European Society of Cardiology launched an initiative to improve guideline adoption in primary care, further emphasising the importance of understanding hypertension management practices in this context.[32] Nonetheless, there remains a notable lack of qualitative research exploring the perspectives, preferences, and practices of GPs and other treating physicians on hypertension management.

Strengths and limitations

To our knowledge, this is the first qualitative study to explore GPs' insights when prescribing AHM for primary, uncomplicated hypertension. Understanding their decision-making processes can offer valuable insights into the application of clinical guidelines in practice, potentially guiding future adaptations to enhance their relevance and usability.

Despite the challenge of capturing a full range of perspectives in qualitative research, we believe our interviews included a diverse sample of Dutch GPs with a variety of backgrounds, practice types, and levels of experience.

Some potential limitations need consideration when interpreting our results. Several interviews were conducted via telephone due to physician preferences and COVID-19 restrictions, potentially limiting non-verbal communication. However, we believe this impact was minimal, as the quality and openness of these audio-only interviews were comparable to those conducted in person or via video. With less than half of the invited GP participating, responder bias may have been introduced, as those more interested in hypertension management may have been more likely to respond. Finally, this study focused on GPs management of newly diagnosed hypertension, while follow-up care is often handled by practice nurses. Future studies incorporating nurses' perspectives could provide a more comprehensive understanding of hypertension management in primary care.

Conclusion

GPs navigate a multifaceted, patient-centred decision-making process in managing primary, uncomplicated hypertension, prioritising lifestyle interventions while balancing short-term risks, such as medicalisation, potential side effects, and non-adherence, against long-term cardiovascular benefits. This study identified several discrepancies between clinical practice and guideline recommendations, particularly regarding the perceived non-equivalence of AHM classes and the reluctance to initiate hypertension treatment with combination therapy, which GPs neither supported nor consistently followed. Acknowledging healthcare professionals' perspectives in updating hypertension guidelines may enhance adherence while still promoting new evidence. Further qualitative research, for instance further zooming in on GP's views on combination therapy, could help bridge the gap between guidelines and real-world practice, leading to more tailored recommendations that enhance adherence and ultimately improve patient outcomes.

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SUPPLEMENTARY MATERIAL

Supplementary Methods 1. Interview guide.

Part I: Background
To gain a comprehensive understanding of your work experience and approach for this study, I'd like to begin by asking you some questions about yourself and your practice.

- Could you tell me a bit about yourself and your background as a general practitioner?
  - (Years of experience, type of practice—urban or rural, solo or group practice, experience prior to GP training, additional specializations, socioeconomic status and composition of your neighbourhood)
- What does hypertension management look like in your practice? (Do you have a practice nurse who handles this, or do you manage it yourself?)
  - How do you and the practice nurse divide responsibilities in hypertension care?
- How do you approach the prevention of cardiovascular diseases in your practice?
  - Do you invite all patients above a certain age for screening?
  - Do you assess cardiovascular risk when patients visit for other reasons?
- What role does lifestyle intervention play in hypertension management within your practice?

Part II: Main Section
I'd now like to ask you some questions about antihypertensive medications, starting with how you choose them.

- Can you describe your approach when prescribing antihypertensive medication to a patient for the first time?
- What are your thoughts on the section of the hypertension guideline regarding antihypertensives?
  - Is it too detailed or specific (more information or recommendations than necessary)?
  - Is it not detailed or specific enough (are there recommendations or guidance you feel are missing)?
  - Is it clear when certain recommendations apply and when they do not?

In recent years, the hypertension guideline has stated that various groups of antihypertensives—ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and diuretics—are considered equivalent options for people with hypertension without comorbidities, providing similar blood pressure-lowering effects.

- Do you find this equivalence holds true in your experience, or do you feel certain medications work better?
- Do you have a preference for a particular group of antihypertensives or a specific medication?
  - Clarification: When you initiate antihypertensive therapy, which group or medication do you typically choose?
  - Clarification 2: How do side effects influence your choice of antihypertensive?
  - Clarification 3: If certain medication classes (ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, diuretics) aren't mentioned, could you explain why?
  - Clarification 4: If you prefer ACE inhibitors over ARBs, why do you choose them despite the risk of a dry cough, a side effect not associated with ARBs?
- How did your preference or order of choice develop?
  - Clarification: How fixed is this order for you? If new evidence showed that a particular class of antihypertensives had a significant advantage for a specific organ system (beyond blood pressure reduction and cardiovascular event impact), would that influence your preferences?
- Are there specific patient groups—for example, ethnic minorities, patients with diabetes, or older adults—for whom you prefer a particular drug or drug class? Could you describe different patient scenarios where you'd choose different antihypertensive classes?
  - If you choose a beta-blocker for a nervous patient, is this initiated as monotherapy? If the beta-blocker doesn't sufficiently lower blood pressure, what is your next step in treatment?
- Does age play a role in your decision to prescribe antihypertensives, and if so, how?
  - Clarification: For a 45-year-old with newly diagnosed hypertension, would you start medication immediately or begin with lifestyle interventions? How about for a 65-year-old? What about a frail 75-year-old?
- How does the level of blood pressure influence your management of newly diagnosed hypertension?
  - Clarification: Would you choose a different medication for a patient with a blood pressure of 145 mmHg compared to one with 170 mmHg?

- Do you sometimes start treatment with two antihypertensives simultaneously?
  - Clarification: If not, why? Research indicates that starting with two medications can improve both mortality and morbidity compared to starting with one.

The upcoming [*National General Practitioners'*] hypertension guideline is expected to recommend initiating treatment with two medications for systolic blood pressure over 150 mmHg.

- What are your thoughts on this forthcoming recommendation?
  - Clarification: How might this influence your prescribing habits?
- Are you concerned about losing patients to follow-up, and would it be better to start directly with two antihypertensive medications?
  - Example: If a patient starts on one medication but doesn't return for follow-up, their blood pressure may remain poorly controlled. Wouldn't starting with two medications from the outset improve outcomes?

Supplementary Methods 2. Braun and Clarke's framework

1. Familiarization, the interviewers (JLS & MPW) listened to audio recordings and read transcripts to familiarize themselves with the data;
2. Initial coding, both interviewers independently generated initial coding trees using MaxQDA13;
3. Theme Development, a coding system was developed to generate a thematic map of main themes and subthemes;
4. 3.Review and Refinement, codes were reviewed and refined by the interviewers to reach consensus, with input from the research group (JLS, MPW & EPMvC);
5. Narrative Development, the themes were further refined and discussed to create a narrative of the main findings;
6. Reporting, themes were used to produce the final report, with illustrative quotes translated from Dutch to English.

Supplementary Methods 3. Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist.

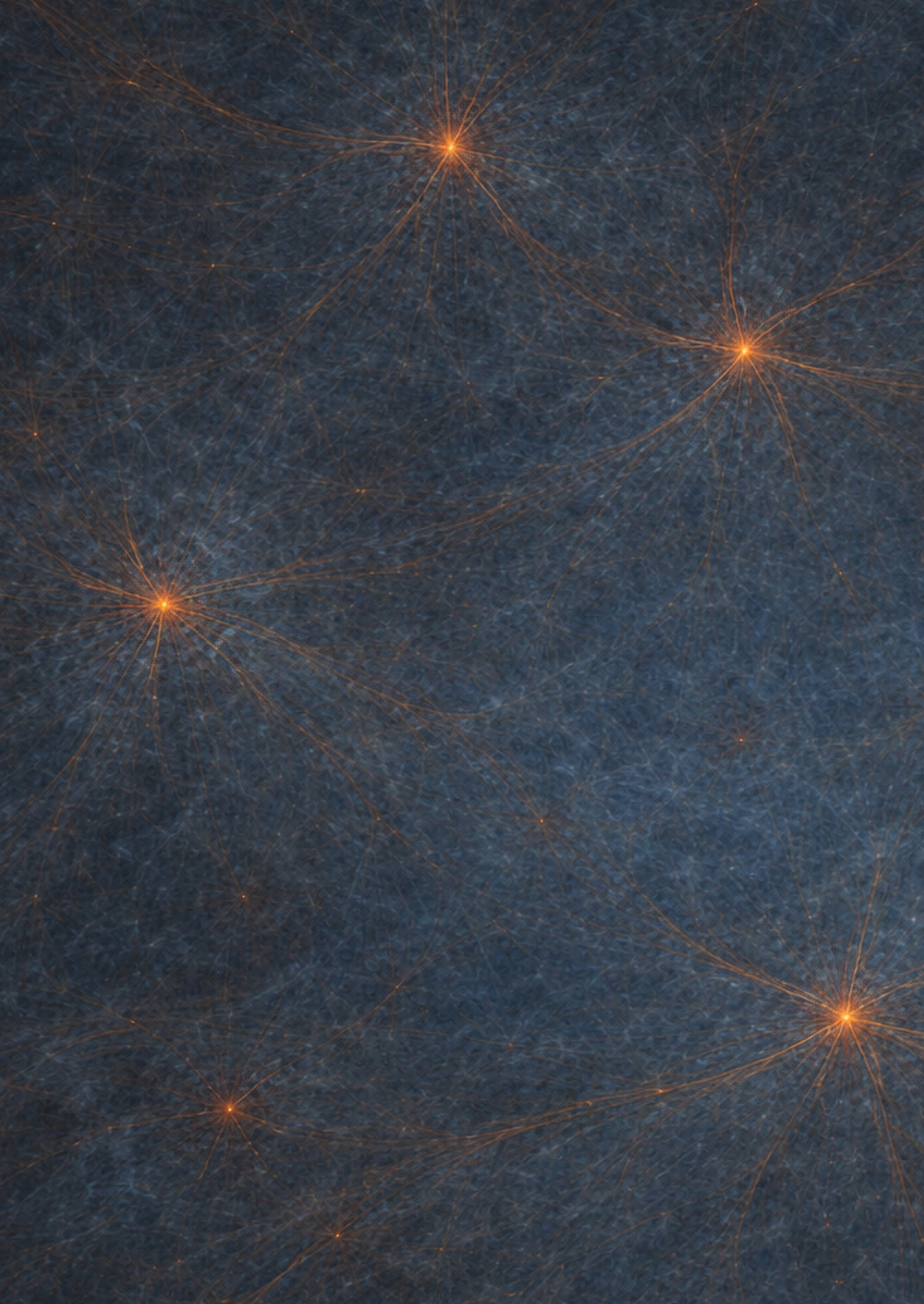
No. Item	Guide questions/description	Reported on Page #
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Inter viewer/facilitator	Which author/s conducted the interview or focus group?	4
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	1, 4
3. Occupation	What was their occupation at the time of the study?	4
4. Gender	Was the researcher male or female?	4
5. Experience and training	What experience or training did the researcher have?	4
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	4
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	N/A
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	5, supplementary methods 2
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	4
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	4
12. Sample size	How many participants were in the study?	4
13. Non-participation	How many people refused to participate or dropped out? Reasons?	4

No. Item	Guide questions/description	Reported on Page #
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	4
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	4
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	6, Table 1, Supplementary Table 1.
Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	4, Supplementary Methods 1.
18. Repeat interviews	Were repeat inter views carried out? If yes, how many?	4
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	4
20. Field notes	Were field notes made during and/or after the interview or focus group?	5
21. Duration	What was the duration of the inter views or focus group?	4
22. Data saturation	Was data saturation discussed?	4
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	Supplementary Methods 2.
25. Description of the coding tree	Did authors provide a description of the coding tree?	Supplementary Methods 2.
26. Derivation of themes	Were themes identified in advance or derived from the data?	5, Supplementary Methods 2.
27. Software	What software, if applicable, was used to manage the data?	5
28. Participant checking	Did participants provide feedback on the findings?	N/A

No. Item	Guide questions/description	Reported on Page #
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number?	6-11, Table 2.
30. Data and findings consistent	Was there consistency between the data presented and the findings?	12-15
31. Clarity of major themes	Were major themes clearly presented in the findings?	6,12
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	6-11

Supplementary Table 1. Individual General Practitioners' Characteristics

General Practitioner	Sex	Years of Experience	Practice setting	Practice size
1	Male	27	Rural	Small
2	Female	7	Urban	Small
3	Female	10	Urban	Large
4	Male	1	Urban	Large
5	Female	1	Urban	Large
6	Female	5	Rural	Small
7	Female	7	Urban	Small
8	Female	10	Rural	Small
9	Male	20	Rural	Small
10	Male	17	Urban	Large
11	Male	8	Rural	Large
12	Male	19	Urban	Large
13	Male	37	Rural	Large
14	Female	4	Rural	Large
15	Female	9	Urban	Large
16	Male	25	Urban	Large
17	Female	8	Urban	Large
18	Female	27	Rural	Small



Chapter VI

Adverse lipid profiles are associated with lower dementia risk in older people

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ABSTRACT

Objective: Mid-life dyslipidaemia is associated with higher risk of dementia in late-life dementia, but the impact of late-life dyslipidaemia on dementia risk is uncertain. This may be due to the large heterogeneity in cholesterol measures and study designs employed. We used detailed data from a large prospective cohort of older persons to comprehensively assess the relation between a broad range of cholesterol measures and incident dementia, addressing potential biases, confounders and modifiers.

Design: Post hoc observational analysis based on data from a dementia prevention trial (PreDIVA)

Setting and participants: 3392 community-dwelling individuals, without dementia, aged 70-78 years at baseline (recruited between June 2006, until March 2009)

Methods: Total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides and apolipoprotein A1 and B were assessed. Over a median of 6.7 years follow-up, dementia was established by clinical diagnosis confirmed by independent outcome adjudication. Hazard ratios (HR) for dementia and mortality were calculated using Cox regression.

Results: Dementia occurred in 231 (7%) participants. One SD increase in LDL/HDL conveyed a 19% (p=0.01) lower dementia risk and a 10% (p=0.02) lower risk of dementia/mortality combined. This was independent of age, cardiovascular risk factors, cognitive function, apolipoprotein E genotype and cholesterol lowering drugs (CLD). This association was not influenced by the competing risk of mortality. Consistent and significant interactions suggested these associations were predominant in individuals with low BMI and higher education.

Conclusions and implications: Dyslipidaemia in older individuals was associated with a lower risk of dementia. Low BMI and higher education level mitigate poor outcomes associated with dyslipidaemia. These findings suggest that a different approach may be appropriate for interpreting lipid profiles that are conventionally considered adverse in older adults. Such an approach may aid predicting dementia risk and designing intervention studies aimed at reducing dementia risk in older populations.

INTRODUCTION

The worldwide dementia prevalence is expected to almost triple over the coming decades.[1] Next to age, cardiovascular risk factors are among the most important predictors for dementia in later life.[2] Since lipid fractions are easily measurable and can be treated using diet, exercise, and cholesterol lowering drugs (CLD),[3] their relation with incident dementia is of interest, being a potentially modifiable risk factor. Dyslipidaemia is an independent predictor of cardiovascular and cerebrovascular disease and mortality[4], though its relation with dementia is less clear. The association between adverse lipid profiles in mid-life and increased risk of late-life dementia has been well established,[5] but whether dyslipidaemia in older age is also associated with dementia remains uncertain. Recent studies have yielded inconsistent results, reporting increased, unchanged and decreased dementia risk for various adverse lipid profiles.[6-9] These heterogeneous findings may be due to differences in cholesterol measures assessed, age at measurement, follow-up duration, and adjustment for confounders. Counter-intuitive associations of reduced dementia risk with dyslipidaemia might be explained by selective observation (e.g. individuals with dyslipidaemia being under closer inspection), differential drop-out, competing risk of mortality on dementia risk, statin therapy or reverse causality. Therefore, this study aimed to assess the relation between various common serum lipids and incident dementia using longitudinal data from a large cohort of community-dwelling older individuals participating in a pragmatic, population-based randomized controlled trial, specifically addressing potential biases, confounders and modifiers that may influence this relation in late-life.

METHODS

Participants

Data stem from the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial.[10] PreDIVA tested the effect of a nurse-led, multi-component cardiovascular intervention on dementia incidence, compared to usual care. Community-dwelling older people (aged 70-78 years) registered with participating general practices were followed for 6-8 years (**Figure 1**). Exclusion criteria were dementia and disorders likely to hinder successful long-term follow-up. Participants were assessed at baseline, and during 2-yearly follow-up assessments, collecting data on medical history, medication use, cardiovascular risk factors, cognitive status, and disability. At baseline, blood laboratory measures and apolipoprotein E genotype were obtained. Participants were referred to their GP for medical treatment, including CLD, if indicated based on these assessments, according in accordance with the prevailing guidelines at the time. After

baseline, participants in the intervention group visited a practice nurse at their GP's office every four months for the duration of the study. During these visits, various cardiovascular risk factors, such as smoking habits, diet, and weight, were assessed, and tailored lifestyle advice was given. Blood pressure was also measured, and participants were referred to their GP for optimization of antihypertensive treatment. Participants in the control group received routine care in accordance with current cardiovascular risk management guidelines at that time. The primary outcome was all-cause dementia, on which the trial intervention had no effect. Therefore, we analyzed the control and intervention groups as a single cohort for this study. The study was approved by the medical ethics committee of the Academic Medical Center (Amsterdam, Netherlands), and all participants provided written consent.

Cholesterol measures

Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), apolipoprotein A1 (ApoA1) and apolipoprotein B (ApoB) were derived from baseline serum samples. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula,[11] excluding participants with TG >4.5 mmol/l.[121] From these measures TC/HDL, LDL/HDL, non-HDL, TG/HDL, and remnant cholesterol were calculated. Serum was taken according to Dutch guidelines, wherein fasting was recommended, but not compulsory.[13]

Outcomes

Outcome data were collected during follow-up visits and supplemented with information extracted from both general practitioners' (GP) electronic health records and the National Death Registry. Dementia was established as a clinical diagnosis according to DSM-IV criteria,[14] confirmed by two members of an independent, blinded outcome adjudication committee based on all available clinical information. Dementia diagnoses were re-evaluated after one year of additional follow-up to avoid false-positive diagnoses. For participants who dropped-out of the study, a research nurse retrieved dementia status from health records and/or contact with the general practitioner at the end of the study, which was presented to the blinded outcome adjudication committee. A detailed description of the outcome assessment is provided in *Supplementary Methods 1*. The complete study protocol has been published previously.[10]

Statistical analyses

Participants with missing values on baseline cholesterol measures, or dementia status were excluded from analyses. Cox regression was used to assess the relations of z-scores of baseline TC, LDL-C, HDL-C, TC/HDL-ratio and LDL/HDL-ratio separately with incident dementia. To investigate the potentially important influence

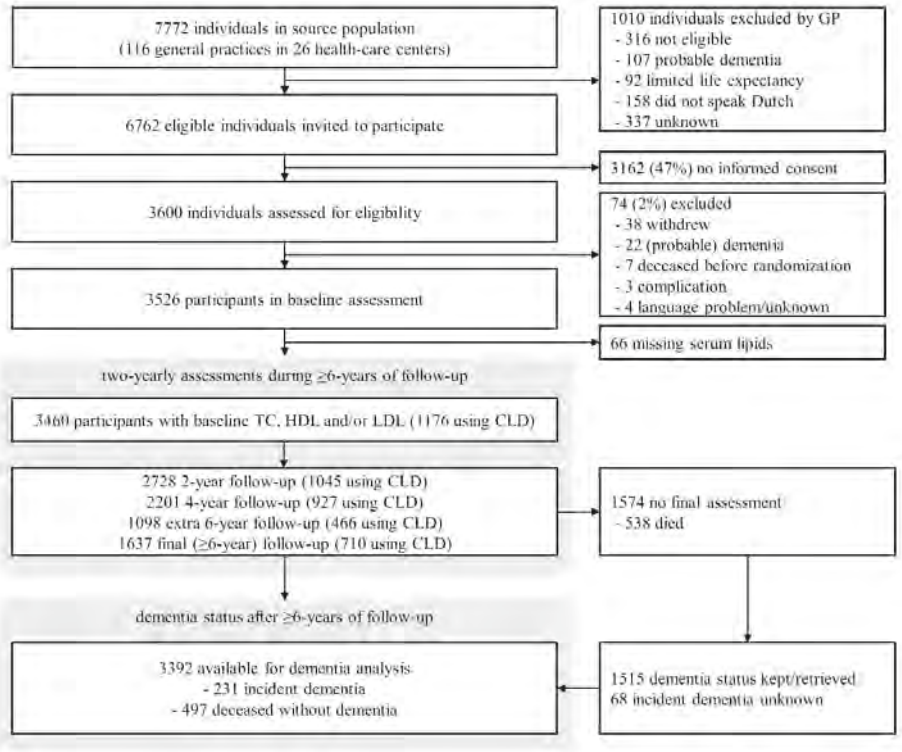
of mortality as a competing event on dementia risk, we repeated all analyses with mortality and dementia/mortality as outcomes. This is crucial because individuals at higher mortality risk may die before reaching the ages at which dementia commonly manifests, resulting in a apparently lower dementia risk. LDL/HDL was log transformed to attain a normal distribution, improving model fit. Possible non-linear relations were evaluated using quadratic terms, penalized cubic splines, and by evaluating quintiles of lipid values. Age was used as timescale with baseline age as time of entry. Model 1 was unadjusted. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, CLD use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, cardiovascular disease (CVD), and diabetes. Interactions were assessed for all covariates. Since previous studies evaluated a great range of cholesterol measures and it may be debated which is the most relevant,[8,15] for completeness, analyses above were also conducted with TG, remnant cholesterol, ApoA1, ApoB, and ApoB/ApoA1-ratio as exposure.

To comprehensively address potential sources of bias, confounders and moderators, and to maximize comparability to previous studies, a number of subgroup and sensitivity analyses were performed. To exclude differential effects resulting from the PreDIVA intervention, subgroup analyses were conducted separately for the treatment and control groups. Since relations between serum lipids and adverse outcomes may be influenced by CLD use[16], subgroup analyses were performed based on CLD use at baseline. In addition, to assess the influence of CLD initiation in response to baseline lipid measurements, subgroup analyses were performed comparing participants who at any point during the study used CLD vs. those who never used CLD during the study. For the same purpose, Cox analyses were repeated, adjusted for CLD use at the 2-yearly assessments during the study as time-dependent variables. To assess the influence of follow-up duration and reverse causality, sensitivity analyses were performed comparing risks for events occurring after short and long follow-up. For the long follow-up analysis, individuals who developed dementia before the median follow-up time to dementia diagnosis (5.04 years) were left out of the analysis. For short follow-up, maximum follow-up time was set at the median time to dementia and individuals who developed dementia later were censored as non-events. Because there may be a strong influence of age at diagnosis on the association between dyslipidaemia and dementia[17], we performed subgroup analyses based on tertiles of age at baseline and age at diagnosis, in addition to assessing the continuous interaction between baseline age and predictors. We interpreted results with Bonferroni adjustment for the number of interactions tested (p-value: 0.05/20=0.0025).

RESULTS

Of the 3526 participants included in the study, 66 (2%) did not have baseline TC, HDL-C or LDL-C available and 68 (2%) had missing dementia status at follow-up, leaving 3392 (96%) for the analyses (**Figure 1**).

Figure 1. Study flow-chart.



Abbreviations: TC: total cholesterol, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol, CLD: cholesterol lowering drugs

Baseline characteristics are listed in **Table 1**. Mean baseline age was 74.4(±2.5) years and 55% were women. Mean baseline TC was 5.2mmol/l(±1.1), HDL-C 1.5mmol/l(±0.4) and LDL-C 3.1mmol/l(±1.0). The mean TC/HDL-ratio was 3.7(±2.4) and the mean LDL/HDL-ratio 2.2(±0.9). At baseline, 34% were on CLD and 48% used CLD at any point during the study. In total, 231 (7%) participants developed dementia and 545 (16%) died. Of the 1350 individuals without CLD at baseline

with ≥1 follow-up measurement available, 455 (35%) initiated CLD treatment during the study. This percentage did not significantly differ between the trial intervention and control arms (37% vs 31%; p=0.11). Baseline characteristics, split by median TC, LDL-C, HDL-C, TC/HDL-ratio, and LDL/HDL-ratio are provided in *Supplementary Tables 1a through 1e*. Comparisons with baseline characteristics of participants not included in this study are depicted in *Supplementary Table 2*.

The relation between baseline cholesterol values and dementia, mortality and dementia/mortality combined are listed in **Table 2**. In the text we report hazard ratios (HR) per standard deviation increase in *Z*-score according to model 3 (fully adjusted) unless stated otherwise.

Table 1. Baseline characteristics of participants.

	Total n=3392
Age	74.4 (±2.5)
Women	1853/3392 (55%)
Education:	
low	807/3392 (24%)
middle	1902/3392 (57%)
high	649/3392 (19%)
MMSE score	28(±1)
Mean systolic BP	155.3 (±21.3)
Mean diastolic BP	81.4 (±11.0)
Antihypertensive drugs	1860/3392 (55%)
BMI	27.4 (±4.1)
≤25.5	1156/3390 (34%)
25.5-28.7	1104/3390 (33%)
>28.7	1130/3390 (33%)
Smoking	440/3385 (13%)
Diabetes	613/3392 (18%)
History of stroke	334/3348 (10%)
History of CVD	993/3369 (30%)
Apo allele e4 positive	793/2861 (28%)
Cholesterol medication at baseline	1152/3386 (34%)
Cholesterol medication initiation after baseline	517/2734 (19%)

Table 1. Baseline characteristics of participants. *(Continued)*

	Total n=3392
Serum cholesterol measures:	
TC	5.2 (±1.1)
HDL-C	1.5 (±0.4)
LDL-C	3.1 (±1.0)
TC/HDL-C	3.7 (±1.1)
LDL-C/HDL-C	2.2 (±0.9)
Remnant C	0.6 (±0.3)
Apolipoprotein A1	1.5 (±0.3)
Apolipoprotein B	1.0 (±0.3)
ApoA1/ApoB	0.7 (±0.2)
Outcome measures:	
Dementia	231/3392 (7%)
Mortality	545/3388 (16%)
Dementia/mortality	728/3390 (22%)

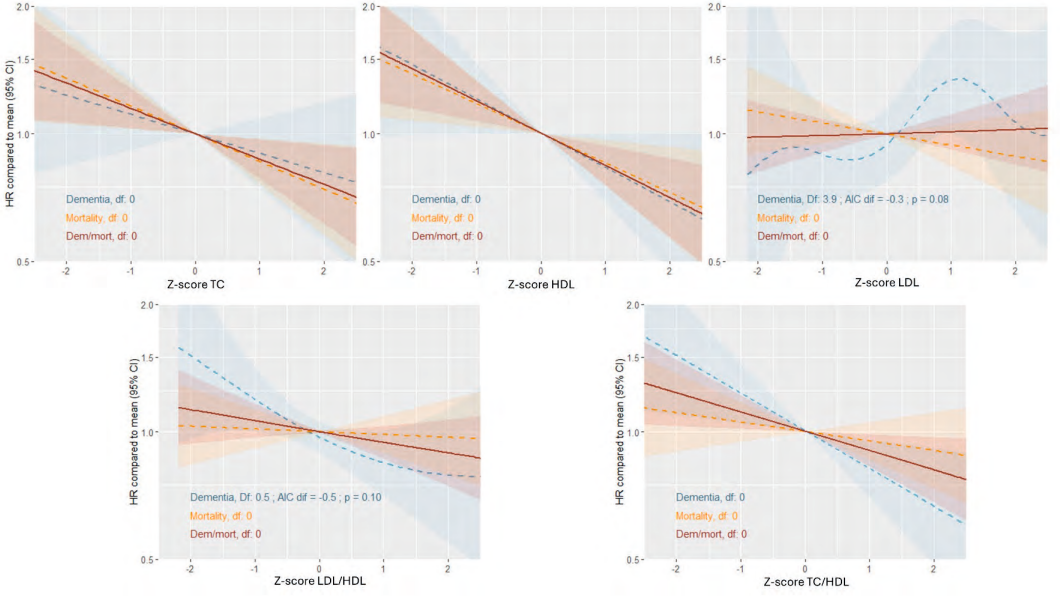
Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol. Missings: Education: 34, MMSE score: 5, systolic BP: 3, diastolic BP: 2, BMI: 2, smoking: , history of stroke: 54, history of CD: 23, cholesterol medication: 6, cholesterol: 7, HDL-C: 1, LDL-C: 28, TCHDL: 8, HDL/LDL: 28, RC: 28, ApoA1: 183, ApoB: 184, ApoBA: 184, dementia: 0, mortality: 4, dementia/mortality: 2

Table 2. Cox regression of dementia, mortality without dementia and dementia/mortality combined, predicted by z-scores of serum lipids at baseline.

	Model 1				Model 2				Model 3			
	events/total	**HR**	**95%CI**	**p**	**events/total**	**HR**	**95%CI**	**p**	**events/total**	**HR**	**95%CI**	**p**
Dementia:												
TC	230/3385	1.01	(0.89-1.15)	0.87	173/2816	0.92	(0.77-1.11)	0.39	169/2752	0.90	(0.74-1.09)	0.28
LDL-C	228/3364	0.97	(0.85-1.11)	0.66	171/2796	0.84	(0.70-1.01)	0.07	167/2733	0.83	(0.69-1.00)	0.054
HDL-C	231/3391	1.13	(1.00-1.28)	**0.048**	174/2821	1.19	(1.02-1.38)	**0.02**	170/2757	1.13	(0.97-1.33)	0.12
TC/HDL	230/3384	0.90	(0.78-1.03)	0.12	169/2761	0.82	(0.69-0.97)	**0.02**	169/2751	0.86	(0.73-1.02)	0.08
LDL/HDL	228/3364	0.89	(0.78-1.00)	0.06	171/2796	0.79	(0.67-0.92)	**0.002**	167/2733	0.81	(0.69-0.96)	**0.01**
Dementia/Mortality:												
TC	725/3383	0.84	(0.78-0.91)	**<0.001**	576/2814	0.83	(0.75-0.92)	**<0.001**	563/2750	0.87	(0.78-0.97)	**0.01**
LDL-C	719/3362	0.85	(0.79-0.91)	**<0.001**	571/2794	0.80	(0.72-0.89)	**<0.001**	558/2731	0.84	(0.75-0.93)	**0.001**
HDL-C	728/3389	0.89	(0.83-0.96)	**0.003**	579/2819	0.97	(0.89-1.06)	0.52	566/2755	1.01	(0.92-1.11)	0.82
TC/HDL	725/3382	1.00	(0.93-1.08)	0.95	576/2813	0.95	(0.87-1.04)	0.26	563/2749	0.94	(0.86-1.03)	0.20
LDL/HDL	719/3362	0.95	(0.89-1.02)	0.19	571/2794	0.90	(0.82-0.98)	**0.01**	558/2731	0.90	(0.82-0.98)	**0.02**
Mortality:												
TC	495/3383	0.77	(0.71-0.85)	**<0.001**	403/2814	0.78	(0.69-0.89)	**<0.001**	394/2750	0.85	(0.75-0.96)	**0.01**
LDL-C	491/3362	0.79	(0.72-0.87)	**<0.001**	400/2794	0.78	(0.69-0.88)	**<0.001**	391/2731	0.84	(0.74-0.95)	**0.01**
HDL-C	497/3389	0.78	(0.71-0.86)	**<0.001**	405/2819	0.87	(0.77-0.97)	**0.01**	396/2755	0.94	(0.83-1.05)	0.26
TC/HDL	495/3382	1.05	(0.96-1.15)	0.26	403/2813	1.01	(0.91-1.12)	0.86	394/2749	0.99	(0.89-1.10)	0.82
LDL/HDL	491/3362	0.99	(0.90-1.08)	0.77	400/2794	0.95	(0.85-1.05)	0.31	391/2731	0.95	(0.85-1.06)	0.34

Approximate lipid values for 1 point increase in z-score: TC=1.10 mmol/L; LDL-C=0.97 mmol/L; HDL=0.42 mmol/L ; TC/HDL=1.07 ; LDL/HDL=0.25. Model 1 was unadjusted. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, HR: hazard ratio, 95%CI: 95% confidence interval

Figure 2. Assessment of non-linear relations using penalized splines of serum lipids with incident dementia as outcome.



Hazard ratios (HR) relative to the mean hazard (y-axis) for dementia (blue), mortality (orange) and dementia/mortality (red) with 95% confidence intervals (colored shading) set out against z-scores of serum lipid values, incorporating penalized splines allowing for the optimal degrees of freedom based on the Aikake Information Criterion (AIC). Models with 0 degrees of freedom (df) suggest the linear model has the best fit. For non-linear models (df >0), the AIC improvement (AIC dif) compared to the linear model is given (the lower the better; rule of thumb <-5 points constitutes a substantially better model fit). The p-value is for the loglikelihood ratio test between the non-linear model and a linear model. A p-value <0.05 suggests that the non-linear model has a significantly better fit than the linear model (not true for any of the models). All models were fully adjusted (for sex, education, MMSE score, apolipoprotein E e4, systolic blood pressure, antihypertensive medication, body mass index, smoking, history of stroke, history of cardiovascular disease and diabetes mellitus). Abbreviations: TC: total cholesterol, HDL: high-density lipid cholesterol, LDL: low-density lipid cholesterol. MMSE: mini-mental state examination.

Overall, one standard deviation (SD) increase in TC, LDL-C, TC/HDL-ratio and LDL/HDL-ratio was associated with a 10-19% lower dementia risk, although in model 3 this was only significant for LDL/HDL (HR=0.81, 95%CI:0.69-0.96;p=0.01). These lower dementia risks cannot be attributed to increased risk of death, as mortality risks associated with these measures were also 5-16% lower per SD increase, although only significantly for TC (HR=0.85;95%CI:0.75-0.96;p=0.01) and LDL-C (HR=0.84;95%CI:0.74-0.95;p=0.01). For the combined outcome of mortality/dementia, one SD increase was associated with a 6-16% lower risk, being significant for TC (HR=0.87,95%CI:0.78-0.97,p=0.01), LDL-C (HR=0.84;95%CI:0.75-0.93,p=0.001) and LDL/HDL (HR=0.90;95%CI:0.82-0.98,p=0.02). For HDL-C, one SD increase conveyed a 13% higher dementia risk (HR=1.13;95%CI:0.97-1.33p=0.12) but a 6% lower mortality risk (HR=0.94;95%CI:0.83-1.05p=0.26) although neither significantly in model 3. Analysis of the combined outcome of dementia/mortality suggested that any increased dementia risk with higher HDL levels may have resulted from the lower risk of mortality (HR=1.01;95%CI:0.92-1.11;p=0.82).

Quadratic terms, and subdivisions of lipid fractions into quintiles did not suggest clear non-linear relationships between any lipid measures and dementia risk. Assessment using penalized splines using the optimal degrees of freedom also did not give significantly better model fits (**Figure 2,** *Supplementary Figure 1*). *Supplementary Figure 2* depicts survival plots in tertiles for each lipid measure. Reference alternative cholesterol measures (*Supplementary Table 3*) showed comparable results for ApoA1 and ApoB, although generally more attenuated after adjustment. Associations with TG and remnant cholesterol were neutral.

Interaction analyses

Consistent interactions across multiple cholesterol measures were observed for BMI and education (*Supplementary Table 4*), suggesting the incremental associations between lipid levels and dementia and mortality risks diminished with higher BMI and less education. Isolated interactions were found for HDL with CVD, increasing the dementia risk; HDL with APOE4, increasing dementia/mortality risk; and sex with HDL, attenuating the association between HDL and dementia in women. We explored these interactions in subgroup analyses based on tertiles of BMI, education, APOE4 genotype, CVD history, sex, trial allocation, baseline CLD, and CLD during the study.

Interactions between cholesterol and tertiles of BMI were consistent across models and lipid measures (*Supplementary Table 5*). They suggested that lower HDL-C and higher TC, LDL-C, TC/HDL and LDL/HDL were associated with a lower de-

mentia and mortality risk in individuals in the lowest BMI categories in particular (BMI≤25.5kg/m^2). These associations were reversed in individuals in the highest BMI category (BMI>28.7kg/m^2). A strong and consistent interaction was also found for lipids and education subgroups (*Supplementary Table 6*). In the subgroup with the highest educational attainment (>12 years), lower HDL-C and higher TC, LDL-C, TC/HDL and LDL/HDL were associated with a lower dementia and mortality risk, while in those with the lowest educational attainment (<7 years), these relations were reversed. Interactions with APOE4, cardiovascular disease history and sex were relatively inconsistent and largely restricted to isolated interactions between single cholesterol measures and outcomes (*Supplementary Table 7-9*).

Subgroup and sensitivity analyses

Findings were similar in subgroups according to treatment allocation in the original trial (*Supplementary Table 10*). Subgroup analyses based on CLD at baseline (*Supplementary Table 11*) and CLD initiation during the study (*Supplementary Table 12*) showed no clear differences. Sensitivity analyses incorporating CLD use during the study as a time dependent covariate in the Cox regression model also did not alter results (*Supplementary Table 13*). Subgroup analyses stratified according to short versus long follow-up (*Supplementary Table 14*) suggested the relations of high TC and LDL-C levels with lower dementia/mortality risks were mainly present for events after long follow-up (≥5.04 years). Similarly, the relation for high TC/HDL and LDL/HDL with lower dementia/mortality risks was found predominantly in participants with longer follow-up. There were no consistent differences between subgroups based on tertiles of baseline age (*Supplementary Table 15*), nor tertiles of censoring age (*Supplementary Table 16*) regarding the associations with dementia. Post-hoc analyses incorporating interactions with BMI and education into one single model suggested these were largely independent of each other (*Supplementary Table 17*). Analyses according to disease history (DM, CVD, or stroke vs none) showed no clear differences between subgroups (*Supplementary Table 18*). Finally, post-hoc, we compared participant characteristics between education categories, to assess potential mechanisms by which education may moderate the relation between cholesterol and dementia risk. These showed that participants in higher education categories overall had lower (vascular) disease burden (*Supplementary Table 19*).

DISCUSSION

In 3392 community-dwelling individuals aged 70-78 years, dyslipidaemia according to TC, LDL-C, HDL-C measures, particularly a high LDL/HDL-ratio, was associated

with lower dementia risk during a median follow-up of 6.7 years. This was independent of age, other cardiovascular risk factors, cognition, and CLD use. These findings were consistent across lipid measures, except for TG and remnant cholesterol. Results seemed mainly driven by higher LDL-C being associated with a lower dementia risk and less so by higher HDL-C being associated with a higher dementia risk. The concomitant increased or neutral hazards for mortality and dementia/mortality combined suggest these associations are not attributable to reductions in the competing risk of death. Strong and consistent interactions with BMI and education suggested that these associations predominantly prevail in older persons with a low BMI and higher education, and may be reversed in groups with high BMI and lower education.

Strengths of this study include the use of incident all-cause dementia as a clinically relevant outcome, completeness of follow-up on dementia (98.0%) and mortality (99.9%), assessment of a broad panel of serum lipids, adjustment for a large number of potential confounders and modifiers, comprehensive sensitivity and subgroup analyses, and repeating of analyses for mortality and dementia/mortality accounting for competing risk of death.

Several factors need consideration when interpreting these results. First, although serum collection guidelines recommended fasting, fasting was not compulsory. This may have affected TC and particularly LDL-C levels.[12] However, recent consensus suggests this effect is small and of little impact on prediction of vascular disease at TG levels included in our study (≤4.5mmol/l).[12,18] Moreover, directions of the associations with HDL-C, ApoB and ApoA1, which are not influenced by fasting state, were consistent with our overall results. Finally, it is unlikely that non-fasting lipid measurements were selectively collected in those who did or did not develop dementia during follow-up. Second, PreDIVA was an RCT involving cardiovascular risk profile optimization. After baseline, CLD were initiated in approximately one third of both intervention and control participants. If CLD treatment would lower dementia risk, this could have led to reduced dementia risk for individuals with dyslipidaemia at baseline. Although some observational studies associate statin use with lower dementia risk, a Cochrane review of RCTs concluded that there is good evidence that statins do not lower the risk of cognitive decline or dementia.[19,20] Moreover, analyses accounting for baseline CLD use, CLD initiation during the study, and trial intervention allocation did not change results, suggesting CLD initiation after baseline did not play a major role in our findings. Third, lipids were not systematically collected during the follow-up visits of this study, impeding analyses on whether declining cholesterol trajectories rather than low point-estimates are associated with dementia risk. Fourth, we refrained from examining associations between dyslipidaemia and

dementia subtypes. This decision was driven by the limited number of non-Alzheimer's dementias cases, which would have inevitably resulted in insufficient statistical power. Furthermore, diagnostic differentiations were solely based on clinical criteria, lacking neuropathological confirmation, thus potentially compromising the accuracy of subtype distinctions. Fifth, the number of covariates may have led to over-adjustment in some subgroup analyses, especially in model 3 for dementia. Assessing interactions with covariates over a large number of subgroup analyses may have introduced spurious results. However, the most important interactions, with BMI and education categories, were strong, consistent, dose-responsive, and generally robust to stringent Bonferroni adjustment.

Several mechanisms may underlie the somewhat counter-intuitive association between dyslipidaemia and lower dementia risk. It has been hypothesized that low cholesterol in late life may induce cognitive impairment,[21] but this has been refuted by a study showing that higher TC, LDL-C, and non-HDL-C are associated with better memory function.[22] Alternatively, it may be hypothesized that individuals susceptible to dyslipidaemia related vascular disease and dementia may not have entered the study, because they had already died or developed other medical conditions that prohibited them from entering the study.

Few studies have examined possible other interactions and, if so, mostly tested possible interaction with age, sex and APOE4 status.[7,8,23,24] One prospective cohort study suggested that dyslipidaemia is associated with lower dementia risk only in individuals diagnosed at a high age (>84 years), whereas a recent meta-analysis observed that the association between elevated total TC and higher dementia risk attenuated with age.[7,17] The narrow age range of our sample may explain the absence of interactions with age at the time of diagnosis.

The interplay between dyslipidaemia and education is likely shaped by an intricate network of diverse, partly non-biological factors. The consistency of the interaction, independent of confounders, is however compelling. Since analyses were adjusted for MMSE score and MMSE subgroup analyses were nondifferential, education in this context is more likely a marker of socio-economic status rather than cognitive function, and may be even more so in low- and middle income countries.[25] In individuals with lower education, dyslipidaemia may be a marker of worse (vascular) health, whereas the opposite is true for individuals with higher education, as supported by the differences in disease burden across education groups in our study.[25,26]

Several traditional cardiovascular risk factors seem less clearly or inversely associated with poor outcome when present in older age, including mild hypertension, elevated BMI and dyslipidaemia.[5,17,27-30] Late life low cholesterol could be a marker of more advanced bodily aging, frailty, and catabolic state.[17] Reports suggest TC and LDL-C decline with aging and declining cholesterol trajectories may predict dementia.[5,17,30] Declining BMI may interact with dyslipidaemia through the metabolic syndrome, e.g. by inducing chronic inflammation or oxidative stress.[26,31] Hence, in low BMI categories, elevated cholesterol levels may distinguish individuals not in a catabolic state. However, the relation may be more complex as high BMI in old age is less reliable as adiposity measure and associated with lower dementia risk.[32-34] Possibly this all relates to an overarching phenomenon, but it remains unclear whether this is caused by survival effects, catabolic state or causal mechanisms. Negative associations with HDL-C may reflect changes in composition and function of HDL-C occurring with ageing that have been suggested to make HDL-C detrimental or by HDL-particles becoming less functional with increasing serum levels.[29,35]

Conclusion and implications

In this study, dyslipidaemia, specifically high TC and LDL-C and low HDL-C, in older age was associated with lower dementia risk, contributing to the accumulating evidence that traditionally adverse lipid profiles in older age are not necessarily associated with adverse outcome.[5,8,36] Low BMI and higher education level may mitigate poor outcomes associated with dyslipidaemia. Although these interactions may not explain all heterogeneity in literature, they may provide an important lead, suggesting that associations not only differ, but may be reversed in different subpopulations. These findings suggest that a different approach may be appropriate for interpreting lipid profiles that are conventionally considered adverse in older adults. Such an approach may aid predicting dementia risk and designing intervention studies aimed at reducing dementia risk in older populations.

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SUPPLEMENTARY MATERIAL

Supplementary Methods 1. Outcome adjudication of the PreDIVA trial.

Sources of information to identify incident cases of dementia

The following three main sources were used to identify potential incident cases of dementia during the study

1. End-of-study form

At every 2-yearly follow-up visit, consultation of the family physician (GP) was indicated for the practice nurse in case of: (a) specific complaints about cognition of participants and/or caregivers, (b) a decline of ≥3 points from the baseline Mini-Mental State Examination (MMSE) score or (c) ≥2 points from the preceding visit or (d) an MMSE score of ≤24. In case of a decline of ≥3 points from the baseline MMSE or ≥2 points from the preceding visit, the GP was advised by the study protocol to perform further evaluation to rule out other potential reasons for the decline in MMSE (e.g. depression, medication side effect). If no other reason was likely, the protocol prescribed to repeat the MMSE within two weeks. If the decline of ≥3 points from baseline or ≥2 points from the preceding visit was confirmed, the GP was advised to refer the participant for further diagnostic work-up. In case of a MMSE score of ≤24 at a 2-yearly visit, the GP was also advised to refer the participant. During the course of the study, GPs could also establish a diagnosis of dementia based on all available clinical information. If needed, the preDIVA research group was available for consultation at all times. After a diagnosis of dementia had been established in a participant, the research group was notified by the practice nurse through an end-of-study form. Upon this notification, all available clinical information was collected (e.g. reports on neuropsychological assessment, neuroimaging, hospital admissions, outpatient diagnostic evaluations by geriatricians, neurologists, psychiatrists) to enable blinded outcome adjudication.

2. Retrieved drop-out form

For all individuals who did not attend the final follow-up assessment and no end-of study form indicating a diagnosis of dementia was received, information on dementia status was collected by a research nurse through contact with GPs, practice nurses, nursing home physicians, dementia case managers, and occasionally with relatives. If a participant had developed dementia, clinical information on dementia diagnosis was collected from medical records for blinded outcome adjudication, as described above.

3. MMSE score at final follow-up visit

Indications for the preDIVA research group to contact the GP to inquire about the cognitive status of the participant were: (a) a decline of ≥3 points from the baseline MMSE or (b) ≥2 points from the preceding visit or (c) an MMSE score of ≤24 at the final follow-up visit. In case the GP indicated that no dementia was present, this judgment was used in the analysis. In other cases, further evaluation was performed. In case the GP indicated that a diagnosis of dementia was already established, clinical information on the diagnosis was shared with a dementia expert panel consisting of two senior neurologists and a GP who were blinded to the treatment allocation. In case dementia was suspected and a participant provided consent for further cognitive evaluation, the participant was referred by the GP and the outcome of this evaluation was shared with the dementia expert panel and used in the analysis. In case of suspected dementia and the participant declined further cognitive evaluation, all available information was evaluated and sometimes the GP and practice nurse were interviewed by one of the members of the masked dementia expert panel in order to reach a conclusion.

Outcome adjudication

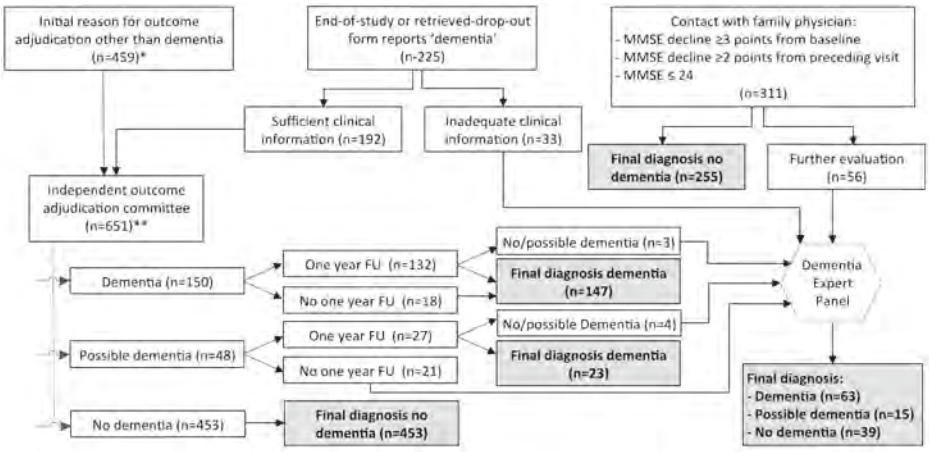
During the study, an independent outcome adjudication committee, consisting of neurologists, old age psychiatrists, geriatricians, family physicians, and cardiologists, evaluated all clinical outcomes (e.g. dementia, mortality) blinded to treatment allocation. This committee evaluated the dementia diagnoses as derived from the end-of-study form and the retrieved drop-out form using a standard format if sufficient clinical information was available (e.g. reports on hospital admissions, outpatient diagnostic evaluations by geriatricians, neurologists, psychiatrists, neuroimaging, neuropsychological examinations). A final judgment on dementia diagnosis and type was established by consensus between two adjudicators. In case of disagreement between two adjudicators a third independent adjudicator was consulted and a final judgment was made if two of the three adjudicators reached consensus. If still no consensus was reached the judgment was based upon the opinion of a dementia expert panel. If only inadequate clinical information was available a judgment on dementia diagnosis and type was established by the dementia expert panel as well. Possible outcomes of the adjudication process were dementia, possible dementia, and no dementia. Possible outcomes regarding types of dementia were probable and possible Alzheimer's dementia, probable and possible vascular dementia, probable and possible dementia with Lewy bodies, Parkinson dementia, frontotemporal dementia, primary progressive aphasia, and 'other'. Dementia diagnosis was made according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV.1 Diagnosis of Alzheimer's dis-

ease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia was made according to widely accepted guidelines.[2-5]

Quality check of dementia diagnoses

As a quality check, dementia diagnoses (dementia and possible dementia) were re-evaluated after one year by asking family physicians, practice nurses, nursing home physicians and/or dementia case managers whether dementia was still the most likely diagnosis. In case of doubt concerning a previous diagnosis of dementia or possible dementia one year later, a final judgment was established, by the dementia expert panel, based upon the most recent available clinical information, while blinding for treatment allocation was preserved. In case the initial judgment was possible dementia and after one year dementia was most likely, the diagnosis dementia was used in the analysis. In case the initial judgment was dementia and no one year follow-up could be obtained, the initial diagnosis dementia was used (see Figure below). In case the initial judgment was possible dementia and no one year follow-up could be retrieved, a final judgment was established by the dementia expert panel masked for the treatment group. Eventually, none of the participants diagnosed with dementia reverted to normal cognition during the 1-year follow-up after diagnosis.

Flow-chart of dementia diagnoses during the preDIVA study.



Abbreviations: MMSE: Mini-Mental State Examination; FU: follow-up.

*Number of individuals with an initial reason for outcome adjudication other than dementia (e.g. mortality, serious illness). For these individuals the dementia status was also assessed by the independent outcome adjudication committee.

**If no consensus was reached after three independent adjudicators the final diagnosis was based upon the opinion of the dementia expert panel blinded for treatment allocation

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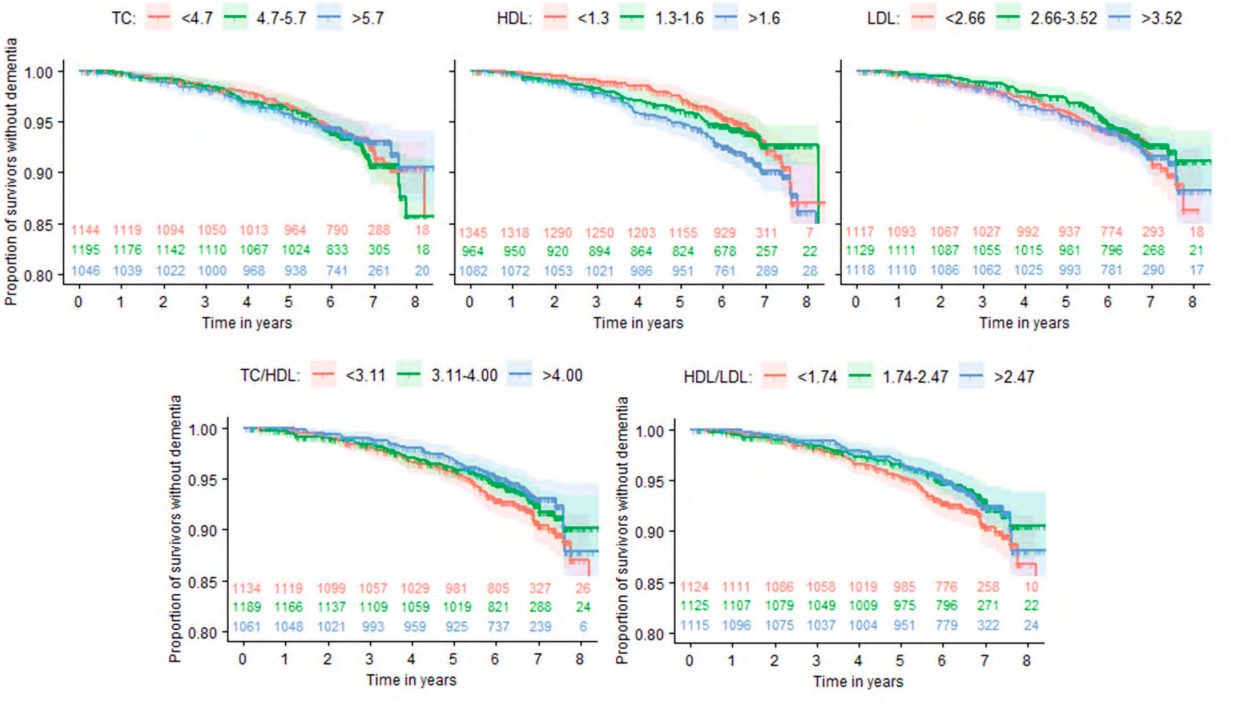
Supplementary Figure 1. Model 1 dementia survival plots according to tertiles of baseline lipid values.



Tables at the bottom indicate the number at risk per group per year of follow-up. Perpendicular bars indicate point of censoring, shaded area depicts 95% confidence intervals. For illustrative purposes only, Cox regression analyses were conducted using continuous lipid measures adjusted for age at baseline. Abbreviations: TC: total cholesterol, HDL: high density lipoprotein cholesterol, LDL: low density lipoprotein cholesterol, TC/HDL: total cholesterol divided by HDL cholesterol, LDL/HDL: LDL cholesterol divided by HCL cholesterol

Supplementary Table 1a. Baseline characteristics of participants, split up by median total cholesterol.

	Total Cholesterol		
Characteristic	**Median and lower (≤5.2 mmol/L)**	**Above median (>5.2 mmol/L)**	**P-value**
Age	74.5 ±2.5	74.3 ±2.5	0.06
Women	738/1717 (43.0%)	1111/1668 (66.6%)	<0.001
Education:			
low	404/1700 (23.8%)	402/1651 (24.3%)	0.78
middle	951/1700 (55.9%)	945/1651 (57.2%)	0.71
high	345/1700 (20.3%)	304/1651 (18.4%)	0.27
MMSE score, median [IQR]	28 [27-29]	29 [27-29]	0.06
Mean systolic BP	154.7 ±20.9	155.8 ±21.7	0.14
Mean diastolic BP	80.6 ±11	82.3 ±10.9	<0.001
Antihypertensive drugs	1126/1717 (65.6%)	721/1668 (43.2%)	<0.001
BMI	27.7 ±4.2	27.1 ±4.0	<0.001
≤25.5	552/1715 (32.2%)	602/1668 (36.1%)	0.10
25.5-28.7	563/1715 (32.8%)	579/1668 (34.7%)	0.43
>28.7	600/1715 (35.0%)	487/1668 (29.2%)	0.01
Smoking	232/1714 (13.5%)	207/1664 (12.4%)	0.36
Diabetes	476/1717 (27.7%)	136/1668 (8.2%)	<0.001
History of stroke	239/1696 (14.1%)	95/1645 (5.8%)	<0.001
History of CVD	687/1706 (40.3%)	301/1656 (18.2%)	<0.001
Apo allele e4 positive	381/1450 (26.3%)	410/1405 (29.2%)	0.09
CLD at baseline	909/1714 (53.0%)	238/1665 (14.3%)	<0.001
CLD initiation after baseline	134/1367 (9.8%)	321/1361 (23.6%)	<0.001
Serum cholesterol measures:			
TC	4.4 ±0.6	6.1 ±0.7	<0.001
HDL-C	1.4 ±0.4	1.6 ±0.4	<0.001
LDL-C	2.4 ±0.6	3.9 ±0.7	<0.001
TC/HDL-C	3.3 ±0.9	4.0 ±1.1	<0.001
LDL-C/HDL-C	0.6 ±0.3	0.4 ±0.2	<0.001
Remnant C	0.6 ±0.3	0.6 ±0.3	<0.001
Apolipoprotein A1	1.4 ±0.3	1.6 ±0.3	<0.001
Apolipoprotein B	0.8 ±0.2	1.1 ±0.2	<0.001
ApoA1/ApoB	0.6 ±0.2	0.7 ±0.2	<0.001
Outcome measures			
Dementia	106/1717 (6.2%)	124/1668 (7.4%)	0.15
Mortality	324/1715 (18.9%)	219/1666 (13.1%)	<0.001
Dementia/mortality	406/1716 (23.7%)	319/1667 (19.1%)	0.001

Depicted are numbers with %, means ±standard deviations, or medians [IQR]. P-values derived from Fisher's exact tests for proportions, Student's t-tests for means, and Mann-Whitney U tests for medians.
Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol.

Supplementary Table 1b. Baseline characteristics of participants, split up by median LDL cholesterol.

	LDL Cholesterol		
Characteristic	**Median and lower (≤3.1 mmol/L)**	**Above median (>3.1 mmol/L)**	**P-value**
Age	74.4 ±2.5	74.3 ±2.4	0.06
Women	804/1682 (47.8%)	1036/1682 (61.6%)	<0.001
Education:			
low	415/1665 (24.9%)	385/1665 (23.1%)	0.35
middle	926/1665 (55.6%)	958/1665 (57.5%)	0.56
high	324/1665 (19.5%)	322/1665 (19.3%)	0.97
MMSE score, median [IQR]	28 [27-29]	29 [27-29]	0.01
Mean systolic BP	154.5 ±21	156.0 ±21.6	0.04
Mean diastolic BP	80.2 ±10.9	82.7 ±10.9	<0.001
Antihypertensive drugs	1106/1682 (65.8%)	725/1682 (43.1%)	<0.001
BMI	27.7 ±4.3	27.2 ±4	0.002
≤25.5	563/1681 (33.5%)	586/1681 (34.9%)	0.56
25.5-28.7	533/1681 (31.7%)	601/1681 (35.8%)	0.09
>28.7	585/1681 (34.8%)	494/1681 (29.4%)	0.02
Smoking	225/1679 (13.4%)	210/1678 (12.5%)	0.47
Diabetes	476/1682 (28.3%)	132/1682 (7.8%)	<0.001
History of stroke	228/1661 (13.7%)	103/1659 (6.2%)	<0.001
History of CVD	679/1675 (40.5%)	302/1667 (18.1%)	<0.001
Apo allele e4 positive	372/1406 (26.5%)	416/1429 (29.1%)	0.12
CLD at baseline	926/1679 (55.2%)	212/1679 (12.6%)	<0.001
CLD initiation after baseline	112/1336 (8.4%)	340/1379 (24.7%)	<0.001
Serum cholesterol measures:			
TC	4.4 ±0.7	6.0 ±0.8	<0.001
HDL-C	1.5 ±0.4	1.5 ±0.4	0.001
LDL-C	2.3 ±0.5	3.9 ±0.6	<0.001
TC/HDL-C	3.2 ±0.9	4.1 ±1.0	<0.001
LDL-C/HDL-C	0.7 ±0.3	0.4 ±0.1	<0.001
Remnant C	0.6 ±0.3	0.6 ±0.3	0.01
Apolipoprotein A1	1.5 ±0.3	1.5 ±0.3	<0.001
Apolipoprotein B	0.8 ±0.2	1.1 ±0.2	<0.001
ApoA1/ApoB	0.6 ±0.2	0.8 ±0.2	<0.001

Supplementary Table 1b. Baseline characteristics of participants, split up by median LDL cholesterol. *(Continued)*

	LDL Cholesterol		
Characteristic	**Median and lower (≤3.1 mmol/L)**	**Above median (>3.1 mmol/L)**	**P-value**
Outcome measures			
Dementia	114/1682 (6.8%)	114/1682 (6.8%)	1.00
Mortality	318/1681 (18.9%)	221/1679 (13.2%)	<0.001
Dementia/mortality	408/1682 (24.3%)	311/1680 (18.5%)	<0.001

Depicted are numbers with %, means ±standard deviations, or medians [IQR]. P-values derived from Fisher's exact tests for proportions, Student's t-tests for means, and Mann-Whitney U tests for medians.
Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol.

Supplementary Table 1c. Baseline characteristics of participants, split up by median HDL cholesterol.

	HDL Cholesterol		
Characteristic	**Median and lower (≤1.4)**	**Above median (>1.4)**	**P-value**
Age	74.4 ±2.5	74.4 ±2.5	0.68
Women	680/1703 (39.9%)	1173/1688 (69.5%)	<0.001
Education:			
low	414/1685 (24.6%)	393/1672 (23.5%)	0.58
middle	932/1685 (55.3%)	969/1672 (58.0%)	0.42
high	339/1685 (20.1%)	310/1672 (18.5%)	0.35
MMSE score, median [IQR]	28 [27-29]	29 [27-29]	<0.001
Mean systolic BP	155.7 ±20.9	154.9 ±21.7	0.30
Mean diastolic BP	81.4 ±11	81.4 ±10.9	0.88
Antihypertensive drugs	1079/1703 (63.4%)	772/1688 (45.7%)	<0.001
BMI	28.2 ±4	26.7 ±4.1	<0.001
≤25.5	443/1701 (26.0%)	712/1688 (42.2%)	<0.001
25.5-28.7	600/1701 (35.3%)	543/1688 (32.2%)	0.18
>28.7	658/1701 (38.7%)	433/1688 (25.7%)	<0.001
Smoking	245/1701 (14.4%)	194/1683 (11.5%)	0.01
Diabetes	389/1703 (22.8%)	224/1688 (13.3%)	<0.001
History of stroke	198/1675 (11.8%)	136/1672 (8.1%)	<0.001
History of CVD	627/1693 (37.0%)	365/1675 (21.8%)	<0.001
Apo allele e4 positive	415/1463 (28.4%)	377/1397 (27.0%)	0.43

Supplementary Table 1c. Baseline characteristics of participants, split up by median HDL cholesterol. *(Continued)*

	HDL Cholesterol		
Characteristic	**Median and lower (≤1.4)**	**Above median (>1.4)**	**P-value**
CLD at baseline	688/1701 (40.4%)	463/1684 (27.5%)	<0.001
CLD initiation after baseline	248/1360 (18.2%)	207/1374 (15.1%)	0.06
Serum cholesterol measures:			
TC	4.9 ±1.1	5.5 ±1.0	<0.001
HDL-C	1.2 ±0.2	1.8 ±0.3	<0.001
LDL-C	3.0 ±1.0	3.2 ±1.0	<0.001
TC/HDL-C	4.3 ±1.1	3.1 ±0.7	<0.001
LDL-C/HDL-C	0.4 ±0.2	0.6 ±0.3	<0.001
Remnant C	0.7 ±0.3	0.5 ±0.2	<0.001
Apolipoprotein A1	1.3 ±0.2	1.7 ±0.3	<0.001
Apolipoprotein B	1.0 ±0.3	0.9 ±0.2	0.04
ApoA1/ApoB	0.8 ±0.2	0.6 ±0.2	<0.001
Outcome measures			
Dementia	98/1703 (5.8%)	133/1688 (7.9%)	0.01
Mortality	321/1700 (18.9%)	224/1687 (13.3%)	<0.001
Dementia/mortality	397/1701 (23.3%)	331/1688 (19.6%)	0.008

Depicted are numbers with %, means ±standard deviations, or medians [IQR]. P-values derived from Fisher's exact tests for proportions, Student's t-tests for means, and Mann-Whitney U tests for medians.
Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol.

Supplementary Table 1d. Baseline characteristics of participants, split up by median TC/HDL cholesterol.

	TC / HDL Cholesterol		
Characteristic	**Median and lower (≤3.53)**	**Above median (>3.53)**	**P-value**
Age	74.5 ±2.5	74.2 ±2.5	0.003
Women	1012/1698 (59.6%)	837/1686 (49.6%)	<0.001
Education:			
low	403/1680 (24.0%)	403/1670 (24.1%)	0.97
middle	960/1680 (57.1%)	935/1670 (56.0%)	0.73
high	317/1680 (18.9%)	332/1670 (19.9%)	0.55
MMSE score, median [IQR]	29 [27-29]	28 [27-29]	0.02

Supplementary Table 1d. Baseline characteristics of participants, split up by median TC/HDL cholesterol. *(Continued)*

	TC / HDL Cholesterol		
Characteristic	**Median and lower (≤3.53)**	**Above median (>3.53)**	**P-value**
Mean systolic BP	154.7 ±21.5	155.9 ±21.2	0.10
Mean diastolic BP	80.5 ±11	82.3 ±10.8	<0.001
Antihypertensive drugs	928/1698 (54.7%)	918/1686 (54.4%)	0.92
BMI	26.9 ±4.1	27.9 ±4.1	<0.001
≤25.5	664/1697 (39.1%)	489/1685 (29.0%)	<0.001
25.5-28.7	552/1697 (32.5%)	590/1685 (35.0%)	0.29
>28.7	481/1697 (28.3%)	606/1685 (36.0%)	0.001
Smoking	204/1693 (12.0%)	234/1684 (13.9%)	0.11
Diabetes	364/1698 (21.4%)	248/1686 (14.7%)	<0.001
History of stroke	196/1677 (11.7%)	138/1663 (8.3%)	0.001
History of CVD	527/1687 (31.2%)	460/1674 (27.5%)	0.02
Apo allele e4 positive	360/1403 (25.7%)	430/1451 (29.6%)	0.02
CLD at baseline	715/1694 (42.2%)	431/1684 (25.6%)	<0.001
CLD initiation after baseline	137/1355 (10.1%)	318/1373 (23.2%)	<0.001
Serum cholesterol measures:			
TC	4.9 ±1.0	5.6 ±1.0	<0.001
HDL-C	1.7 ±0.4	1.3 ±0.3	<0.001
LDL-C	2.7 ±0.8	3.6 ±0.9	<0.001
TC/HDL-C	2.8 ±0.4	4.5 ±0.8	<0.001
LDL-C/HDL-C	0.7 ±0.3	0.4 ±0.1	<0.001
Remnant C	0.5 ±0.2	0.7 ±0.3	<0.001
Apolipoprotein A1	1.6 ±0.3	1.4 ±0.2	<0.001
Apolipoprotein B	0.8 ±0.2	1.1 ±0.2	<0.001
ApoA1/ApoB	0.5 ±0.1	0.8 ±0.2	<0.001
Outcome measures			
Dementia	129/1698 (7.6%)	101/1686 (6.0%)	0.07
Mortality	272/1697 (16.0%)	271/1683 (16.1%)	0.96
Dementia/mortality	374/1698 (22.0%)	351/1684 (20.8%)	0.43

Depicted are numbers with %, means ±standard deviations, or medians [IQR]. P-values derived from Fisher's exact tests for proportions, Student's t-tests for means, and Mann-Whitney U tests for medians.
Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol.

Supplementary Table 1e. Baseline characteristics of participants, split up by median HDL/LDL cholesterol.

	HDL / LDL Cholesterol		
Characteristic	**Median and lower (≤0.48)**	**Above median (>0.48)**	**P-value**
Age	74.4 ±2.5	74.3 ±2.5	0.10
Women	995/1682 (59.2%)	845/1682 (50.2%)	<0.001
Education:			
low	412/1665 (24.7%)	388/1665 (23.3%)	0.46
middle	950/1665 (57.1%)	934/1665 (56.1%)	0.77
high	303/1665 (18.2%)	343/1665 (20.6%)	0.16
MMSE score, median [IQR]	29 [27-29]	28 [27-29]	0.15
Mean systolic BP	154.9 ±21.4	155.6 ±21.3	0.35
Mean diastolic BP	80.5 ±11	82.3 ±10.9	<0.001
Antihypertensive drugs	985/1682 (58.6%)	846/1682 (50.3%)	<0.001
BMI	27.2 ±4.3	27.7 ±4	0.001
≤25.5	627/1682 (37.3%)	522/1680 (31.1%)	0.008
25.5-28.7	523/1682 (31.1%)	611/1680 (36.4%)	0.02
>28.7	532/1682 (31.6%)	547/1680 (32.6%)	0.70
Smoking	201/1677 (12.0%)	234/1680 (13.9%)	0.10
Diabetes	402/1682 (23.9%)	206/1682 (12.2%)	<0.001
History of stroke	197/1661 (11.9%)	134/1659 (8.1%)	<0.001
History of CVD	578/1672 (34.6%)	403/1670 (24.1%)	<0.001
Apo allele e4 positive	367/1391 (26.4%)	421/1444 (29.2%)	0.10
CLD at baseline	799/1678 (47.6%)	339/1680 (20.2%)	<0.001
CLD initiation after baseline	118/1354 (8.7%)	334/1361 (24.5%)	<0.001
Serum cholesterol measures:			
TC	4.8 ±1.0	5.7 ±1.0	<0.001
HDL-C	1.7 ±0.4	1.3 ±0.3	<0.001
LDL-C	2.5 ±0.8	3.7 ±0.8	<0.001
TC/HDL-C	2.9 ±0.5	4.4 ±0.8	<0.001
LDL-C/HDL-C	0.7 ±0.3	0.4 ±0.1	<0.001
Remnant C	0.5 ±0.3	0.7 ±0.3	<0.001
Apolipoprotein A1	1.6 ±0.3	1.4 ±0.2	<0.001
Apolipoprotein B	0.8 ±0.2	1.1 ±0.2	<0.001
ApoA1/ApoB	0.5 ±0.1	0.8 ±0.2	<0.001
Outcome measures			
Dementia	117/1682 (7.0%)	111/1682 (6.6%)	0.73
Mortality	272/1681 (16.2%)	267/1679 (15.9%)	0.85

Supplementary Table 1e. Baseline characteristics of participants, split up by median HDL/LDL cholesterol. *(Continued)*

	HDL / LDL Cholesterol		
Characteristic	**Median and lower (≤0.48)**	**Above median (>0.48)**	**P-value**
Dementia/mortality	366/1682 (21.8%)	353/1680 (21.0%)	0.61

Depicted are numbers with %, means ±standard deviations, or medians [IQR]. P-values derived from Fisher's exact tests for proportions, Student's t-tests for means, and Mann-Whitney U tests for medians.
Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol.

Supplementary Table 2. Baseline characteristics of participants included and not included in the analyses.

	Included (n=3392)	**Not included (n=134)**	**p-value**
Age	74.4 (2.5)	74.5 (2.6)	0.68
Women	1853/3392 (55%)	66/134 (49%)	0.25
Education:			
low	807/3392 (24%)	29/133 (22%)	0.69
middle	1902/3392 (57%)	76/133 (57%)	0.94
high	649/3392 (19%)	28/133 (21%)	0.66
MMSE score	28 (27-29)	28 (27) (29)	0.26
Mean systolic BP	155.3 (21.3)	156.7 (22.2)	0.48
Mean diastolic BP	81.4 (11.0)	82 (12.3)	0.58
Antihypertensive drugs	1860/3392 (55%)	79/134 (59%)	0.38
BMI	27.4 (4.1)	27.9 (4.5)	0.27
≤25.5	1156/3390 (34%)	43/134 (32%)	0.79
25.5-28.7	1104/3390 (33%)	44/134 (33%)	1.00
>28.7	1130/3390 (33%)	47/134 (35%)	0.79
Smoking	440/3385 (13%)	28/134 (21%)	**0.01**
Diabetes	613/3392 (18%)	33/134 (25%)	0.07
History of stroke	334/3348 (10%)	13/132 (10%)	1.00
History of CVD	993/3369 (30%)	51/134 (38%)	**0.04**
Apo allele e4 positive	793/2861 (28%)	22/105 (21%)	0.15
Cholesterol medication at baseline	1152/3386 (34%)	48/134 (36%)	0.71
Cholesterol medication initiation after baseline	517/2734 (19%)	18/92 (20%)	0.90
Serum cholesterol measures:			
TC	5.2 (1.1)	5.1 (1.2)	0.49

Supplementary Table 2. Baseline characteristics of participants included and not included in the analyses. *(Continued)*

	Included (n=3392)	Not included (n=134)	p-value
HDL-C	1.5 (0.4)	1.5 (0.4)	0.86
LDL-C	3.1 (1.0)	3.0 (1.1)	0.39
TC/HDL-C	3.7 (1.1)	3.6 (1.2)	0.64
LDL-C/HDL-C	2.2 (0.9)	2.1 (0.9)	0.22
Remnant C	0.6 (0.3)	0.6 (0.3)	0.26
Apolipoprotein A1	1.5 (0.3)	1.5 (0.3)	0.85
Apolipoprotein B	1.0 (0.3)	0.9 (0.3)	0.28
ApoA1/ApoB	0.7 (0.2)	0.7 (0.2)	0.44
Outcome:			
Dementia	231/3392 (7%)	2/62 (32%)	0.44
Mortality	545/3388 (16%)	33/131 (25%)	**0.01**
Dementia/mortality	728/3390 (22%)	10/62 (16%)	0.35

Abbreviations: MMSE: mini-mental state examination, BMI: body mass index, CVD: cardiovascular disease, Apo: apolipoprotein, TC: total cholesterol, HDL-C: high-density lipid cholesterol, LDL-C: low-density lipid cholesterol, remnant C: remnant cholesterol.

Missings included/not included: Education: 34/1, MMSE score: 5/1, systolic BP: 3/0, diastolic BP: 2/9, BMI: 2/0, smoking: 7/0, history of stroke: 54/2, history of CD: 23/0, cholesterol medication: 6/0, cholesterol: 7/66, HDL-C: 1/66, LDL: 28/68, TCHDL: 8/66, HDLLDL: 28/68, RC: 28/68, ApoA1: 183/66, ApoB: 184/66, ApoBA: 184/66, dementia: 0/72, mortality: 4/3, dementia/mortality: 2/72

Supplementary Table 3. Cox regression of dementia, mortality without dementia and dementia/mortality combined predicted by z-scores of reference serum lipids at baseline.

	Model 1				Model 2				Model 3			
	events/total	HR	95%CI	p	events/total	HR	95%CI	p	events/total	HR	95%CI	p
Dementia												
ApoA1	219/3213	1.08	(0.94-1.23)	0.27	164/2678	1.10	(0.94-1.30)	0.24	160/2616	1.05	(0.89-1.25)	0.55
ApoB	219/3212	0.95	(0.83-1.09)	0.45	164/2677	0.86	(0.72-1.02)	0.08	160/2615	0.87	(0.73-1.04)	0.14
Apo B/A1	219/3212	0.92	(0.80-1.06)	0.24	164/2677	0.84	(0.71-1.00)	**0.045**	160/2615	0.88	(0.74-1.04)	0.14
Triglycerides	231/3386	0.92	(0.76-1.12)	0.40	174/2817	0.96	(0.77-1.19)	0.69	170/2753	1.02	(0.82-1.26)	0.88
Non HDL	230/3384	0.96	(0.84-1.09)	0.53	173/2815	0.85	(0.71-1.01)	0.06	169/2751	0.86	(0.72-1.02)	0.09
TG/HDL	231/3386	0.94	(0.81-1.10)	0.45	174/2817	0.97	(0.82-1.15)	0.74	170/2753	1.02	(0.87-1.21)	0.80
Remnant-C	228/3363	0.88	(0.76-1.02)	0.09	171/2796	0.87	(0.74-1.03)	0.11	167/2733	0.91	(0.77-1.08)	0.30
Dem/Mort												
ApoA1	694/3211	0.86	(0.80-0.93)	**<0.001**	550/2676	0.94	(0.85-1.03)	0.16	537/2614	0.98	(0.89-1.08)	0.69
ApoB	694/3210	0.90	(0.83-0.97)	**0.01**	550/2675	0.90	(0.82-0.99)	**0.03**	537/2613	0.93	(0.84-1.02)	0.12
Apo B/A1	694/3210	1.01	(0.93-1.08)	0.87	550/2675	0.96	(0.88-1.05)	0.39	537/2613	0.96	(0.87-1.05)	0.35
Triglycerides	728/3384	1.06	(0.96-1.16)	0.25	579/2815	1.05	(0.94-1.17)	0.36	566/2751	1.03	(0.92-1.15)	0.61
Non HDL	725/3382	0.87	(0.81-0.94)	**<0.001**	576/2813	0.85	(0.77-0.93)	**0.001**	563/2749	0.88	(0.79-0.97)	**0.01**
TG/HDL	728/3384	1.09	(1.02-1.16)	**0.01**	579/2815	1.06	(0.98-1.14)	0.14	566/2751	1.04	(0.96-1.13)	0.36
Remnant-C	719/3361	1.03	(0.95-1.10)	0.49	571/2794	1.02	(0.94-1.11)	0.63	558/2731	0.99	(0.91-1.08)	0.87
Mortality												
ApoA1	475/3211	0.77	(0.71-0.85)	**<0.001**	386/2676	0.86	(0.77-0.96)	**0.01**	377/2614	0.93	(0.83-1.05)	0.25
ApoB	475/3210	0.87	(0.80-0.96)	**0.004**	386/2675	0.92	(0.82-1.02)	0.12	377/2613	0.95	(0.85-1.07)	0.38
Apo B/A1	475/3210	1.05	(0.96-1.14)	0.33	386/2675	1.02	(0.92-1.13)	0.74	377/2613	1.00	(0.90-1.12)	0.99

Supplementary Table 3. Cox regression of dementia, mortality without dementia and dementia/mortality combined predicted by z-scores of reference serum lipids at baseline. *(Continued)*

	Model 1				Model 2				Model 3			
	events/total	**HR**	**95%CI**	**p**	**events/total**	**HR**	**95%CI**	**p**	**events/total**	**HR**	**95%CI**	**p**
Non HDL	566/3445	0.85	(0.78-0.92)	**<0.001**	448/2866	0.87	(0.78-0.97)	0.01	438/2801	0.91	(0.81-1.02)	0.10
Triglycerides	497/3384	1.12	(1.00-1.24)	**0.049**	405/2815	1.09	(0.96-1.23)	0.17	396/2751	1.04	(0.91-1.19)	0.55
TG/HDL	497/3384	1.14	(1.06-1.22)	**<0.001**	405/2815	1.09	(1.00-1.18)	**0.049**	396/2751	1.05	(0.95-1.16)	0.32
Remnant-C	491/3361	1.09	(1.00-1.19)	**0.046**	400/2794	1.08	(0.99-1.19)	0.10	391/2731	1.03	(0.93-1.14)	0.56

Model 1 was unadjusted. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), Non HDL: TC-HDL, HR: hazard ratio, 95%CI: 95% confidence interval.

Supplementary Table 4. Interactions.

Moderator - outcome	**Predictors**	**events/total**	**HR**	**95%CI**	**P**
BMI:					
- Dementia:	TC/HDL	169/2751	0.17	(0.06-0.45)	**<0.001**
	BMI	169/2751	0.95	(0.91-0.99)	**0.01**
	Interaction	169/2751	1.06	(1.03-1.10)	**0.001**
	LDL/HDL	167/2733	0.29	(0.10-0.79)	**0.02**
	BMI	167/2733	0.95	(0.91-0.99)	**0.01**
	Interaction	167/2733	1.04	(1.00-1.08)	**0.04**
- Dementia/mort	HDL	566/2755	1.89	(1.10-3.22)	**0.02**
	BMI	566/2755	0.97	(0.95-1.00)	**0.03**
	Interaction	566/2755	0.98	(0.96-1.00)	**0.02**
	TC/HDL	563/2749	0.52	(0.29-0.95)	**0.03**
	BMI	563/2749	0.98	(0.96-1.00)	0.06
	Interaction	563/2749	1.02	(1.00-1.04)	**0.048**
Education:					
- Dementia:	LDL	167/2733	1.05	(0.79-1.39)	0.75
	Education	167/2733	1.04	(0.81-1.34)	0.74
	Interaction	167/2733	0.78	(0.61-0.98)	**0.04**
	HDL	170/2757	0.91	(0.7-1.19)	0.50
	Education	170/2757	0.96	(0.74-1.24)	0.74
	Interaction	170/2757	1.25	(1.02-1.54)	**0.04**
	TC/HDL	169/2751	1.27	(1.00-1.61)	0.052
	Education	169/2751	0.94	(0.72-1.21)	0.61
	Interaction	169/2751	0.63	(0.49-0.79)	**<0.001**
	LDL/HDL	167/2733	1.10	(0.85-1.43)	0.48
	Education	167/2733	0.99	(0.76-1.27)	0.92
	Interaction	167/2733	0.73	(0.59-0.90)	**0.003**

Supplementary Table 4. Interactions. *(Continued)*

Moderator - outcome	Predictors	events/total	HR	95%CI	P
- Mortality:	TC/HDL	394/2749	1.19	(1.00-1.41)	**0.045**
	Education	394/2749	0.91	(0.78-1.07)	0.25
	TC/HDL	394/2749	0.82	(0.71-0.95)	**0.01**
	LDL/HDL	391/2731	0.91	(0.76-1.08)	0.28
	Education	391/2731	0.91	(0.77-1.06)	0.23
	Interaction	391/2731	1.17	(1.01-1.36)	**0.03**

Interactions tested in Model 1 (i.e. unadjusted with age as timescale and baseline age as time of entry). Interactions were tested for all confounders from model 3, including: sex (female vs male), age (years), BMI (kg/m^2), APOE-e4 genotype (positive vs negative), MMSE score, education (ordinal low/middle/high), smoking (current vs former or never), systolic blood pressure (mmHg), antihypertensive medication use (yes/no), history of stroke (yes/no), history of cardiovascular disease (yes/no), history of diabetes (yes/no) and cholesterol lowering drug use (yes/no). Only significant ($p<0.05$) interactions for the main (i.e. not reference) cholesterol measures are depicted. To interpret the effect size of the interaction terms, the natural logarithm of the HR from the interaction term needs to be added to the natural logarithm of the HR from the predictor. E.g. according to the results above, for a participant with a BMI of 25 kg/m^2, one SD higher TC/HDL was associated with an HR of dementia of exp[ln(0.17)+ln(1.06)*25]=0.73. Abbreviations: BMI: body mass index, TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 4. Interactions *(Continued)*

Moderator - outcome	Predictors	events/total	HR	95%CI	P
Education:					
- Dementia/Mort	TC	563/2750	1.00	(0.86-1.17)	1.00
	Education	563/2750	0.91	(0.79-1.04)	0.16
	Interaction	563/2750	0.86	(0.75-0.98)	**0.02**
	LDL	558/2731	0.97	(0.82-1.13)	0.67
	Education	558/2731	0.92	(0.81-1.06)	0.25
	Interaction	558/2731	0.86	(0.75-0.98)	**0.02**
	HDL	566/2755	0.89	(0.76-1.04)	0.14
	Education	566/2755	0.95	(0.83-1.08)	0.42
	Interaction	566/2755	1.14	(1.01-1.29)	**0.04**
	TC/HDL	563/2749	1.21	(1.05-1.39)	**0.01**
	Education	563/2749	0.93	(0.81-1.06)	0.27
	Interaction	563/2749	0.76	(0.67-0.86)	**<0.001**
	LDL/HDL	558/2731	1.09	(0.94-1.27)	0.23
	Education	558/2731	0.93	(0.81-1.07)	0.30
	Interaction	558/2731	0.82	(0.72-0.92)	**0.001**

Supplementary Table 4. Interactions *(Continued)*

Moderator - outcome	Predictors	events/total	HR	95%CI	P
History of CVD:					
- Dementia	HDL	170/2757	1.03	(0.86-1.24)	0.72
	Heart2	170/2757	0.76	(0.52-1.12)	0.17
	Interaction	170/2757	1.47	(1.06-2.04)	**0.02**
APOE allel e4					
- Dementia/mort	HDL	566/2755	0.94	(0.84-1.06)	0.32
	APOE4+	566/2755	1.79	(1.51-2.13)	**<0.001**
	Interaction	566/2755	1.19	(1.00-1.41)	**0.045**
Sex					
- Dementia	HDL	170/2757	1.40	(1.11-1.76)	**0.01**
	Female sex	170/2757	1.21	(0.86-1.68)	0.27
	Interaction	170/2757	0.72	(0.53-0.96)	**0.03**

Interactions tested in Model 1 (i.e. unadjusted with age as timescale and baseline age as time of entry). Interactions were tested for all confounders from model 3, including: sex (female vs male), age (years), BMI (kg/m2), APOE-e4 genotype (positive vs negative), MMSE score, education (ordinal low/middle/high), smoking (current vs former or never), systolic blood pressure (mmHg), antihypertensive medication use (yes/no), history of stroke (yes/no), history of cardiovascular disease (yes/no), history of diabetes (yes/no) and cholesterol lowering drug use (yes/no). Only significant ($p<0.05$) interactions for the main (i.e. not reference) cholesterol measures are depicted. To interpret the effect size of the interaction terms, the natural logarithm of the HR from the interaction term needs to be added to the natural logarithm of the HR from the predictor. E.g. according to the results above, for a participant with a BMI of 25 kg/m2, one SD higher TC/HDL was associated with an HR of dementia of exp[ln(0.17)+ln(1.06)*25]=0.73. Abbreviations: BMI: body mass index, TC: total cholesterol, LDL: low-density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, HR: hazard ratio, 95%CI: 95% confidence interval.

Supplementary Table 5. Subgroup analyses based on tertiles of baseline body mass index (BMI).

Model	Cholesterol	BMI category	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	≤25.5	69/954	0.75	(0.55-1.01)	0.06	0.051	203/953	0.77	(0.65-0.92)	0.003	0.90	134/953	0.78	(0.63-0.96)	0.02	0.38
		25.5-28.7	57/953	0.97	(0.71-1.32)	0.85		200/953	0.79	(0.66-0.94)	0.01		143/953	0.71	(0.58-0.88)	0.002	
		>28.7	47/907	1.10	(0.79-1.54)	0.57		173/906	0.92	(0.77-1.11)	0.40		126/906	0.86	(0.69-1.08)	0.19	
	LDL	≤25.5	69/950	0.69	(0.51-0.93)	0.01	**0.04**	202/949	0.75	(0.63-0.89)	0.001	0.77	133/949	0.79	(0.64-0.97)	0.02	0.41
		25.5-28.7	56/946	0.94	(0.70-1.27)	0.70		199/946	0.78	(0.66-0.93)	0.01		143/946	0.72	(0.59-0.88)	0.002	
		>28.7	46/898	1.04	(0.72-1.50)	0.83		170/897	0.90	(0.74-1.10)	0.30		124/897	0.85	(0.68-1.08)	0.18	
	HDL	≤25.5	69/955	1.29	(1.05-1.60)	0.02	0.08	203/954	1.03	(0.90-1.18)	0.63	**0.02**	134/954	0.88	(0.73-1.05)	0.16	0.21
		25.5-28.7	57/954	1.02	(0.76-1.38)	0.89		200/954	0.89	(0.75-1.05)	0.18		143/954	0.82	(0.66-1.01)	0.07	
		>28.7	48/910	0.83	(0.58-1.19)	0.32		176/909	0.82	(0.68-1.00)	0.049		128/909	0.81	(0.65-1.03)	0.08	
	TC/HDL	≤25.5	69/953	0.56	(0.41-0.77)	<0.001	**<0.001**	203/952	0.86	(0.74-1.02)	0.08	0.050	134/952	1.05	(0.87-1.27)	0.59	0.77
		25.5-28.7	57/953	0.92	(0.71-1.20)	0.54		200/953	0.95	(0.83-1.1)	0.51		143/953	0.97	(0.82-1.15)	0.74	
		>28.7	47/907	1.27	(0.98-1.64)	0.07		173/906	1.11	(0.96-1.29)	0.17		126/906	1.06	(0.88-1.26)	0.55	
	LDL/HDL	≤25.5	69/950	0.64	(0.50-0.82)	<0.001	**0.005**	202/949	0.83	(0.72-0.96)	0.01	0.13	133/949	0.96	(0.80-1.16)	0.69	0.86
		25.5-28.7	56/946	0.93	(0.71-1.21)	0.60		199/946	0.91	(0.79-1.05)	0.19		143/946	0.91	(0.77-1.07)	0.26	
		>28.7	46/898	1.15	(0.81-1.65)	0.44		170/897	1.06	(0.89-1.27)	0.52		124/897	1.04	(0.84-1.28)	0.73	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 5. Subgroup analyses based on tertiles of baseline body mass index (BMI). *(Continued)*

Model	Cholesterol	BMI category	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 3	TC	≤25.5	68/935	0.78	(0.57-1.06)	0.11	**0.04**	199/934	0.85	(0.71-1.01)	0.07	0.99	131/934	0.88	(0.70-1.10)	0.25	0.25
		25.5-28.7	56/930	0.97	(0.70-1.35)	0.87		196/930	0.83	(0.69-1.00)	0.051		140/930	0.76	(0.61-0.95)	0.02	
		>28.7	45/887	1.14	(0.8-1.62)	0.46		168/886	0.94	(0.77-1.15)	0.55		123/886	0.87	(0.68-1.11)	0.26	
	LDL	≤25.5	68/931	0.71	(0.52-0.97)	0.03	**0.03**	198/930	0.81	(0.68-0.97)	0.02	0.84	130/930	0.87	(0.70-1.08)	0.21	0.29
		25.5-28.7	55/923	0.95	(0.69-1.31)	0.76		195/923	0.83	(0.69-1.00)	0.045		140/923	0.77	(0.62-0.96)	0.02	
		>28.7	44/879	1.08	(0.73-1.59)	0.69		165/878	0.91	(0.74-1.13)	0.40		121/878	0.86	(0.67-1.10)	0.24	
	HDL	≤25.5	68/936	1.33	(1.08-1.65)	0.01	0.14	199/935	1.12	(0.98-1.28)	0.09	**0.03**	131/935	0.99	(0.82-1.18)	0.87	0.21
		25.5-28.7	56/931	1.04	(0.76-1.41)	0.82		196/931	0.94	(0.79-1.12)	0.50		140/931	0.89	(0.72-1.09)	0.27	
		>28.7	46/890	0.86	(0.59-1.24)	0.42		171/889	0.88	(0.72-1.07)	0.19		125/889	0.88	(0.69-1.11)	0.27	
	TC/HDL	≤25.5	68/934	0.55	(0.39-0.76)	<0.001	**<0.001**	199/933	0.82	(0.69-0.97)	0.02	**0.03**	131/933	0.99	(0.82-1.21)	0.96	0.89
		25.5-28.7	56/930	0.90	(0.69-1.19)	0.47		196/930	0.94	(0.81-1.08)	0.39		140/930	0.96	(0.81-1.13)	0.60	
		>28.7	45/887	1.25	(0.97-1.62)	0.09		168/886	1.09	(0.93-1.27)	0.31		123/886	1.02	(0.84-1.25)	0.82	
	LDL/HDL	≤25.5	68/931	0.64	(0.50-0.82)	0.001	**0.005**	198/930	0.82	(0.71-0.95)	0.01	0.11	130/930	0.94	(0.78-1.13)	0.53	0.93
		25.5-28.7	55/923	0.95	(0.73-1.24)	0.71		195/923	0.92	(0.80-1.07)	0.27		140/923	0.92	(0.77-1.09)	0.32	
		>28.7	44/879	1.16	(0.80-1.67)	0.43		165/878	1.04	(0.86-1.25)	0.68		121/878	1.02	(0.82-1.26)	0.89	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 6. Subgroup analyses based on education categories

Model	Cholesterol	Education category	Dementia events/ tot	HR	95%CI	p-value	p-trend	Dem/ mort events/ tot	HR	95%CI	p-value	p-trend	Mortality events/ tot	HR	95%CI	p-value	p-trend
Model 2	TC	<7 years	55/671	1.19	(0.85-1.65)	0.31	0.15	169/670	0.90	(0.74-1.10)	0.30	0.04	114/670	0.78	(0.62-1.00)	0.046	0.15
		7-12 years	89/1593	0.94	(0.73-1.19)	0.60		304/1593	0.85	(0.74-0.97)	0.02		215/1593	0.81	(0.68-0.95)	0.01	
		>12 years	29/552	0.61	(0.40-0.94)	0.03		103/551	0.67	(0.53-0.85)	0.001		74/551	0.70	(0.52-0.94)	0.02	
	LDL	<7 years	53/666	1.18	(0.83-1.68)	0.37	0.07	166/665	0.89	(0.73-1.09)	0.26	0.08	113/665	0.78	(0.61-1.00)	0.046	0.36
		7-12 years	89/1581	0.86	(0.68-1.09)	0.22		302/1581	0.81	(0.70-0.93)	0.002		213/1581	0.78	(0.66-0.93)	0.004	
		>12 years	29/549	0.53	(0.35-0.81)	0.004		103/548	0.68	(0.54-0.86)	0.001		74/548	0.75	(0.57-1.00)	0.047	
	HDL	<7 years	55/672	0.87	(0.63-1.20)	0.41	**0.04**	169/671	0.74	(0.61-0.89)	0.002	0.05	114/671	0.67	(0.53-0.85)	0.001	0.40
		7-12 years	90/1597	1.28	(1.06-1.55)	0.01		307/1597	1.07	(0.95-1.20)	0.27		217/1597	0.97	(0.84-1.12)	0.66	
		>12 years	29/552	1.36	(0.97-1.91)	0.08		103/551	1.04	(0.84-1.27)	0.74		74/551	0.88	(0.68-1.14)	0.34	
	TC/HDL	<7 years	55/671	1.28	(0.99-1.64)	0.06	**<0.001**	169/670	1.23	(1.07-1.43)	0.01	**<0.001**	114/670	1.21	(1.01-1.45)	0.04	**0.03**
		7-12 years	89/1592	0.74	(0.59-0.94)	0.01		304/1592	0.88	(0.78-1.00)	0.04		215/1592	0.95	(0.82-1.10)	0.48	
		>12 years	29/552	0.51	(0.33-0.78)	0.002		103/551	0.76	(0.62-0.93)	0.01		74/551	0.89	(0.70-1.12)	0.32	
	LDL/HDL	<7 years	53/666	1.17	(0.85-1.61)	0.34	**0.01**	166/665	1.15	(0.96-1.38)	0.12	**0.004**	113/665	1.14	(0.71-1.09)	0.23	0.10
		7-12 years	89/1581	1.31	(1.07-1.61)	0.01		302/1581	1.19	(1.06-1.34)	0.004		213/1581	1.13	(0.98-1.31)	0.09	
		>12 years	29/549	0.55	(0.39-0.77)	0.001		103/548	0.77	(0.64-0.93)	0.01		74/548	0.89	(0.89-1.40)	0.33	
		>12 years	27/539	0.48	(0.33-0.71)	<0.001		99/538	0.70	(0.57-0.85)	<0.001		72/538	0.79	(0.62-1.01)	0.06	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 6. Subgroup analyses based on education categories *(Continued)*

Model	Cholesterol	Education category	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	**p-trend**	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 3	TC	<7 years	54/655	1.19	(0.84-1.70)	0.32	0.09	164/654	0.92	(0.75-1.12)	0.41	**0.02**	110/654	0.81	(0.63-1.04)	0.10	0.11
		7-12 years	88/1555	0.98	(0.76-1.27)	0.90		300/1555	0.93	(0.80-1.07)	0.30		212/1555	0.91	(0.76-1.08)	0.27	
		>12 years	27/542	0.50	(0.30-0.82)	0.01		99/541	0.64	(0.49-0.84)	0.001		72/541	0.70	(0.51-0.97)	0.03	
	LDL	<7 years	52/650	1.19	(0.82-1.73)	0.35	**0.04**	161/649	0.91	(0.74-1.13)	0.39	**0.02**	109/649	0.81	(0.62-1.04)	0.10	0.20
		7-12 years	88/1544	0.92	(0.72-1.19)	0.54		298/1544	0.88	(0.76-1.02)	0.09		210/1544	0.87	(0.73-1.04)	0.13	
		>12 years	27/539	0.42	(0.26-0.69)	0.001		99/538	0.64	(0.49-0.82)	0.001		72/538	0.74	(0.55-1.01)	0.06	
	HDL	<7 years	54/656	0.80	(0.56-1.13)	0.21	**0.04**	164/655	0.76	(0.62-0.93)	0.01	**0.04**	110/655	0.72	(0.56-0.93)	0.01	0.30
		7-12 years	89/1559	1.19	(0.98-1.46)	0.09		303/1559	1.08	(0.96-1.22)	0.20		214/1559	1.00	(0.86-1.17)	0.96	
		>12 years	27/542	1.44	(0.98-2.12)	0.07		99/541	1.19	(0.96-1.49)	0.11		72/541	1.06	(0.80-1.40)	0.69	
	TC/HDL	<7 years	54/655	1.37	(1.05-1.80)	0.02	**<0.001**	164/654	1.25	(1.06-1.47)	0.01	**<0.001**	110/654	1.19	(0.98-1.46)	0.09	**0.01**
		7-12 years	88/1554	0.83	(0.66-1.04)	0.11		300/1554	0.92	(0.81-1.04)	0.16		212/1554	0.97	(0.84-1.13)	0.73	
		>12 years	27/542	0.44	(0.26-0.72)	0.001		99/541	0.65	(0.52-0.82)	<0.001		72/541	0.76	(0.58-0.98)	0.04	
	LDL/HDL	<7 years	52/650	1.24	(0.89-1.74)	0.21	**0.003**	161/649	1.15	(0.95-1.39)	0.15	**0.001**	109/649	1.12	(0.89-1.40)	0.33	**0.03**
		7-12 years	88/1544	0.85	(0.69-1.05)	0.13		298/1544	0.89	(0.79-1.00)	0.05		210/1544	0.92	(0.80-1.07)	0.29	
		>12 years	27/539	0.48	(0.33-0.71)	<0.001		99/538	0.70	(0.57-0.85)	<0.001		72/538	0.79	(0.62-1.01)	0.06	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 7. Subgroup analyses based on apolipoprotein E allele e4 positivity.

Model	Cholesterol	APOE category	Dementia events/ tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/ tot	HR	95%CI	p-value	p-trend
Model 2	TC	APOE4 -	75/2036	0.90	(0.69-1.17)	0.42	0.37	355/2034	0.82	(0.72-0.93)	0.002	0.47	280/2034	0.80	(0.69-0.92)	0.002	0.46
		APOE4 +	98/780	0.94	(0.73-1.20)	0.60		221/780	0.84	(0.71-0.99)	0.04		123/780	0.76	(0.60-0.96)	0.02	
	LDL	APOE4 -	75/2019	0.88	(0.67-1.15)	0.34	0.84	352/2017	0.81	(0.71-0.92)	0.001	0.93	277/2017	0.79	(0.68-0.91)	0.001	0.50
		APOE4 +	96/777	0.81	(0.63-1.04)	0.09		219/777	0.79	(0.66-0.93)	0.01		123/777	0.77	(0.61-0.98)	0.03	
	HDL	APOE4 -	76/2040	1.04	(0.82-1.32)	0.72	0.09	356/2038	0.92	(0.81-1.03)	0.15	**0.041**	280/2038	0.88	(0.77-1.01)	0.06	0.78
		APOE4 +	98/781	1.29	(1.07-1.57)	0.01		223/781	1.05	(0.91-1.21)	0.49		125/781	0.85	(0.69-1.05)	0.12	
	TC/HDL	APOE4 -	75/2036	0.91	(0.71-1.16)	0.43	0.44	355/2034	0.96	(0.86-1.08)	0.52	0.52	280/2034	0.98	(0.87-1.11)	0.75	0.68
		APOE4 +	98/779	0.77	(0.62-0.97)	0.03		221/779	0.93	(0.81-1.07)	0.34		123/779	1.08	(0.90-1.29)	0.40	
	LDL/HDL	APOE4 -	75/2019	0.86	(0.69-1.08)	0.21	0.36	352/2017	0.92	(0.83-1.03)	0.14	0.26	277/2017	0.94	(0.83-1.06)	0.31	0.84
		APOE4 +	96/777	0.72	(0.58-0.90)	0.003		219/777	0.85	(0.73-0.99)	0.03		123/777	0.98	(0.81-1.20)	0.87	
Model 3	TC	APOE4 -	72/1990	0.91	(0.68-1.21)	0.51	0.33	348/1988	0.88	(0.77-1.00)	0.05	0.46	276/1988	0.86	(0.74-1.00)	0.06	0.44
		APOE4 +	97/762	0.88	(0.68-1.15)	0.36		215/762	0.86	(0.72-1.03)	0.10		118/762	0.84	(0.65-1.08)	0.17	
	LDL	APOE4 -	72/1974	0.88	(0.66-1.18)	0.39	0.68	345/1972	0.86	(0.75-0.98)	0.03	0.94	273/1972	0.85	(0.73-0.99)	0.04	0.42
		APOE4 +	95/759	0.80	(0.62-1.04)	0.09		213/759	0.81	(0.67-0.97)	0.02		118/759	0.84	(0.65-1.08)	0.18	
	HDL	APOE4 -	73/1994	1.08	(0.84-1.38)	0.56	0.16	349/1992	0.97	(0.86-1.09)	0.58	**0.045**	276/1992	0.93	(0.81-1.07)	0.32	0.93
		APOE4 +	97/763	1.13	(0.91-1.39)	0.26		217/763	1.06	(0.92-1.23)	0.43		120/763	0.95	(0.77-1.17)	0.62	
	TC/HDL	APOE4 -	72/1990	0.90	(0.7-01.16)	0.40	0.64	348/1988	0.96	(0.86-1.08)	0.51	0.37	276/1988	0.98	(0.86-1.11)	0.76	0.97
		APOE4 +	97/761	0.86	(0.69-1.08)	0.19		215/761	0.93	(0.80-1.07)	0.31		118/761	1.02	(0.84-1.23)	0.88	
	LDL/HDL	APOE4 -	72/1974	0.86	(0.68-1.09)	0.21	0.62	345/1972	0.93	(0.83-1.04)	0.21	0.23	273/1972	0.95	(0.84-1.08)	0.46	0.62
		APOE4 +	95/759	0.80	(0.64-1.01)	0.06		213/759	0.87	(0.74-1.01)	0.06		118/759	0.96	(0.78-1.18)	0.68	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 8. Subgroup analyses based on cardiovascular disease (CVD) history at baseline.

Model	Cholesterol	CVD history	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	No CVD	129/1968	0.92	(0.75-1.12)	0.40	0.88	345/1966	0.83	(0.73-0.94)	0.004	0.40	216/1966	0.77	(0.66-0.91)	0.002	0.14
		CVD	43/825	0.82	(0.55-1.23)	0.34		227/825	0.88	(0.74-1.05)	0.16		184/825	0.88	(0.73-1.07)	0.21	
	LDL	No CVD	127/1956	0.87	(0.71-1.07)	0.18	0.56	342/1954	0.82	(0.73-0.93)	0.002	0.84	215/1954	0.79	(0.67-0.93)	0.004	0.42
		CVD	43/818	0.66	(0.43-1.02)	0.06		225/818	0.80	(0.67-0.96)	0.02		182/818	0.82	(0.67-1.01)	0.06	
	HDL	No CVD	129/1969	1.08	(0.90-1.28)	0.41	**0.04**	345/1967	0.97	(0.87-1.09)	0.62	0.64	216/1967	0.90	(0.78-1.05)	0.17	0.95
		CVD	44/829	1.51	(1.15-1.98)	0.003		230/829	1.03	(0.88-1.19)	0.74		186/829	0.89	(0.75-1.07)	0.22	
	TC/HDL	No CVD	129/1968	0.90	(0.75-1.08)	0.25	0.07	345/1966	0.93	(0.84-1.04)	0.22	0.53	216/1966	0.96	(0.84-1.10)	0.54	0.21
		CVD	43/824	0.56	(0.37-0.83)	0.004		227/824	0.96	(0.83-1.12)	0.62		184/824	1.07	(0.91-1.25)	0.40	
	LDL/HDL	No CVD	127/1956	0.86	(0.72-1.02)	0.09	0.11	342/1954	0.90	(0.81-1.01)	0.07	0.93	215/1954	0.93	(0.81-1.07)	0.33	0.54
		CVD	43/818	0.60	(0.44-0.82)	0.001		225/818	0.87	(0.76-1.01)	0.07		182/818	0.96	(0.82-1.13)	0.63	
Model 3	TC	No CVD	126/1945	0.94	(0.76-1.16)	0.56	0.99	341/1943	0.87	(0.76-0.99)	0.03	0.73	215/1943	0.82	(0.70-0.97)	0.02	0.45
		CVD	43/807	0.79	(0.52-1.21)	0.29		222/807	0.89	(0.74-1.06)	0.19		179/807	0.89	(0.72-1.09)	0.26	
	LDL	No CVD	124/1933	0.89	(0.73-1.10)	0.30	0.66	338/1931	0.86	(0.76-0.98)	0.03	0.84	214/1931	0.85	(0.72-1.00)	0.048	0.83
		CVD	43/800	0.64	(0.42-1.00)	0.05		220/800	0.80	(0.66-0.97)	0.02		177/800	0.83	(0.67-1.03)	0.10	
	HDL	No CVD	126/1946	1.04	(0.87-1.25)	0.68	**0.02**	341/1944	0.99	(0.88-1.11)	0.89	0.62	215/1944	0.94	(0.81-1.10)	0.45	0.98
		CVD	44/811	1.49	(1.11-2.00)	0.01		225/811	1.04	(0.90-1.22)	0.59		181/811	0.92	(0.77-1.11)	0.39	
	TC/HDL	No CVD	126/1945	0.94	(0.78-1.12)	0.47	0.07	341/1943	0.94	(0.84-1.05)	0.25	0.76	215/1943	0.95	(0.83-1.09)	0.45	0.35
		CVD	43/806	0.59	(0.39-0.89)	0.01		222/806	0.96	(0.82-1.11)	0.56		179/806	1.05	(0.89-1.24)	0.56	
	LDL/HDL	No CVD	124/1933	0.90	(0.75-1.08)	0.24	0.10	338/1931	0.92	(0.83-1.03)	0.15	0.79	214/1931	0.95	(0.82-1.09)	0.45	0.81
		CVD	43/800	0.61	(0.44-0.85)	0.003		220/800	0.87	(0.75-1.01)	0.07		177/800	0.96	(0.81-1.13)	0.60	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 9. Subgroup analyses based on sex.

Model	Cholesterol	Sex	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	Men	71/1261	0.94	(0.69-1.28)	0.70	0.31	316/1260	0.83	(0.72-0.96)	0.01	0.82	245/1260	0.79	(0.67-0.93)	0.01	0.89
		Women	102/1555	0.91	(0.73-1.15)	0.44		260/1554	0.83	(0.72-0.96)	0.01		158/1554	0.77	(0.64-0.93)	0.01	
	LDL	Men	70/1249	0.82	(0.61-1.12)	0.21	0.44	315/1248	0.83	(0.72-0.95)	0.01	0.57	245/1248	0.82	(0.69-0.96)	0.02	0.56
		Women	101/1547	0.86	(0.68-1.08)	0.19		256/1546	0.79	(0.68-0.91)	0.001		155/1546	0.73	(0.61-0.89)	0.001	
	HDL	Men	71/1263	1.38	(1.11-1.72)	0.004	**0.048**	317/1262	0.97	(0.85-1.10)	0.60	0.99	246/1262	0.83	(0.71-0.97)	0.02	0.48
		Women	103/1558	1.08	(0.89-1.31)	0.44		262/1557	0.99	(0.87-1.12)	0.83		159/1557	0.91	(0.78-1.08)	0.29	
	TC/HDL	Men	71/1260	0.71	(0.55-0.92)	0.01	0.34	316/1259	0.95	(0.85-1.07)	0.42	0.91	245/1259	1.03	(0.91-1.17)	0.64	0.67
		Women	102/1555	0.90	(0.73-1.11)	0.34		260/1554	0.94	(0.83-1.07)	0.36		158/1554	0.97	(0.82-1.15)	0.73	
	LDL/HDL	Men	70/1249	0.71	(0.57-0.90)	0.01	0.72	315/1248	0.92	(0.81-1.03)	0.14	0.56	245/1248	0.98	(0.86-1.13)	0.83	0.49
		Women	101/1547	0.84	(0.69-1.03)	0.09		256/1546	0.87	(0.76-0.99)	0.04		155/1546	0.89	(0.75-1.05)	0.18	
Model 3	TC	Men	69/1234	0.90	(0.65-1.23)	0.50	0.44	307/1233	0.87	(0.75-1.02)	0.08	0.99	238/1233	0.85	(0.71-1.02)	0.07	0.90
		Women	100/1518	0.96	(0.76-1.21)	0.72		256/1517	0.88	(0.76-1.03)	0.11		156/1517	0.83	(0.69-1.01)	0.06	
	LDL	Men	68/1223	0.79	(0.57-1.09)	0.15	0.64	306/1222	0.87	(0.74-1.01)	0.07	0.75	238/1222	0.88	(0.74-1.05)	0.16	0.68
		Women	99/1510	0.91	(0.72-1.16)	0.45		252/1509	0.83	(0.72-0.97)	0.02		153/1509	0.78	(0.64-0.95)	0.01	
	HDL	Men	69/1236	1.29	(1.02-1.64)	0.03	**0.03**	308/1235	1.02	(0.89-1.17)	0.76	0.81	239/1235	0.91	(0.77-1.07)	0.26	0.52
		Women	101/1521	1.00	(0.82-1.23)	0.96		258/1520	1.00	(0.88-1.14)	1.00		157/1520	0.98	(0.83-1.16)	0.82	
	TC/HDL	Men	69/1233	0.75	(0.57-0.98)	0.04	0.22	307/1232	0.93	(0.82-1.05)	0.25	0.78	238/1232	0.99	(0.87-1.14)	0.92	0.87
		Women	100/1518	0.98	(0.80-1.20)	0.83		256/1517	0.96	(0.84-1.10)	0.56		156/1517	0.96	(0.80-1.14)	0.64	
	LDL/HDL	Men	68/1223	0.75	(0.59-0.96)	0.02	0.49	306/1222	0.91	(0.80-1.03)	0.12	0.92	238/1222	0.97	(0.84-1.12)	0.68	0.69
		Women	99/1510	0.93	(0.76-1.14)	0.50		252/1509	0.91	(0.80-1.04)	0.15		153/1509	0.90	(0.76-1.06)	0.21	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 10. Subgroup analysis based on trial treatment allocation.

Model	Cholesterol	RCT group	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	Intervention	79/1293	0.85	(0.64-1.13)	0.26	0.63	266/1292	0.75	(0.64-0.88)	0.00	0.25	187/1292	0.71	(0.59-0.85)	0.00	0.30
		Control	94/1523	0.98	(0.77-1.24)	0.87		310/1522	0.89	(0.78-1.02)	0.11		216/1522	0.85	(0.72-1.01)	0.06	
	LDL	Intervention	78/1287	0.78	(0.59-1.05)	0.10	0.76	264/1286	0.74	(0.63-0.86)	0.00	0.33	186/1286	0.71	(0.59-0.85)	0.00	0.31
		Control	93/1509	0.88	(0.69-1.12)	0.31		307/1508	0.85	(0.74-0.98)	0.02		214/1508	0.84	(0.71-0.99)	0.04	
	HDL	Intervention	79/1294	1.05	(0.84-1.31)	0.66	0.10	267/1293	0.93	(0.82-1.06)	0.30	0.35	188/1293	0.87	(0.74-1.03)	0.11	0.89
		Control	95/1527	1.35	(1.10-1.65)	0.00		312/1526	1.01	(0.89-1.15)	0.83		217/1526	0.86	(0.74-1.01)	0.07	
	TC/HDL	Intervention	79/1292	0.87	(0.69-1.11)	0.27	0.38	266/1291	0.93	(0.82-1.06)	0.31	0.84	187/1291	0.96	(0.82-1.12)	0.61	0.41
		Control	94/1523	0.78	(0.61-0.98)	0.03		310/1522	0.96	(0.86-1.08)	0.53		216/1522	1.05	(0.92-1.21)	0.45	
	LDL/HDL	Intervention	78/1287	0.79	(0.62-1.00)	0.05	0.69	264/1286	0.87	(0.76-0.99)	0.04	0.73	186/1286	0.90	(0.77-1.06)	0.21	0.45
		Control	93/1509	0.77	(0.63-0.95)	0.02		307/1508	0.91	(0.81-1.02)	0.12		214/1508	0.98	(0.85-1.14)	0.84	
Model 3	TC	Intervention	77/1262	0.82	(0.61-1.10)	0.19	0.46	259/1261	0.77	(0.65-0.90)	0.002	0.21	182/1261	0.73	(0.60-0.89)	0.002	0.27
		Control	92/1490	0.96	(0.75-1.24)	0.77		304/1489	0.95	(0.83-1.10)	0.50		212/1489	0.94	(0.79-1.11)	0.47	
	LDL	Intervention	76/1256	0.76	(0.56-1.03)	0.08	0.54	257/1255	0.76	(0.64-0.90)	0.002	0.36	181/1255	0.75	(0.61-0.92)	0.01	0.41
		Control	91/1477	0.88	(0.68-1.13)	0.31		301/1476	0.89	(0.77-1.02)	0.10		210/1476	0.90	(0.75-1.06)	0.21	
	HDL	Intervention	77/1263	1.01	(0.80-1.28)	0.94	0.13	260/1262	0.94	(0.82-1.08)	0.39	0.26	183/1262	0.90	(0.76-1.06)	0.21	0.87
		Control	93/1494	1.29	(1.04-1.60)	0.02		306/1493	1.10	(0.96-1.25)	0.17		213/1493	0.98	(0.83-1.15)	0.80	
	TC/HDL	Intervention	77/1261	0.90	(0.71-1.15)	0.40	0.47	259/1260	0.95	(0.83-1.08)	0.42	0.98	182/1260	0.97	(0.83-1.14)	0.71	0.59
		Control	92/1490	0.80	(0.63-1.02)	0.07		304/1489	0.93	(0.82-1.05)	0.25		212/1489	1.00	(0.86-1.15)	0.98	
	LDL/HDL	Intervention	76/1256	0.81	(0.64-1.03)	0.09	0.90	257/1255	0.89	(0.78-1.02)	0.10	0.86	181/1255	0.93	(0.79-1.10)	0.39	0.68
		Control	91/1477	0.79	(0.64-0.99)	0.04		301/1476	0.89	(0.79-1.01)	0.07		210/1476	0.95	(0.82-1.10)	0.51	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 11. Subgroup analyses based on cholesterol lowering drug (CLD) use at baseline (BL).

Model	Cholesterol	CLD category	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	No CLD at BL	112/1846	0.91	(0.73-1.14)	0.42	0.40	355/1846	0.82	(0.72-0.93)	0.003	0.59	243/1846	0.78	(0.66-0.91)	0.002	0.84
		CLD at BL	61/970	0.96	(0.71-1.30)	0.79		221/968	0.85	(0.72-0.99)	0.04		160/968	0.80	(0.65-0.97)	0.02	
	LDL	No CLD at BL	110/1835	0.80	(0.64-1.00)	0.051	0.27	351/1835	0.79	(0.70-0.90)	<0.001	0.63	241/1835	0.79	(0.67-0.92)	0.002	0.95
		CLD at BL	61/961	0.95	(0.69-1.29)	0.74		220/959	0.82	(0.69-0.97)	0.02		159/959	0.77	(0.63-0.95)	0.01	
	HDL	No CLD at BL	112/1848	1.20	(1.00-1.43)	0.04	0.58	356/1848	0.96	(0.86-1.08)	0.52	0.68	244/1848	0.85	(0.74-0.98)	0.03	0.89
		CLD at BL	62/973	1.19	(0.91-1.55)	0.20		223/971	0.99	(0.84-1.15)	0.85		161/971	0.88	(0.73-1.07)	0.22	
	TC/HDL	No CLD at BL	112/1846	0.81	(0.66-0.98)	0.04	0.98	355/1846	0.95	(0.85-1.06)	0.36	0.95	243/1846	1.02	(0.90-1.16)	0.77	0.93
		CLD at BL	61/969	0.84	(0.62-1.12)	0.24		221/967	0.95	(0.82-1.10)	0.48		160/967	1.00	(0.84-1.19)	1.00	
	LDL/HDL	No CLD at BL	110/1835	0.75	(0.62-0.91)	0.003	0.58	351/1835	0.88	(0.79-0.99)	0.03	0.74	241/1835	0.96	(0.83-1.10)	0.55	0.96
		CLD at BL	61/961	0.85	(0.65-1.09)	0.20		220/959	0.91	(0.80-1.04)	0.18		159/959	0.94	(0.80-1.10)	0.46	
Model 3	TC	No CLD at BL	109/1801	0.89	(0.70-1.12)	0.31	0.32	345/1801	0.85	(0.75-0.98)	0.02	0.40	236/1801	0.83	(0.71-0.98)	0.03	0.64
		CLD at BL	60/951	0.98	(0.71-1.37)	0.93		218/949	0.91	(0.77-1.09)	0.30		158/949	0.89	(0.72-1.10)	0.27	
	LDL	No CLD at BL	107/1791	0.78	(0.62-0.98)	0.03	0.19	341/1791	0.83	(0.73-0.95)	0.01	0.44	234/1791	0.85	(0.72-0.99)	0.04	0.87
		CLD at BL	60/942	1.00	(0.71-1.39)	0.98		217/940	0.87	(0.73-1.05)	0.15		157/940	0.84	(0.67-1.05)	0.13	
	HDL	No CLD at BL	109/1803	1.18	(0.98-1.43)	0.08	0.67	346/1803	0.99	(0.89-1.12)	0.93	0.74	237/1803	0.90	(0.77-1.04)	0.14	0.90
		CLD at BL	61/954	1.10	(0.83-1.46)	0.49		220/952	1.05	(0.89-1.23)	0.58		159/952	0.99	(0.81-1.20)	0.89	
	TC/HDL	No CLD at BL	109/1801	0.82	(0.67-1.00)	0.06	0.84	345/1801	0.94	(0.84-1.04)	0.24	0.57	236/1801	0.99	(0.87-1.13)	0.94	0.56
		CLD at BL	60/950	0.91	(0.68-1.21)	0.52		218/948	0.96	(0.82-1.12)	0.59		158/948	1.00	(0.83-1.20)	0.99	
	LDL/HDL	No CLD at BL	107/1791	0.75	(0.62-0.92)	0.01	0.43	341/1791	0.89	(0.79-1.00)	0.04	0.48	234/1791	0.96	(0.84-1.11)	0.61	0.73
		CLD at BL	60/942	0.92	(0.70-1.19)	0.51		217/940	0.92	(0.80-1.06)	0.25		157/940	0.94	(0.80-1.12)	0.52	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 12. Subgroup analyses based on cholesterol lowering drug (CLD) use during the study.

Model	Cholesterol	CLD category	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	No CLD during study	71/1136	0.95	(0.71-1.29)	0.76	0.12	172/1136	0.92	(0.76-1.12)	0.41	0.55	101/1136	0.90	(0.71-1.16)	0.43	0.56
		CLD at BL	15/374	0.62	(0.36-1.07)	0.08		43/374	0.78	(0.54-1.12)	0.18		28/374	0.96	(0.60-1.53)	0.87	
		CLD initiated after BL	48/781	1.01	(0.74-1.37)	0.97		138/779	0.84	(0.68-1.03)	0.09		90/779	0.73	(0.56-0.95)	0.02	
	LDL	No CLD during study	70/1131	0.76	(0.57-1.02)	0.07	0.22	171/1131	0.82	(0.68-0.99)	0.04	0.96	101/1131	0.86	(0.68-1.10)	0.23	0.58
		CLD at BL	15/371	0.71	(0.43-1.19)	0.19		43/371	0.84	(0.60-1.19)	0.33		28/371	0.98	(0.63-1.54)	0.94	
		CLD initiated after BL	48/775	1.01	(0.73-1.40)	0.95		138/773	0.82	(0.66-1.01)	0.06		90/773	0.71	(0.53-0.93)	0.02	
	HDL	No CLD during study	71/1137	1.23	(1.00-1.52)	0.06	0.73	172/1137	1.04	(0.89-1.21)	0.62	0.56	101/1137	0.90	(0.73-1.11)	0.33	0.77
		CLD at BL	15/374	1.07	(0.57-1.99)	0.84		43/374	0.99	(0.67-1.45)	0.94		28/374	0.94	(0.58-1.53)	0.81	
		CLD initiated after BL	49/785	1.20	(0.90-1.59)	0.22		140/783	1.08	(0.89-1.30)	0.43		91/783	1.00	(0.78-1.29)	0.97	
	TC/HDL	No CLD during study	71/1136	0.81	(0.62-1.05)	0.11	0.70	172/1136	0.97	(0.83-1.15)	0.75	0.58	101/1136	1.10	(0.89-1.36)	0.37	0.35
		CLD at BL	15/374	0.68	(0.40-1.16)	0.16		43/374	0.86	(0.63-1.16)	0.32		28/374	0.96	(0.68-1.38)	0.84	
		CLD initiated after BL	48/781	0.88	(0.64-1.19)	0.40		138/779	0.86	(0.71-1.04)	0.12		90/779	0.84	(0.65-1.07)	0.16	
	LDL/HDL	No CLD during study	70/1131	0.71	(0.56-0.90)	0.01	0.65	171/1131	0.86	(0.73-1.01)	0.07	0.98	101/1131	1.00	(0.80-1.24)	0.99	0.70
		CLD at BL	15/371	0.79	(0.47-1.33)	0.37		43/371	0.88	(0.62-1.24)	0.47		28/371	0.98	(0.63-1.52)	0.91	
		CLD initiated after BL	48/775	0.89	(0.67-1.18)	0.42		138/773	0.87	(0.74-1.03)	0.11		90/773	0.85	(0.69-1.05)	0.14	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 12. Subgroup analyses based on cholesterol lowering drug (CLD) use during the study. *(Continued)*

Model	Cholesterol	CLD category	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 3	TC	No CLD during study	70/1104	0.97	(0.70-1.33)	0.83	0.49	168/1104	1.01	(0.83-1.23)	0.91	0.54	98/1104	1.02	(0.79-1.31)	0.88	0.24
		CLD at BL	15/370	0.60	(0.32-1.14)	0.12		42/370	0.85	(0.57-1.27)	0.43		27/370	1.14	(0.67-1.93)	0.63	
		CLD initiated after BL	47/767	1.08	(0.77-1.52)	0.64		137/765	0.91	(0.73-1.13)	0.40		90/765	0.81	(0.60-1.08)	0.15	
	LDL	No CLD during study	69/1099	0.77	(0.57-1.06)	0.11	0.24	167/1099	0.92	(0.76-1.11)	0.37	0.88	98/1099	1.00	(0.78-1.27)	0.97	0.32
		CLD at BL	15/368	0.74	(0.40-1.36)	0.33		42/368	0.94	(0.64-1.38)	0.76		27/368	1.17	(0.71-1.95)	0.54	
		CLD initiated after BL	47/761	1.09	(0.77-1.56)	0.62		137/759	0.89	(0.71-1.12)	0.31		90/759	0.77	(0.57-1.04)	0.09	
	HDL	No CLD during study	70/1105	1.21	(0.96-1.52)	0.11	0.67	168/1105	1.07	(0.91-1.25)	0.43	0.79	98/1105	0.94	(0.75-1.17)	0.58	0.85
		CLD at BL	15/370	1.01	(0.48-2.12)	0.99		42/370	1.10	(0.73-1.66)	0.64		27/370	1.18	(0.71-1.96)	0.53	
		CLD initiated after BL	48/771	1.17	(0.88-1.56)	0.28		139/769	1.11	(0.91-1.34)	0.30		91/769	1.08	(0.84-1.38)	0.57	
	TC/HDL	No CLD during study	70/1104	0.84	(0.64-1.11)	0.22	0.97	168/1104	0.99	(0.83-1.17)	0.88	0.45	98/1104	1.11	(0.89-1.38)	0.36	0.28
		CLD at BL	15/370	0.72	(0.39-1.34)	0.30		42/370	0.83	(0.60-1.15)	0.27		27/370	0.88	(0.60-1.30)	0.53	
		CLD initiated after BL	47/767	0.92	(0.68-1.24)	0.57		137/765	0.89	(0.73-1.08)	0.24		90/765	0.85	(0.66-1.10)	0.23	
	LDL/HDL	No CLD during study	69/1099	0.73	(0.57-0.94)	0.02	0.41	167/1099	0.91	(0.77-1.07)	0.25	0.94	98/1099	1.06	(0.85-1.33)	0.62	0.53
		CLD at BL	15/368	0.84	(0.45-1.59)	0.60		42/368	0.89	(0.62-1.30)	0.55		27/368	0.94	(0.59-1.49)	0.79	
		CLD initiated after BL	47/761	0.95	(0.72-1.24)	0.70		137/759	0.91	(0.77-1.08)	0.28		90/759	0.87	(0.70-1.09)	0.24	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 13. Analyses adjusted for cholesterol lowering drug use during study as time dependent variable.

Model	Cholesterol	Dementia				Dem/mort				Mortality			
		events/total	HR	95%CI	p	events/total	HR	95%CI	p	events/total	HR	95%CI	p
Model 2	TC	173/8345	0.91	(0.77-1.08)	0.28	577/8345	0.82	(0.74-0.90)	**<0.001**	404/8345	0.77	(0.69-0.87)	**<0.001**
	LDL	171/8289	0.85	(0.71-1.00)	0.052	572/8289	0.80	(0.72-0.87)	**<0.001**	401/8289	0.77	(0.69-0.87)	**<0.001**
	HDL	174/8361	1.21	(1.04-1.40)	**0.01**	580/8361	0.98	(0.90-1.08)	0.73	406/8361	0.88	(0.79-0.99)	**0.03**
	TC/HDL	173/8344	0.81	(0.69-0.96)	**0.01**	577/8344	0.92	(0.85-1.00)	0.06	404/8344	0.97	(0.88-1.07)	0.56
	LDL/HDL	171/8289	0.78	(0.67-0.91)	**0.001**	572/8289	0.87	(0.8-0.95)	**0.001**	401/8289	0.91	(0.83-1.01)	0.08
Model 3	TC	169/8162	0.90	(0.75-1.09)	0.28	564/8162	0.88	(0.80-0.98)	**0.02**	395/8162	0.87	(0.77-0.98)	**0.02**
	LDL	167/8109	0.84	(0.71-1.01)	0.07	559/8109	0.86	(0.77-0.95)	**0.003**	392/8109	0.86	(0.76-0.97)	**0.02**
	HDL	170/8178	1.16	(0.99-1.36)	0.07	567/8178	1.03	(0.94-1.13)	0.54	397/8178	0.95	(0.85-1.07)	0.42
	TC/HDL	169/8161	0.85	(0.72-1.00)	0.053	564/8161	0.93	(0.85-1.02)	0.12	395/8161	0.98	(0.88-1.09)	0.68
	LDL/HDL	167/8109	0.81	(0.70-0.95)	**0.01**	559/8109	0.90	(0.83-0.98)	**0.02**	392/8109	0.95	(0.85-1.05)	0.33

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 14. Subgroup analyses based on follow-up (FU) time, dichotomized at the median time-event.

Model	Cholesterol	Follow-up category	Dementia events/tot	HR	95%CI	p-value	Dem/mort events/tot	HR	95%CI	p-value	Mortality events/tot	HR	95%CI	p-value
Model 2	TC	FU <5.04 years	87/2816	1.23	(0.96-1.57)	0.10	298/2814	0.94	(0.82-1.09)	0.41	234/2867	0.82	(0.70-0.96)	**0.02**
		FU ≥5.04 years	86/2460	0.65	(0.50-0.85)	**0.002**	278/2512	0.73	(0.62-0.84)	**<0.001**	214/2628	0.82	(0.69-0.97)	**0.02**
	LDL	FU <5.04 years	85/2796	1.03	(0.80-1.34)	0.80	293/2794	0.90	(0.78-1.04)	0.15	231/2845	0.82	(0.70-0.97)	**0.02**
		FU ≥5.04 years	86/2445	0.63	(0.48-0.83)	**0.001**	278/2497	0.70	(0.60-0.81)	**<0.001**	212/2609	0.79	(0.67-0.94)	**0.01**
	HDL	FU <5.04 years	87/2821	1.31	(1.08-1.60)	**0.01**	299/2819	0.97	(0.85-1.09)	0.60	235/2872	0.82	(0.71-0.96)	**0.01**
		FU ≥5.04 years	87/2463	1.03	(0.83-1.29)	0.77	280/2516	0.95	(0.83-1.08)	0.45	215/2632	0.90	(0.77-1.04)	0.16
	TC/HDL	FU <5.04 years	87/2815	0.86	(0.69-1.08)	0.20	298/2813	1.02	(0.91-1.15)	0.69	234/2866	1.07	(0.94-1.21)	0.34
		FU ≥5.04 years	86/2459	0.77	(0.61-0.98)	**0.03**	278/2511	0.90	(0.79-1.03)	0.12	214/2627	1.02	(0.89-1.17)	0.76
	LDL/HDL	FU <5.04 years	85/2796	0.80	(0.64-1.01)	0.06	293/2794	0.96	(0.85-1.09)	0.51	231/2845	1.01	(0.88-1.16)	0.87
		FU ≥5.04 years	86/2445	0.74	(0.59-0.92)	**0.01**	278/2497	0.84	(0.74-0.95)	**0.01**	212/2609	0.93	(0.81-1.07)	0.30
Model 3	TC	FU <5.04 years	85/2752	1.18	(0.90-1.54)	0.23	290/2750	0.99	(0.86-1.15)	0.93	229/2802	0.90	(0.76-1.07)	0.23
		FU ≥5.04 years	84/2406	0.62	(0.47-0.82)	**0.001**	273/2456	0.75	(0.64-0.88)	**<0.001**	209/2568	0.85	(0.71-1.02)	0.08
	LDL	FU <5.04 years	83/2733	1.01	(0.77-1.32)	0.93	285/2731	0.94	(0.81-1.09)	0.42	226/2781	0.89	(0.75-1.06)	0.20
		FU ≥5.04 years	84/2392	0.61	(0.46-0.81)	**<0.001**	273/2442	0.72	(0.62-0.85)	**<0.001**	207/2550	0.83	(0.70-0.99)	0.04
	HDL	FU <5.04 years	85/2757	1.15	(0.93-1.42)	0.18	291/2755	1.00	(0.88-1.14)	0.98	230/2807	0.89	(0.76-1.04)	0.14
		FU ≥5.04 years	85/2409	1.04	(0.82-1.30)	0.77	275/2460	0.99	(0.87-1.14)	0.93	210/2572	0.94	(0.81-1.10)	0.46
	TC/HDL	FU <5.04 years	85/2751	0.96	(0.76-1.20)	0.71	290/2749	1.02	(0.90-1.15)	0.75	229/2801	1.04	(0.91-1.20)	0.53
		FU ≥5.04 years	84/2405	0.76	(0.59-0.97)	**0.03**	273/2455	0.89	(0.78-1.02)	0.09	209/2567	1.01	(0.87-1.17)	0.91
	LDL/HDL	FU <5.04 years	83/2733	0.89	(0.70-1.12)	0.30	285/2731	0.96	(0.85-1.09)	0.55	226/2781	1.00	(0.86-1.16)	0.96
		FU ≥5.04 years	84/2392	0.73	(0.59-0.91)	**0.01**	273/2442	0.84	(0.74-0.96)	**0.01**	207/2550	0.93	(0.80-1.07)	0.31

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 15. Subgroup analyses based on tertiles of age at baseline.

Model	Cholesterol	Age at baseline	Dementia events/tot	HR	95%CI	p-value		Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	≤73.0 years	44/946	0.97	(0.68-1.38)	0.85	0.63	137/945	0.86	(0.70-1.05)	0.14	0.53	93/945	0.77	(0.59-1.00)	0.05	0.34
		73.0-75.7 years	52/943	0.86	(0.62-1.20)	0.38		188/943	0.87	(0.73-1.03)	0.10		136/943	0.87	(0.71-1.06)	0.17	
		>75.7 years	77/927	0.93	(0.70-1.22)	0.60		251/926	0.78	(0.67-0.92)	0.003		174/926	0.72	(0.59-0.87)	0.001	
	LDL	≤73.0 years	43/938	0.92	(0.65-1.30)	0.62	0.34	135/937	0.82	(0.67-1.01)	0.07	0.53	92/937	0.75	(0.58-0.97)	0.03	0.19
		73.0-75.7 years	51/938	0.68	(0.49-0.95)	0.03		186/938	0.85	(0.71-1.01)	0.07		135/938	0.92	(0.75-1.12)	0.41	
		>75.7 years	77/920	0.90	(0.69-1.19)	0.48		250/919	0.75	(0.64-0.88)	<0.001		173/919	0.68	(0.56-0.83)	<0.001	
	HDL	≤73.0 years	45/948	1.24	(0.92-1.67)	0.16	0.39	138/947	1.02	(0.85-1.22)	0.85	0.61	93/947	0.89	(0.71-1.12)	0.33	0.95
		73.0-75.7 years	52/943	1.32	(0.99-1.75)	0.06		188/943	0.95	(0.80-1.12)	0.52		136/943	0.80	(0.65-1.00)	0.046	
		>75.7 years	77/930	1.11	(0.89-1.38)	0.36		253/929	0.97	(0.85-1.11)	0.64		176/929	0.90	(0.76-1.06)	0.21	
	TC/HDL	≤73.0 years	44/946	0.80	(0.56-1.13)	0.20	0.24	137/945	0.94	(0.78-1.13)	0.49	0.99	93/945	1.01	(0.82-1.25)	0.92	0.47
		73.0-75.7 years	52/943	0.76	(0.56-1.04)	0.09		188/943	0.98	(0.85-1.13)	0.80		136/943	1.07	(0.91-1.26)	0.42	
		>75.7 years	77/926	0.88	(0.69-1.12)	0.29		251/925	0.93	(0.81-1.06)	0.28		174/925	0.96	(0.81-1.12)	0.58	
	LDL/HDL	≤73.0 years	43/938	0.86	(0.62-1.17)	0.33	0.29	135/937	0.89	(0.75-1.07)	0.21	0.82	92/937	0.91	(0.73-1.14)	0.40	0.32
		73.0-75.7 years	51/938	0.65	(0.50-0.86)	0.002		186/938	0.94	(0.81-1.10)	0.45		135/938	1.09	(0.91-1.32)	0.34	
		>75.7 years	77/920	0.84	(0.67-1.06)	0.15		250/919	0.86	(0.76-0.98)	0.02		173/919	0.87	(0.75-1.02)	0.08	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 15. Subgroup analyses based on tertiles of age at baseline. *(Continued)*

Model	Cholesterol	Age at baseline	Dementia events/tot	HR	95%CI	p-value		Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 3	TC	≤73.0 years	43/924	1.02	(0.70-1.47)	0.93	0.74	134/923	0.91	(0.73-1.13)	0.40	0.60	91/923	0.84	(0.64-1.11)	0.22	0.41
		73.0-75.7 years	51/924	0.75	(0.52-1.09)	0.13		183/924	0.91	(0.76-1.09)	0.29		132/924	0.96	(0.78-1.18)	0.70	
		>75.7 years	75/904	0.86	(0.64-1.15)	0.32		246/903	0.81	(0.68-0.96)	0.01		171/903	0.77	(0.63-0.95)	0.01	
	LDL	≤73.0 years	42/916	0.96	(0.67-1.37)	0.81	0.47	132/915	0.87	(0.70-1.08)	0.21	0.49	90/915	0.81	(0.61-1.07)	0.13	0.20
		73.0-75.7 years	50/920	0.59	(0.41-0.85)	0.01		181/920	0.89	(0.75-1.07)	0.23		131/920	1.02	(0.83-1.26)	0.82	
		>75.7 years	75/897	0.85	(0.64-1.14)	0.28		245/896	0.77	(0.65-0.91)	0.003		170/896	0.72	(0.58-0.88)	0.002	
	HDL	≤73.0 years	44/926	1.23	(0.88-1.70)	0.22	0.54	135/925	1.07	(0.89-1.29)	0.47	0.83	91/925	0.99	(0.78-1.25)	0.94	0.76
		73.0-75.7 years	51/924	1.25	(0.92-1.71)	0.16		183/924	0.94	(0.78-1.12)	0.48		132/924	0.81	(0.65-1.02)	0.07	
		>75.7 years	75/907	1.07	(0.85-1.35)	0.58		248/906	1.03	(0.90-1.18)	0.71		173/906	0.99	(0.84-1.17)	0.91	
	TC/HDL	≤73.0 years	43/924	0.85	(0.60-1.20)	0.35	0.40	134/923	0.91	(0.76-1.11)	0.36	0.84	91/923	0.95	(0.76-1.19)	0.64	0.43
		73.0-75.7 years	51/924	0.76	(0.55-1.04)	0.09		183/924	1.02	(0.87-1.18)	0.85		132/924	1.13	(0.95-1.35)	0.16	
		>75.7 years	75/903	0.88	(0.68-1.13)	0.32		246/902	0.90	(0.78-1.03)	0.13		171/902	0.91	(0.77-1.08)	0.27	
	LDL/HDL	≤73.0 years	42/916	0.94	(0.69-1.28)	0.68	0.50	132/915	0.91	(0.76-1.10)	0.32	0.51	90/915	0.90	(0.72-1.13)	0.37	0.19
		73.0-75.7 years	50/920	0.62	(0.46-0.83)	0.002		181/920	0.97	(0.83-1.14)	0.72		131/920	1.16	(0.96-1.42)	0.13	
		>75.7 years	75/897	0.84	(0.66-1.07)	0.17		245/896	0.85	(0.74-0.97)	0.01		170/896	0.85	(0.72-1.00)	0.04	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 16. Subgroup analyses based on tertiles of age at censoring.

Model	Cholesterol	Age at censoring	Dementia events/tot	HR	95%CI	p-value		Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	≤79.3 years	71/972	1.10	(0.83-1.44)	0.51	0.26	286/971	0.84	(0.72-0.97)	0.02	0.14	215/971	0.74	(0.62-0.88)	0.001	0.11
		79.3-82.1 years	54/918	0.66	(0.47-0.94)	0.02		177/917	0.72	(0.60-0.87)	0.001		123/917	0.75	(0.59-0.93)	0.01	
		>87.9 years	48/926	0.82	(0.58-1.16)	0.26		113/926	0.75	(0.59-0.95)	0.02		65/926	0.69	(0.51-0.95)	0.02	
	LDL	≤79.3 years	69/962	0.97	(0.74-1.27)	0.81	0.64	281/961	0.83	(0.72-0.95)	0.01	0.11	212/961	0.77	(0.65-0.91)	0.002	**0.03**
		79.3-82.1 years	54/915	0.59	(0.41-0.83)	0.003		177/914	0.69	(0.57-0.83)	<0.001		123/914	0.73	(0.58-0.92)	0.01	
		>87.9 years	48/919	0.80	(0.56-1.14)	0.22		113/919	0.72	(0.57-0.91)	0.01		65/919	0.64	(0.47-0.89)	0.01	
	HDL	≤79.3 years	72/975	1.37	(1.07-1.75)	0.01	0.19	288/974	0.98	(0.86-1.11)	0.71	0.77	216/974	0.86	(0.73-1.00)	0.06	0.60
		79.3-82.1 years	54/919	1.33	(1.02-1.74)	0.03		178/918	1.01	(0.85-1.19)	0.95		124/918	0.86	(0.70-1.06)	0.16	
		>87.9 years	48/927	1.08	(0.81-1.43)	0.62		113/927	1.07	(0.89-1.30)	0.46		65/927	1.08	(0.83-1.40)	0.55	
	TC/HDL	≤79.3 years	71/972	0.82	(0.64-1.06)	0.14	0.80	286/971	0.95	(0.84-1.07)	0.38	0.23	215/971	0.98	(0.85-1.13)	0.78	0.18
		79.3-82.1 years	54/918	0.64	(0.46-0.88)	0.01		177/917	0.86	(0.73-1.01)	0.06		123/917	0.97	(0.81-1.16)	0.71	
		>87.9 years	48/925	0.83	(0.61-1.14)	0.25		113/925	0.83	(0.67-1.02)	0.07		65/925	0.82	(0.62-1.08)	0.16	
	LDL/HDL	≤79.3 years	69/962	0.78	(0.60-1.01)	0.06	0.57	281/961	0.90	(0.79-1.02)	0.11	0.13	212/961	0.93	(0.80-1.08)	0.37	**0.04**
		79.3-82.1 years	54/915	0.59	(0.45-0.79)	<0.001		177/914	0.81	(0.69-0.95)	0.01		123/914	0.94	(0.77-1.14)	0.52	
		>87.9 years	48/919	0.80	(0.60-1.07)	0.13		113/919	0.77	(0.64-0.93)	0.01		65/919	0.74	(0.58-0.94)	0.02	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 16. Subgroup analyses based on tertiles of age at censoring. *(Continued)*

Model	Cholesterol	Age at censoring	Dementia events/tot	HR	95%CI	p-value		Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 3	TC	≤79.3 years	69/945	1.11	(0.82-1.50)	0.50	0.26	277/944	0.88	(0.75-1.03)	0.10	0.17	208/944	0.80	(0.67-0.95)	0.01	0.15
		79.3-82.1 years	54/905	0.67	(0.46-0.96)	0.03		176/904	0.75	(0.61-0.91)	0.01		122/904	0.80	(0.63-1.01)	0.06	
		>87.9 years	46/902	0.72	(0.50-1.04)	0.08		110/902	0.73	(0.57-0.94)	0.02		64/902	0.74	(0.52-1.04)	0.08	
	LDL	≤79.3 years	67/935	0.96	(0.71-1.30)	0.81	0.63	272/934	0.87	(0.74-1.01)	0.06	0.12	205/934	0.82	(0.69-0.98)	0.03	0.051
		79.3-82.1 years	54/903	0.60	(0.42-0.86)	0.01		176/902	0.72	(0.59-0.87)	0.001		122/902	0.79	(0.62-1.00)	0.051	
		>87.9 years	46/895	0.72	(0.50-1.04)	0.08		110/895	0.72	(0.56-0.92)	0.01		64/895	0.70	(0.50-0.99)	0.045	
	HDL	≤79.3 years	70/948	1.36	(1.05-1.77)	0.02	0.26	279/947	1.01	(0.88-1.15)	0.94	0.74	209/947	0.90	(0.77-1.06)	0.22	0.56
		79.3-82.1 years	54/906	1.33	(1.00-1.75)	0.047		177/905	1.05	(0.88-1.24)	0.60		123/905	0.91	(0.73-1.14)	0.43	
		>87.9 years	46/903	1.02	(0.76-1.37)	0.90		110/903	1.09	(0.89-1.32)	0.41		64/903	1.13	(0.87-1.47)	0.36	
	TC/HDL	≤79.3 years	69/945	0.83	(0.64-1.08)	0.17	0.94	277/944	0.94	(0.83-1.07)	0.34	0.30	208/944	0.96	(0.83-1.11)	0.59	0.28
		79.3-82.1 years	54/905	0.66	(0.47-0.91)	0.01		176/904	0.86	(0.73-1.01)	0.07		122/904	0.97	(0.80-1.17)	0.74	
		>87.9 years	46/901	0.83	(0.60-1.14)	0.25		110/901	0.83	(0.67-1.02)	0.08		64/901	0.83	(0.62-1.11)	0.20	
	LDL/HDL	≤79.3 years	67/935	0.79	(0.60-1.04)	0.09	0.65	272/934	0.91	(0.80-1.04)	0.18	0.12	205/934	0.94	(0.81-1.10)	0.44	**0.04**
		79.3-82.1 years	54/903	0.62	(0.46-0.82)	0.001		176/902	0.81	(0.69-0.96)	0.02		122/902	0.94	(0.77-1.16)	0.59	
		>87.9 years	46/895	0.80	(0.60-1.07)	0.14		110/895	0.78	(0.65-0.94)	0.01		64/895	0.77	(0.59-0.99)	0.04	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 17. Analyses in model 3 incorporating interactions with BMI and education tertiles in 1 model.

Age at censoring	Dementia events/tot	HR	95%CI	p-value	Dem/mort events/tot	HR	95%CI	p-value	Mortality events/tot	HR	95%CI	p-value
TC	169/2752	0.90	(0.64-1.26)	0.53	563/2750	1.01	(0.84-1.22)	0.91	394/2750	1.04	(0.83-1.32)	0.72
- Interaction BMI tertiles	169/2752	1.20	(1.00-1.45)	0.05	563/2750	0.99	(0.89-1.10)	0.84	394/2750	0.92	(0.80-1.04)	0.18
- Interaction Education tertiles	169/2752	0.84	(0.66-1.06)	0.14	563/2750	0.86	(0.75-0.98)	**0.02**	394/2750	0.87	(0.74-1.02)	0.08
HDL	170/2757	1.01	(0.76-1.36)	0.93	566/2755	0.99	(0.83-1.18)	0.90	396/2755	0.93	(0.74-1.17)	0.55
- Interaction BMI tertiles	170/2757	0.89	(0.74-1.07)	0.22	566/2755	0.90	(0.81-1.00)	0.04	396/2755	0.93	(0.81-1.06)	0.25
- Interaction Education tertiles	170/2757	1.22	(0.99-1.50)	0.06	566/2755	1.12	(0.99-1.27)	0.08	396/2755	1.08	(0.92-1.26)	0.37
LDL	167/2733	0.88	(0.63-1.23)	0.45	558/2731	0.96	(0.79-1.17)	0.71	391/2731	1.01	(0.79-1.28)	0.96
- Interaction BMI tertiles	167/2733	1.22	(1.00-1.48)	0.05	558/2731	1.00	(0.90-1.11)	1.00	391/2731	0.92	(0.81-1.05)	0.22
- Interaction Education tertiles	167/2733	0.79	(0.62-1.00)	0.052	558/2731	0.86	(0.75-0.98)	**0.03**	391/2731	0.89	(0.76-1.04)	0.16
TC/HDL	169/2751	0.83	(0.59-1.18)	0.30	563/2749	1.09	(0.90-1.32)	0.39	394/2749	1.24	(0.98-1.56)	0.07
- Interaction BMI tertiles	169/2751	1.36	(1.13-1.65)	**0.001**	563/2749	1.09	(0.97-1.21)	0.14	394/2749	0.96	(0.84-1.10)	0.57
- Interaction Education tertiles	169/2751	0.70	(0.55-0.88)	**0.002**	563/2749	0.78	(0.68-0.88)	**0.000**	394/2749	0.81	(0.70-0.95)	**0.01**
LDL/HDL	167/2733	1.13	(0.84-1.53)	0.42	558/2731	0.98	(0.82-1.17)	0.84	391/2731	0.89	(0.71-1.11)	0.29
- Interaction BMI tertiles	167/2733	0.78	(0.64-0.94)	**0.01**	558/2731	0.93	(0.84-1.04)	0.20	391/2731	1.02	(0.90-1.16)	0.72
- Interaction Education tertiles	167/2733	1.34	(1.08-1.66)	**0.01**	558/2731	1.21	(1.08-1.37)	**0.002**	391/2731	1.18	(1.01-1.36)	**0.03**

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 18. Subgroups analyses based on a medical history of DM, CVD and/or stroke at baseline.

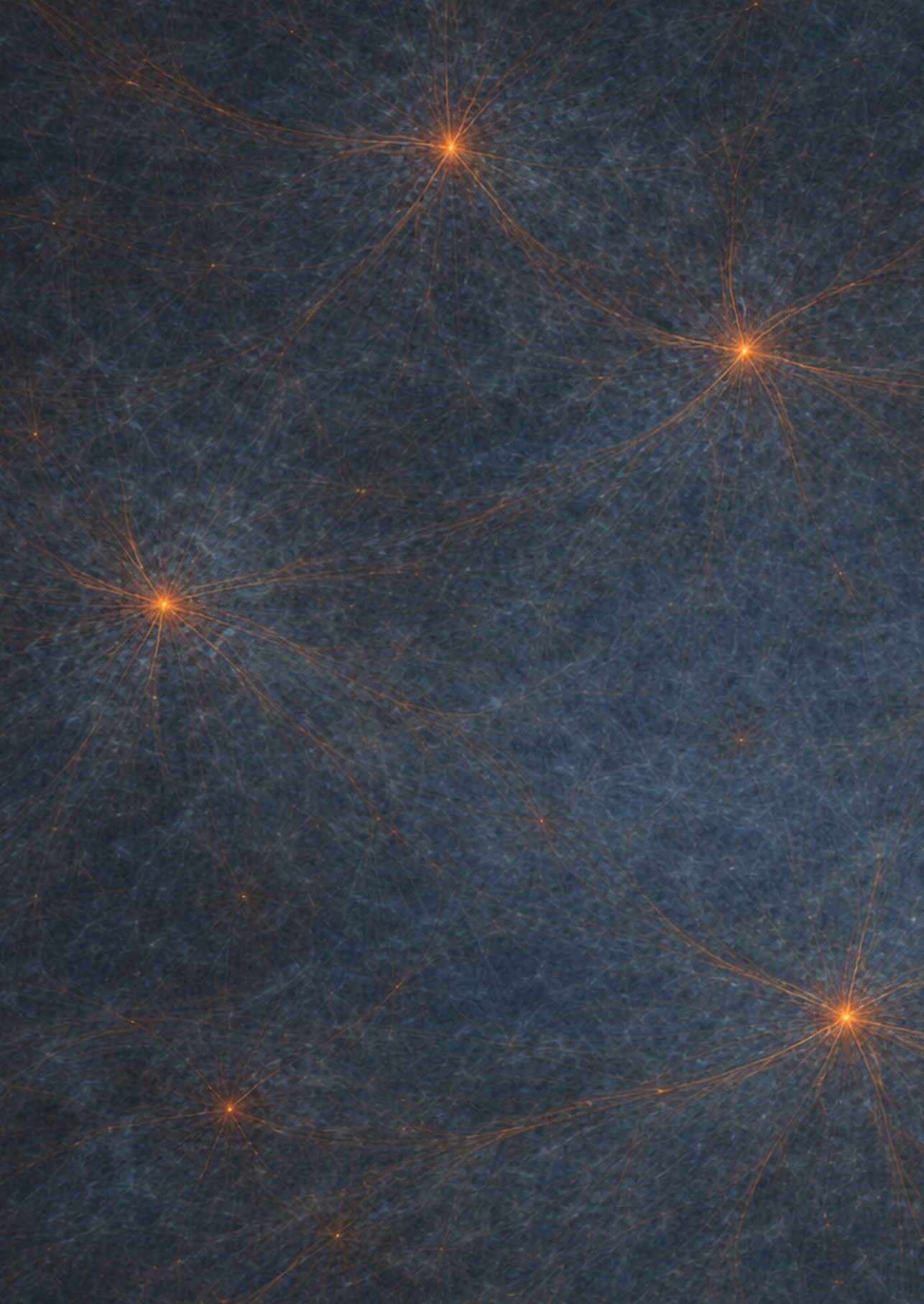
Cholesterol	Cholesterol	Medical history	Dementia events/tot	HR	95%CI	p-value	p-trend	Dem/mort events/tot	HR	95%CI	p-value	p-trend	Mortality events/tot	HR	95%CI	p-value	p-trend
Model 2	TC	No DM/CVD/Stroke	86/1517	1.01	(0.77-1.31)	0.96	0.57	238/1516	0.86	(0.73-1.01)	0.07	0.95	152/1516	0.79	(0.65-0.96)	0.02	0.49
		DM/CVD/Stroke	84/1266	0.82	(0.63-1.07)	0.15		331/1265	0.87	(0.76-1.00)	0.06		247/1265	0.88	(0.75-1.04)	0.14	
	LDL	No DM/CVD/Stroke	84/1510	0.90	(0.69-1.17)	0.44	0.52	235/1509	0.84	(0.72-0.99)	0.03	0.75	151/1509	0.81	(0.67-0.99)	0.04	0.85
		DM/CVD/Stroke	84/1254	0.75	(0.57-0.98)	0.04		329/1253	0.83	(0.72-0.95)	0.01		245/1253	0.85	(0.72-1.01)	0.06	
	HDL	No DM/CVD/Stroke	86/1518	1.10	(0.89-1.36)	0.38	0.11	238/1517	0.95	(0.83-1.09)	0.50	0.26	152/1517	0.87	(0.73-1.04)	0.12	0.54
		DM/CVD/Stroke	85/1270	1.33	(1.08-1.64)	0.01		334/1269	1.05	(0.93-1.18)	0.47		249/1269	0.93	(0.80-1.08)	0.34	
	TC/HDL	No DM/CVD/Stroke	86/1517	0.94	(0.75-1.17)	0.57	**0.045**	238/1516	0.98	(0.86-1.12)	0.78	0.37	152/1516	1.01	(0.86-1.19)	0.93	0.99
		DM/CVD/Stroke	84/1265	0.67	(0.52-0.87)	0.003		331/1264	0.92	(0.82-1.04)	0.19		247/1264	1.02	(0.90-1.17)	0.73	
	LDL/HDL	No DM/CVD/Stroke	84/1510	0.83	(0.66-1.06)	0.14	0.35	235/1509	0.91	(0.79-1.05)	0.20	0.69	151/1509	0.96	(0.80-1.14)	0.64	0.98
		DM/CVD/Stroke	84/1254	0.73	(0.59-0.89)	0.002		329/1253	0.90	(0.80-1.00)	0.06		245/1253	0.98	(0.85-1.12)	0.72	
Model 3	TC	No DM/CVD/Stroke	86/1513	1.03	(0.79-1.34)	0.84	0.56	238/1512	0.87	(0.74-1.02)	0.09	0.93	152/1512	0.81	(0.67-0.99)	0.04	0.69
		DM/CVD/Stroke	84/1243	0.81	(0.62-1.07)	0.14		326/1242	0.87	(0.75-1.01)	0.06		242/1242	0.88	(0.74-1.04)	0.13	
	LDL	No DM/CVD/Stroke	84/1506	0.93	(0.71-1.21)	0.58	0.48	235/1505	0.86	(0.73-1.00)	0.06	0.60	151/1505	0.84	(0.69-1.02)	0.08	0.91
		DM/CVD/Stroke	84/1231	0.75	(0.57-0.99)	0.04		324/1230	0.83	(0.71-0.96)	0.01		240/1230	0.85	(0.71-1.01)	0.07	
	HDL	No DM/CVD/Stroke	86/1514	1.04	(0.83-1.29)	0.74	0.08	238/1513	0.93	(0.81-1.07)	0.33	0.20	152/1513	0.86	(0.71-1.03)	0.10	0.45
		DM/CVD/Stroke	85/1247	1.26	(1.02-1.56)	0.04		329/1246	1.06	(0.94-1.2)	0.35		244/1246	0.97	(0.83-1.13)	0.69	
	TC/HDL	No DM/CVD/Stroke	86/1513	0.99	(0.80-1.24)	0.95	**0.03**	238/1512	0.99	(0.87-1.14)	0.92	0.26	152/1512	1.02	(0.86-1.20)	0.83	0.77
		DM/CVD/Stroke	84/1242	0.72	(0.56-0.94)	0.01		326/1241	0.91	(0.80-1.03)	0.13		242/1241	0.98	(0.85-1.13)	0.77	
	LDL/HDL	No DM/CVD/Stroke	84/1506	0.89	(0.69-1.13)	0.33	0.28	235/1505	0.93	(0.81-1.08)	0.34	0.52	151/1505	0.98	(0.82-1.17)	0.85	0.78
		DM/CVD/Stroke	84/1231	0.77	(0.63-0.95)	0.01		324/1230	0.89	(0.80-1.00)	0.053		240/1230	0.95	(0.83-1.09)	0.47	

P-trend denotes the p-value for the interaction. Model 2 adjusted for factors directly associated with cholesterol levels and cognition, including sex, education, MMSE score, cholesterol medication use and apolipoprotein E e4 allele presence (APOE4). Model 3 additionally adjusted for other cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD) and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, ApoA1: apolipoprotein A1, ApoB: apolipoprotein B, Remnant-C: remnant cholesterol (= TC-(HDL+LDL)), HR: hazard ratio, 95%CI: 95% confidence interval

Supplementary Table 19. Comparison of participant characteristics between education categories.

	Education category			
	<7 years	**7-12 years**	**>12 years**	**p-value**
Baseline:				
Age	74.8 (2.4)	74.3 (2.5)	74.2 (2.6)	**<0.001**
Women	553 (66.1%)	1125 (56.9%)	227 (33.5%)	**<0.001**
Number of prescriptions	4.5 (3.6)	3.8 (3.2)	3.2 (3.0)	**<0.001**
CVD	252 (30.3%)	574 (29.2%)	206 (30.6%)	0.85
Stroke	80 (9.7%)	191 (9.8%)	72 (10.8%)	0.78
Diabetes	188 (22.5%)	350 (17.7%)	97 (14.3%)	**0.002**
WHO physical activity norm	677 (83.0%)	1698 (87.4%)	589 (88.3%)	0.64
Alcohol yes/no	500 (60.0%)	1372 (69.4%)	537 (79.3%)	**0.003**
Quit smoking	426 (51.0%)	1055 (53.5%)	400 (59.2%)	0.21
Current smoker	160 (19.2%)	236 (12.0%)	68 (10.1%)	**<0.001**
BMI	28.1 (4.5)	27.5 (4.1)	26.5 (3.6)	**<0.001**
Systolic BP	155.4 (21.2)	155.2 (21.3)	155.6 (21.9)	0.90
Diastolic BP	80.9 (10.9)	81.5 (10.9)	81.8 (11.4)	0.23
AHD	502 (60.0%)	1066 (53.9%)	349 (51.6%)	0.16
AHD number	1.1 (1.1)	1.0 (1.1)	0.9 (1.0)	**0.001**
LDL	3.06 (0.95)	3.13 (0.98)	3.14 (0.95)	0.19
HDL	1.49 (0.39)	1.52 (0.43)	1.48 (0.42)	**0.03**
TC/HDL	3.66 (1.03)	3.65 (1.07)	3.74 (1.11)	0.16
LDL/HDL	2.16 (0.81)	2.19 (0.87)	2.28 (0.90)	**0.03**
CLD	315 (37.8%)	666 (33.7%)	201 (29.7%)	0.07
MMSE score	27.4 (2.2)	28 .2 (1.6)	28.7 (1.3)	**<0.001**
GDS-15	2.2 (2.5)	1.5 (2.1)	1.3 (1.8)	**<0.001**
Follow-up:				
Mortality	165 (19.8%)	297 (15.0%)	113 (16.7%)	**0.03**
Age at time of death	81.2 (2.7)	80.7 (2.7)	80.6 (2.7)	**<0.001**
Time from randomization-death	6.3 (1.6)	6.4 (1.4)	6.2 (1.4)	0.052
Incident dementia	74 (9.0%)	117 (6.0%)	38 (5.8%)	**0.02**
Age at time of dementia	81.0 (2.7)	80.6 (2.8)	80.5 (2.8)	**0.002**
Time from randomization-dementia	6.1 (1.7)	6.2 (1.5)	6.1 (1.5)	**0.01**

Abbreviations: CVD: cardiovascular disease, WHO: World Health Organisation, BMI: body mass index, BP: blood pressure, AHD: antihypertensive drugs, LDL: low density lipoprotein cholesterol, HDL: high density lipoprotein cholesterol, TC: total cholesterol, CLD: cholesterol lowering drugs, MMSE: mini-mental state examination, GDS-15: 15 item Geriatric Depression Scale



Chapter VII

Response to Comment on "Adverse Lipid Profiles are Associated With Lower Dementia Risk in Older People"

Jakob Laurens Schroevers
Jan Willem van Dalen

Journal of the Medical Directors Association.
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Dear Editor,

We appreciate Prof. Naharci's interest in our recent publication, "Adverse Lipid Profiles Are Associated With Lower Dementia Risk in Older People", and the opportunity to engage in further discussion on this important topic.

Dr. Naharci makes a compelling case that frailty is associated with higher dementia risk. While we previously noted in the discussion of our publication that the associations between adverse lipid profiles and lower dementia risk may have been partly driven by low cholesterol levels being a marker of frailty, we agree it would be informative to explore whether adjusting for frailty, or repeating the analyses in a subgroup of frail participants directly influences our results. Unfortunately, we were unable to implement the suggested Frailty Screening Tool, as not all the necessary data were collected.

As a solution, we attempted to approximate frailty by using the Amsterdam Linear Disability Scale (ALDS), a linear scale measuring independence in activities of daily living (ADL).[1] Although frailty and disability are two different concepts, they are closely intertwined. Fried et all state: "disability is an outcome of frailty".[2] We repeated our main analyses, adjusting for the total ALDS score, and in subgroups of the lowest quartile of ALDS scores at baseline versus those in the remaining quartiles.

Adjusting for the ALDS score did not alter our overall results. When examining subgroups, we found that associations between lipid profiles and dementia risk intensified in participants with the 75% highest ALDS scores (i.e., those with least disability), and were attenuated and partially reversed in those with the 25% lowest scores (i.e., with most disability).

In participants in the highest ALDS quartiles, one standard deviation (SD) higher LDL, TC/HDL, and LDL/HDL was associated with a 22-29% lower dementia risk, while one SD higher HDL was linked to a 30% higher dementia risk. In individuals in the lowest quartile, none of the associations were significant, but one SD higher HDL was associated with a 17% lower dementia risk, and one SD higher TC/HDL with a 19% higher risk, while LDL and LDL/HDL showed neutral associations. Only TC/HDL ratio differed significantly between the two subgroups (**Table 1**). These findings suggest that the beneficial associations of adverse lipid profiles with lower dementia risk are primarily seen in individuals with least disability.

Regarding the use of antidiabetic drugs, we acknowledge that metformin may have impacted individuals' lipid profiles. Our study demonstrated that a higher LDL/HDL ratio was associated with a lower risk of dementia. Since metformin is known to lower both the LDL/HDL ratio and dementia risk, failing to account for this could potentially lead to an overestimation of the association. However, we did adjust for diabetes status in our analyses to account for this potential confounder.

In the Netherlands, over 80% of patients with type 2 diabetes are prescribed antidiabetic medications, primarily metformin, which mirrors prescription practices in the US, where metformin is a cornerstone of diabetes management. Thus, our adjustment for diabetes status likely accounted for the majority of the potential confounding related to antidiabetic drug use.[3-5]

For this response, we performed additional subgroup analyses for individuals with and without diabetes, which were not included in the original publication. These analyses revealed no statistically significant differences for the associations between lipids and dementia risk between individuals with diabetes – of whom approximately 80% were likely using at least metformin – and those without – who highly likely did not use any antidiabetic drugs (**Table 1**). This further supports our conclusion that antidiabetic drugs, including metformin, did not substantially influence the observed relationship between lipid profiles and dementia risk in our study.

On behalf of our coauthors, we would like to thank Prof. Naharci for his insightful comments and for engaging with our work.

Kind regards,

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Table 1. Additional subgroup analyses for frailty (based on ALDS) and diabetes.

	Most disability				**Least disability**				
Dementia:	Events/total	HR	95%CI	p-value	Events/total	HR	95%CI	p-value	p-int
TC	54/744	0.96	(0.67-1.37)	0,80	114/1996	0,89	(0.71-1.11)	0,29	0,54
LDL-C	53/738	0.95	(0.67-1.35)	0.78	113/1983	0.78	(0.62-0.97)	0.03*	0.25
HDL-C	55/746	0.83	(0.6-1.16)	0.28	114/1999	1.3	(1.08-1.56)	0.005*	0.05
TC/HDL	54/744	1.19	(0.9-1.58)	0.23	114/1995	0.72	(0.58-0.89)	0.002*	0.01*
LDL/HDL	53/738	1.02	(0.75–1.39)	0.91	113/1983	0.72	(0.60–0.88)	0.001*	0.07
	Diabetes				***No diabetes***				
Dementia:	Events/total	HR	95%CI	p-value	Events/total	HR	95%CI	p-value	p-int
TC	37/493	0.78	(0.51-1.19)	0.25	132/2259	0.96	(0.78-1.2)	0.74	0.57
LDL-C	37/488	0.84	(0.55-1.3)	0.43	130/2245	0.85	(0.69-1.06)	0.15	0.97
HDL-C	37/493	1.1	(0.77-1.59)	0.60	133/2264	1.14	(0.95-1.35)	0.15	0.73
TC/HDL	37/493	0.81	(0.56-1.18)	0.27	132/2258	0.88	(0.73-1.07)	0.20	0.52
LDL/HDL	37/488	0.88	(0.64–1.22)	0.45	130/2245	0.806	(0.67–0.97)	0.03*	0.85

'Most disability' refers to participants in the lowest 25% of ALDS scores, and 'least disability' refers to those in the highest 75%. Diabetes was operationalized as 'yes' or 'no' at baseline. All HRs are model 3 adjusted (for factors directly associated with cholesterol levels and cognition), including sex, education, MMSE score, cholesterol medication use, apolipoprotein E e4 allele presence (APOE4), cardiovascular risk factors, including systolic blood pressure, antihypertensive medication use, body mass index (BMI), smoking, history of stroke, history of cardiovascular disease (CVD), and diabetes mellitus. Abbreviations: HR: Hazard ratio per standard deviation increase, 95%CI: 95% confidence interval, p-int: p for interaction; TC: total cholesterol, LDL-C: low-density lipoprotein cholesterol, HDL-C: high density lipoprotein cholesterol, HR: hazard ratio, 95%CI: 95% confidence interval, ALDS: Amsterdam Linear Disability Scale. *: statistically significant

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SUPPLEMENTARY MATERIAL

Original publication by Mehmet I. Naharci

Comment on "Adverse Lipid Profiles are Associated With Lower Dementia Risk in Older People"

Journal of the American Medical Directors Association. Published: 2025 February (Online: 2024, December 3rd); DOI: 10.1016/j.jamda.2024.105376

Dear Editor,

We read with great interest the article titled "Adverse lipid profiles are associated with lower dementia risk in older people" reported by Schroevers et al.[1] The study highlighted that dyslipidemia was linked to a lower chance of developing dementia in older adults who live in the community. Interestingly, the poor outcomes linked to dyslipidemia were reduced by low body mass index and higher educational levels. These findings have the potential to guide new approaches for predicting dementia risk and developing interventions to decrease this risk at advanced ages. However, there are some points that merit discussion. The authors could have missed several factors that could have affected their results (eg, frailty, use of antidiabetic drugs).

Age-related declines in physiological reserve and functional capacity lead to frailty, resulting in poor outcomes (e.g., mild cognitive impairment, dementia).[2-4] Recent evidence from cross-sectional and longitudinal studies has revealed an increased risk of mild cognitive impairment (1.9 times) and cognitive decline (3.5 times) in community-dwelling frail older adults.[2,3] Likewise, in a long-term care setting, a retrospective cohort study with up to 9 years of follow-up reported that frailty was associated with an increased risk of all types of dementia and mortality, with further accumulation of deficits making the probability greater.[4] Furthermore, frailty may induce progression of mild cognitive impairment to dementia.[5] On the other hand, existing studies investigating the relationship between dyslipidemia and frailty have conflicting results. A cross-sectional analysis from the UK Biobank with 202,537 participants revealed that prefrailty and frailty were associated with lower levels of total, low-density lipoprotein, and high-density lipoprotein cholesterol in adults.[6] In turn, in an observational study with 11,838 individuals, elevated remnant cholesterol levels showed a significant association with frailty status in middle-aged and older adults.[7] However, no research has examined the prognostic role of cholesterol levels for frailty in older adults. I agree with the authors that, as stated, low cholesterol levels in late life may be a marker of

further physical aging, a presence of catabolism and frailty.[1] Therefore, using the most frequently cited and validated physical frailty screening tool to identify and evaluate frail individuals in subgroup analyses, or if not determined, to consider their physical exercise status, may provide remarkable findings.[8]

Another topic I would like to discuss is antidiabetic drugs, which were not included in the current study as covariates.[1] A total of 18% of the sample was reported to have diabetes, which suggests that a significant portion of them used antidiabetic medications. Metformin, the first-line antihyperglycemic agent, may cause favorable changes in lipid profile, increasing high-density lipoprotein-cholesterol and lowering total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels.[9] Moreover, a recent meta-analysis of 100 reviews and 27 cohort/case-control studies (N = 3,046,661) demonstrated that metformin, thiazolidinediones, pioglitazone, and glucagon-like peptide-1 receptor agonists were related to a significant decrease in dementia risk, whereas meglitinides and sulphonylureas were associated with increased risk. The evidence validates that some antidiabetic drugs have positive effects on lipid profile and cognitive decline in older populations.[10]

Finally, certain additional data on frailty and antidiabetic drugs may make the prediction model more accurate and stronger to show dementia risk in older adults. This would provide new insights on the issue of relationship between serum lipids and the risk of dementia.

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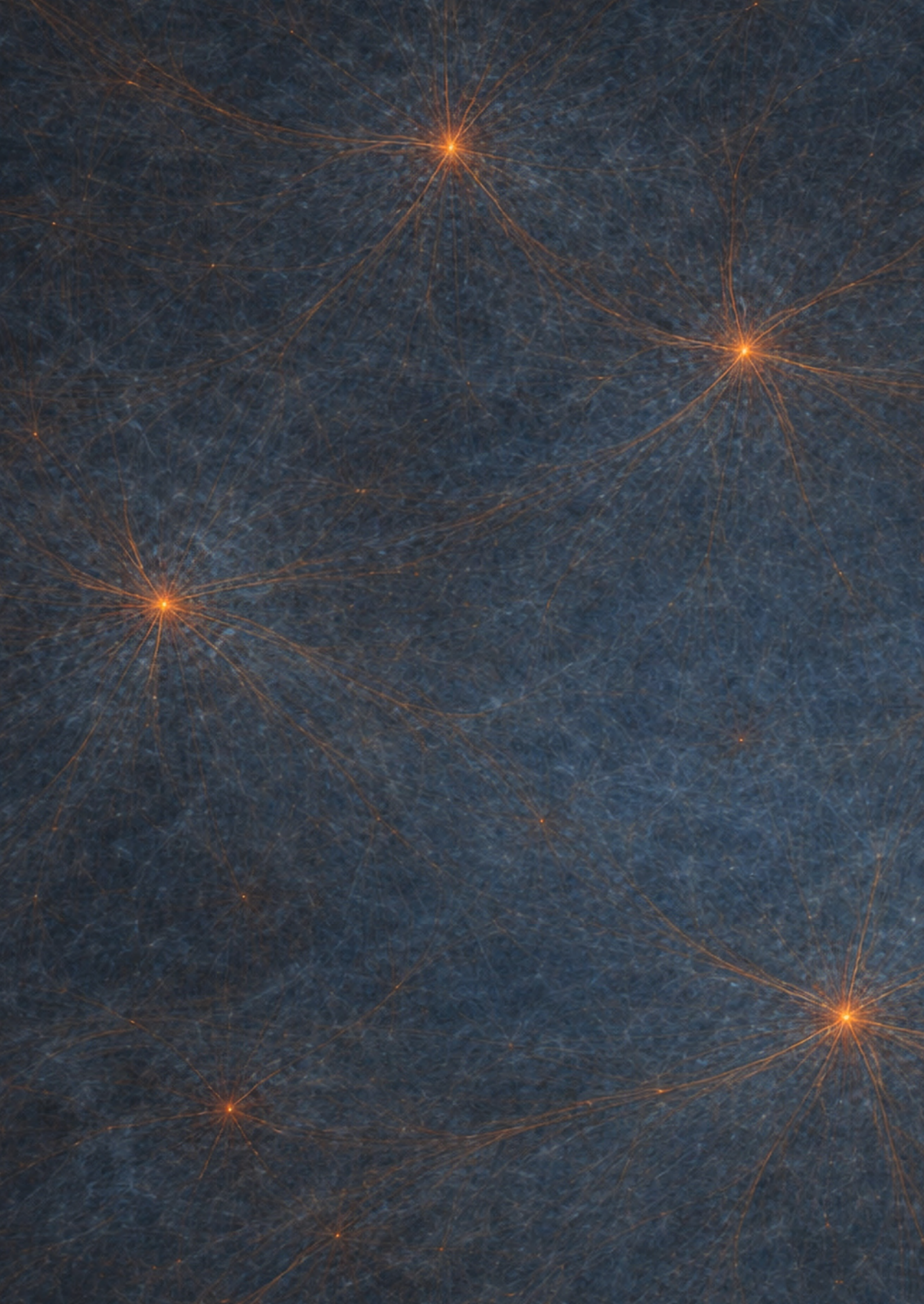

Chapter VIII

General Discussion

This thesis focused on two modifiable risk factors for all-cause dementia in older individuals: hypertension and dyslipidaemia. Specifically, it investigated whether certain antihypertensive medication (AHM) classes are associated with a lower dementia risk and how various lipid profiles relate to dementia risk in older adults. This concluding chapter synthesises the findings from the preceding chapters, discusses considerations relevant to interpreting the results, explores their implications for clinical practice, outlines potential directions for future research, and ends with a general conclusion.

MAIN FINDINGS

In Chapter II, we analysed data of over 1,900 older adults from the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial[1] and its observational extension[2] and found that angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs), and angiotensin II (Ang II)-stimulating AHM were associated with a 32–46% lower dementia risk over 7 years, compared to angiotensin-converting enzyme (ACE) inhibitors and Ang II-inhibiting AHM, respectively; these associations attenuated to a non-significant 20–25% lower dementia risk over 12 years.

In *Chapter III*, using routine primary care data from over 133,000 older adults, we found ARBs, dihydropyridine CCBs, and thiazide diuretics were associated with a 15–25% lower dementia risk than ACE inhibitors, and Ang II-stimulating AHMs with a 12% lower risk than Ang II-inhibiting AHM.

In *Chapter IV*, using the same data as *Chapter III*, selecting 84,000 older adults with primary hypertension without specific comorbidities, ARBs and thiazide diuretics were associated with a 15% and 30% lower risk, respectively, of dementia, mortality, and major cardiovascular events.

In *Chapter V*, interviews with 18 Dutch GPs revealed a patient-centred approach to hypertension, favouring lifestyle changes and often diverging from guidelines by avoiding initiating with dual-class therapy and viewing AHM classes as non-interchangeable.

In *Chapter VI*, among 3,300 older adults from the PreDIVA trial, high TC, high LDL-C, and low HDL-C were associated with lower dementia risk, especially in those with low BMI and high education, suggesting lipid profiles may have different implications in late life.

In *Chapter VII*, in respond to a comment on *Chapter VI*, we demonstrated that associations were most evident in individuals with minimal disability, while antidiabetic drug use did not explain the findings.

RESEARCH IN CONTEXT

In both *Chapters II* and *III*, we found that Ang II-stimulating AHM, comprising of ARBs, dihydropyridine CCBs, and thiazide diuretics, were associated with a 10–25% lower risk of dementia compared to Ang II-inhibiting AHM and ACE inhibitors, respectively. These associations were not explained by competing risk of death.

A large-scale network meta-analysis (n ≈ 649,000 AHM users; 19,600 dementia cases) reported similar lower dementia risks for ARBs (12%) and CCBs (16%), compared to ACE inhibitors, though it did not distinguish between different types of diuretics.[3] However, two smaller individual patient data (IPD) studies did not report clear differences between AHM classes, likely due to limitations in directly comparing these classes.[4,5] The first IPD study (n ≈ 7,500 AHM users; 650–750 dementia cases), which compared AHM users with either non-users or placebo recipients, found no significant differences between individual AHM classes.[2] Nonetheless, a comparison of point estimates from this study with our findings reveals notable similarities: ARBs (OR = 0.95), CCBs (OR = 0.92), and diuretics (OR = 0.84) were associated with a 20–30% lower dementia risk compared to ACE inhibitors (OR = 1.14). The second IPD study (n ≈ 7,800 AHM users; up to 1,250 dementia cases) compared specific AHM classes to "any other AHM" and reported no significant differences between classes.[5] However, point estimates for ARBs (HR = 0.88) and diuretics (HR = 0.95) indicated a 15–20% lower dementia risk compared to ACE inhibitors (HR = 1.11), aligning with our findings. The individual point estimates from these two studies suggest that, had direct comparisons between AHM classes been conducted, significant differences might have emerged. Notably, none of the meta-analyses accounted for the competing risk of death. However, one IPD study included a mortality / dropout analysis, reporting the largest difference between ARBs (OR = 0.79) and ACE inhibitors (OR = 1.04).[4]

Angiotensin hypothesis

In *Chapter I*, we proposed several mechanisms to explain differences in dementia risk between AHM classes, including the angiotensin hypothesis. Briefly, Angiotensin II binds to Angiotensin II type 2 and 4 receptors (ATR2 and ATR4), which are linked to neuroprotection and improved memory function.[6-8] Our findings in *Chapters II–IV* offer some support for this hypothesis: ARBs, dihydropyridine CCBs, and thiazide

diuretics, all Angiotensin II-stimulating AHM, are consistently associated with lower dementia risk than ACE inhibitors, which inhibit Angiotensin II activity.

If the angiotensin hypothesis fully explained these differences between AHM classes, the clearest contrast would be expected to be between ARBs and ACE inhibitors. This as ACE inhibitors directly suppress Angiotensin II, thus reducing ATR2/ATR4 stimulation. On the other side of the spectrum, ARBs block ATR1, increasing Angiotensin II availability for ATR2/ATR4 binding, and also stimulate release of the Angiotensin II precursor, renin, further boosting Angiotensin II levels. In contrast, dihydropyridine CCBs and thiazide diuretics increase, and non-dihydropyridine CCBs and beta blockers inhibit, ATR2/ATR4 activity only indirectly via renin-mediated Angiotensin II production.

However, in *Chapters III* and *IV*, thiazide diuretics, rather than ARBs, were associated with the lowest risk of dementia and dementia/mortality, followed by ARBs and then dihydropyridine CCBs. In *Chapter II*, ARBs and dihydropyridine CCBs were associated with lower dementia risk compared to any other AHM, and ACE inhibitors and diuretics with the highest. However, in that analysis, we did not differentiate between diuretic subclasses. It is possible that had we examined thiazide diuretics separately, they would have been associated with the lowest dementia risk. These findings suggest that while the angiotensin hypothesis may partially explain the observed associations, additional mechanisms are likely involved.

Adherence

Differences in real-world adherence may also explain why ARBs are associated not only with a lower dementia risk but also with a reduced risk of major adverse cardiovascular events and mortality, despite previous evidence suggesting that both classes are equivalent in preventing cardiovascular events.[9,10]. Most of the evidence supporting the equivalence of ARBs and ACE inhibitors comes from randomised controlled trials (RCTs), where patients typically demonstrate better therapy adherence than in real-world settings.[11] Even within these trials, ACE inhibitors had a slightly higher withdrawal rate due to adverse effects.[9,12] In routine clinical practice, the more frequent occurrence of side effects with ACE inhibitors leads to higher withdrawal rates and potentially lower overall adherence compared to ARBs. Several meta-analyses, based on hundreds of studies, report that withdrawal rates for ACE inhibitors can be up to 78% higher than those for ARBs.[9,13-15] Differences in long-term adherence could further explain the observed associations, not only for dementia risk but also for the reduced incidence of other major adverse events.

Physician preferences

A literature search revealed a notable lack of studies on how physicians' preferences and prescribing practices influence AHM use, despite clinical expertise being a core pillar of evidence-based medicine.[16] To address this gap, we conducted a qualitative study among Dutch GPs, highlighting the need to integrate clinical expertise into research and guidelines. For instance, most GPs opposed the guideline recommendation to initiate treatment with two AHMs for systolic blood pressure (BP) ≥150 mmHg. Incorporating physicians' perspectives may improve guideline alignment with real-world practice, enhancing adherence and patient outcomes.

Dyslipidaemia

Dyslipidaemia, specifically elevated midlife LDL-C levels, has recently been recognised as a modifiable risk factor for dementia by the Lancet Commission on Dementia Prevention, Intervention, and Care.[17] This addition was absent in earlier versions of the Commission's reports, as the evidence linking lipid profiles to dementia risk was inconclusive.[18] Nevertheless, other common lipid measures, such as total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C), were excluded due to insufficient and inconclusive evidence regarding their association with dementia risk. This lack of clarity may partly stem from the heterogeneity of lipid measurements (i.e., LDL-C, HDL-C) and populations (e.g., older adults vs. midlife) studied.[19,20] To address these limitations, rather than investigating one or two lipid fractions, we included all commonly used clinical lipid fractions. Furthermore, we focused on a population of community-dwelling older adults. Our findings, indicating that adverse lipid profiles in older adults are associated with lower dementia risk, may seem counterintuitive but are consistent with literature. One meta-analysis found no association between high TC in late life and dementia, while another one demonstrated that the increased dementia risk linked to elevated TC diminished with age.[20,21] A large biobank study identified U-shaped relationships for TC, HDL-C, and LDL-C, where individuals in the two middle quartiles exhibited lower dementia risk compared to those in the lowest and highest quartiles.[22]

The value of low values

U-shaped associations between cardiovascular risk factors and dementia in older age are not unique to dyslipidaemia. A pooled analysis of individual participant data from seven prospective, population-based cohorts reported a lower dementia risk in older adults with higher systolic BP values, with a U-shaped association emerging in those over 75 years of age.[23] These counterintuitive associations between traditionally adverse risk factors and lower dementia risk do not suggest that these risk factors should go untreated to reduce overall adverse event risk. They do imply that lower values may

not necessarily equate to lower risk. This is supported by a study that associated low baseline values of BP, non-HDL cholesterol, and BMI, with a higher dementia risk in older adults, particularly when present in all three commodities, perhaps indicating an overarching phenomenon such as frailty.[24] Another study indicated that years prior to clinical symptoms of dementia emerging, values of BMI, BP, and cholesterol start to decline.[25] These findings highlight the need for a more nuanced interpretation of cardiovascular risk factors in ageing populations, considering the broader context of health status rather than relying solely on traditional risk thresholds.

METHODOLOGICAL CONSIDERATIONS

Strengths

A key strength of this research is the use of clinically relevant dementia outcomes, relying on clinical diagnoses of all-cause dementia rather than cognitive decline measured by test scores. Cognitive tests scores, including the Mini-Mental State Examination (MMSE), reflect cognitive performance at a single point in time and may fluctuate or improve. In contrast, a clinical diagnosis of dementia requires evidence of sustained and progressive cognitive impairment, making it a far more robust, meaningful, and irreversible clinical outcome.

In *Chapters II*, *VI*, and *VII*, using data from the PreDIVA trial and its observational extension study (POE)[1,2], dementia diagnoses were rigorously assessed through in-person study visits, supplemented with data from GP electronic health records (EHRs) and the National Death Registry. Diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) criteria,[26] and independently confirmed by two blinded adjudicators, who reviewed all available clinical information. To minimise false-positive diagnoses, dementia status in PreDIVA was re-evaluated after an additional year of follow-up. For participants who dropped out, a research nurse retrieved dementia status from health records or through GP contact at the end of the study, with final confirmation by the blinded adjudication committee. In *Chapters III* and *IV*, dementia diagnoses were extracted from GPs' EHRs, where they were recorded following prevailing guidelines in accordance with DSM-III or DSM-IV, depending on the time of diagnosis.[26,27] These diagnoses were made either by GPs themselves or by hospital specialists, including neurologists and geriatricians, who in the Netherlands routinely communicate diagnostic information to the patient's GP. This system ensures high diagnostic specificity, reported to be up to 100% for mild and moderate-to-severe dementia.[28,29] However, there is a risk of underestimation, as previous studies have reported sensitivity rates of up to 60%.[29] Nonetheless, this

underestimation is unlikely to be systematically biased toward specific AHM classes, meaning any misclassification would likely be nondifferential. To summarise, by prioritising clinically verified dementia diagnoses over fluctuating cognitive test scores, this research offers a robust and conservative estimation of the associations between AHM and lipid profiles and dementia risk, reinforcing the clinical relevance and translational potential of its findings

Furthermore, in *Chapters II* and *III*, we tested a novel theory, the *angiotensin hypothesis*, by grouping AHM classes based on their presumed effect on Angiotensin II activity, providing new insights into the potential role of the renin-angiotensin system in cognitive decline and dementia risk.[30] Angiotensin II, through stimulation of ATR2 and ATR4, has been linked to neuroprotection and improved memory function.[6-8] By classifying AHM classes according to their ability to stimulate or inhibit these receptors, provided a possible explanation why they are differentially associated with dementia risk beyond conventional BP lowering capabilities. To achieve this, we accounted for AHM class subtypes by distinguishing between dihydropyridine and non-dihydropyridine CCBs, as well as between loop-, thiazide-, and potassium-sparing diuretics. We found that use of non-dihydropyridine CCBs, potassium-sparing diuretics, and loop diuretics was associated with up to a 300% higher mortality risk. This increased mortality is likely explained by the fact that these AHM classes are not primarily prescribed for managing primary hypertension but are instead commonly used for conditions such as cardiac arrhythmias, end-stage kidney disease, and congestive heart failure (CHF), all conditions associated with increased mortality.[31-33] The substantial differences in mortality risk, particularly between thiazide and non-thiazide diuretics, highlight the importance of distinguishing between these subclasses and may help explain discrepancies in dementia and mortality risk observed in studies that did not account for this distinction. These observations led to refinements in the model used in *Chapter IV*, where we focused on the antihypertensive (sub)classes most commonly prescribed for hypertension management: ACE inhibitors, ARBs, beta blockers, dihydropyridine CCBs, and thiazide diuretics. To ensure we studied only participants treated for primary hypertension, where these classes are regarded as equivalent, we excluded and censored participants with a history of, or incident use of non-dihydropyridine CCBs, loop diuretics, and potassium-sparing diuretics, as well as those with associated comorbidities (i.e., non-acute CHD, CHF, AF). In short, refining AHM (sub)class classification clarified their differential associations with clinically relevant outcomes: major cardiovascular events, mortality, and dementia.

Another key improvement between *Chapter II* and *Chapters III-IV* was the shift from baseline medication and confounder data to a time-dependent model.[34] This allowed

us to account for post-baseline changes in medication regimens and health status, and including new diagnoses of diabetes, stroke, and myocardial infarction. To achieve this, we incorporated over eight million individual prescriptions and 27,000 post-baseline diagnoses, providing a comprehensive overview of medication use and health status for more than 133,000 participants. To our knowledge, no other study on AHM classes and dementia risk has applied this methodology at such a scale. By incorporating time-varying exposures and covariates, we created a model that more accurately reflects real-world clinical practice, where treatment regimens and comorbidities often change over time. This is especially important in dementia research, given the long follow-up periods and progressive nature of both disease and treatment patterns. Without accounting for these changes, exposure misclassification could occur, for example, a participant initially classified as an ACE inhibitor user upon entering the cohort (i.e., baseline) may have switched to an ARB during follow-up, leading to misclassification. By using a time-dependent approach, we minimised misclassification and thereby improved the validity of our findings.

Finally, in *Chapters III-V* we improved our analyses by directly comparing AHM classes with one another. This approach avoids using non-use as a reference group, which includes individuals with inherently different dementia risks due to either uncontrolled hypertension (higher risk) or the absence of hypertension (lower risk), and also avoids comparing to 'any other AHM', as done in *Chapter II*, which dilutes contrasts between individual classes. To maintain clarity, we opted for ACE inhibitors fixed reference category throughout all analyses. We decided for ACE inhibitors, as our initial analyses consistently associated ACE inhibitors with the highest dementia and mortality risk. Second, this allowed for a focused comparison with ARBs, which share an identical indication but appeared to have a lower dementia risk in previous studies.[3,35] Lastly, ACE inhibitors are among the most frequently prescribed AHM classes for primary hypertension, making them a clinically relevant reference point.[36]

Limitations

The primary limitation of this thesis concerns potential *confounding by indication*, whereby patients prescribed a specific AHM class may differ systematically from those receiving another, regardless medication's direct effects. Despite guideline assumptions of class equivalency in primary hypertension management, prescribing patterns may still reflect physician preference, comorbidity profiles, or patient characteristics. For instance, ARBs may have been more frequently prescribed to healthier individuals, or their favourable side effect profile may have enhanced adherence. Conversely, beta blockers are often prescribed to patients with cardiovascular comorbidities, possibly explaining their association with poorer outcomes despite statistical adjustment.

Socio-economic status, too, may have contributed to residual confounding, as ARBs, patented and therefore more costly until recently, may have been more accessible to more affluent patients. However, interviews with Dutch GPs (*Chapter V*) did not suggest preferential ARB prescribing to healthier or wealthier patients. Additionally, consistent findings across *Chapters II–IV*, particularly the persistent advantage of ARBs over ACE inhibitors, suggest that confounding by indication alone is unlikely to fully account for the observed associations.

The use of *real-world data* introduced further limitations. In GP prescription records (*Chapters III and IV*), unexplained gaps in medication use were occasionally observed, likely reflecting prescriptions issued by specialists or incomplete EHR integration. However, models that accounted for these gaps yielded comparable results. More problematic was the lack of structured BP data: BP values, where present, were embedded in free text and likely biased towards higher readings due to documentation practices, causing surveillance bias. Although this limited adjustment for BP in *Chapters III and IV*, findings from *Chapter II* and other studies suggest that the associations between AHM classes and dementia are largely independent of BP levels.[37-40]

We initially intended to investigate *dose–effect relationships*, but inconsistent dose notations and missing data rendered this infeasible. As a proxy, we examined duration of use, though this approach lacked sensitivity to treatment intensity or adherence variations.

Our *interview study* provided valuable insight into prescribing behaviour but also had limitations. While we sought diversity among participants, selection bias remains possible; GPs more engaged with hypertension management may have been overrepresented.

This research was conducted in line with the *prevailing cardiovascular guidelines at the time*, namely, the 2019 Dutch College of General Practitioners (NHG) and 2018 European Society of Cardiology (ESC) guidelines.[41,42] Some data even predated these versions, before full AHM class equivalency was established. In *Chapter III*, we accounted for this by stratifying prescriptions by guideline period. Updated versions released during thesis finalisation further deprioritised beta blockers but retained other class equivalencies, supporting the relevance of our core comparisons, particularly between ACE inhibitors and ARBs.[38,39]

Finally, the *setting and population* may affect generalisability. This research was conducted in the Netherlands, where GPs act as primary gatekeepers, and participants

were largely drawn from urban areas around Amsterdam and Utrecht. While this likely ensured some demographic diversity, participants were predominantly white, limiting extrapolation to populations with different ethnic compositions or healthcare systems with different structures.

Recommendations for Clinical Practice and Future Research

With dementia prevalence projected to rise sharply in the coming decades,[43] and no curative treatment expected in the foreseeable future, prevention or delay of onset has become a critical priority. Not only to reduce the personal and societal burden on patients and caregivers, but also to generate substantial economic savings, potentially amounting to billions of euros.[44] Given that the largest projected increases in dementia cases are expected in low- and middle-income countries, cost-effective interventions are urgently needed. One such low-cost and easily implementable strategy could be the prioritisation of specific AHM classes over otherwise equivalent alternatives.

This is facilitated by the fact that most international guidelines consider all AHM classes, except beta blockers, as equivalent for the treatment of primary hypertension.[38,39,45] Particularly ACE inhibitors, currently among the most commonly prescribed AHM classes, and ARBs are often used interchangeably in hypertensive patients with various comorbidities, as they appear similarly effective in reducing cardiovascular events. While high-quality evidence for cardiovascular endpoints is somewhat stronger for ACE inhibitors compared to ARBs,[9] recent studies increasingly support the equivalence of ARBs in preventing cardiovascular events, mortality, and other outcomes, including nephroprotection.[15,46] Notably, ARBs achieve these outcomes at similar costs,[46,47] while offering superior tolerability.[9,13-15] Building on this, the findings from this thesis suggesting that ARBs may provide greater protection against dementia than ACE inhibitors further intensify the question of why ACE inhibitors remain the more commonly prescribed option.[47]

Although this thesis may have advanced the understanding of potential differences between AHM classes and dementia risk, further refinements in observational research are still possible to approximate causal inference. Frameworks for designing and analysing observational studies to estimate causal effects,[48,49] sometimes referred to as 'trial emulation', may help bridge the gap to causality, particularly if key missing factors, such as BP values, dosage information, and participant socio-economic status, are incorporated. However, truly establishing causality remains elusive. This is largely due to confounding, particularly confounding by indication, which often operates at such a deep and pervasive level within observational data that its complete elimination is unlikely.

To establish a definitive causal relationship, an RCT is warranted. Such a trial should directly compare two or more AHM classes, with rigorously assessed dementia incidence as the primary outcome. Secondary outcomes should include mortality and major adverse cardiovascular events, such as myocardial infarction and stroke, as these are key considerations in initiating AHM therapy. Ideally, such a trial would compare ACE inhibitors, ARBs, dihydropyridine CCBs, and thiazide diuretics in community-dwelling older adults with newly diagnosed primary hypertension. Predefined secondary and tertiary AHM options would accommodate cases requiring combination therapy or treatment adjustments, reducing confounding from prior AHM exposure and allowing for better control over regimen changes.

However, such a trial would require thousands of participants per arm and extended follow-up to detect differences in dementia incidence. A more feasible alternative could be a two-arm trial, possibly stratifying by comorbidities to reduce sample size requirements while broadening generalisability. Given their similar indications and consistent differences across key outcomes, ARBs and ACE inhibitors are prime candidates for comparison. The prevailing preference for ACE inhibitors, likely driven by familiarity rather than hard evidence, alongside their comparable cost to ARBs, highlights the potential for safe, cost-neutral, and easily implementable clinical impact if ARBs are confirmed to reduce dementia risk without compromising cardiovascular or mortality outcomes.

With hypertension guidelines further prioritising combination therapy,[38,39] future qualitative studies exploring physician perspectives, should focus more on preferred AHM combinations and thoughts on the importance of secondary benefits of AHM, including on cerebrovascular health, allowing for more in-depth discussions. Furthermore, our study focused on GPs, which is appropriate given that they typically initiate AHM therapy. However, as hypertension management increasingly shifts to practice nurses, particularly after initial AHM initiation, their perspectives should also be explored in future research. Their insights could provide a more comprehensive understanding of real-world hypertension management and the factors influencing treatment decisions. Building a network of diverse health care professionals willing to contribute as sounding board to various topics, could facilitate conducting future qualitative studies, and thus further help bridge the gap between empirical evidence and everyday clinical practice.

Regarding dyslipidaemia, based on the findings of this thesis, no definitive recommendations can be made regarding which lipid measures to prioritise or how they should be used in assessing dementia risk. However, clinicians should be aware that

lipid parameters, including LDL-C, HDL-C, and lipid ratios, may have varying implications for dementia risk depending on individual patient characteristics, including age, cardiovascular comorbidity, and perhaps frailty.

In older adults, traditionally perceived adverse lipid profiles may, paradoxically, be associated with a lower dementia risk compared to lower lipid values. This does not imply that dyslipidaemia should not be managed to reduce overall cardiovascular risk, including dementia. Rather, it suggests that older individuals with low lipid, BMI, and BP values are not necessarily at lower dementia risk, potentially due to an overarching dimension such as increasing frailty. This highlights the need for a nuanced approach when interpreting lipid levels in older adults, balancing cardiovascular risk reduction with broader considerations of ageing and overall health status. Given these complexities, a uniform approach to lipid management in dementia risk assessment is unlikely to be appropriate. Instead, a more personalised strategy, considering a patient's broader health profile, is likely to be warranted.

To better understand the role of lipid profiles in dementia risk, future research should incorporate a broader range of serum lipids, including LDL-C, HDL-C, and lipid ratios, as these may be differentially associated with cognitive decline and dementia. A crucial consideration is the strong influence of age, alongside other factors such as BMI, education, disability, with potentially frailty as an overarching phenomenon, all of which should be systematically accounted for in study designs. This necessitates large studies, with well-delineated health profiles, enabling the possibility for robust subgroup analyses.

Future research should also move beyond single time-point lipid measurements (e.g., baseline) and instead incorporate longitudinal lipid profiles to better capture the dynamic relationship between lipid levels and dementia risk. Similarly, cholesterol-lowering medication use should be rigorously collected and integrated as a time-dependent variable in observational models. This would allow for a more precise assessment of the interplay between lipid levels, statin or other lipid-lowering therapy use, and dementia risk, reducing bias from treatment-related lipid changes. Future studies should target lipid lowering interventions in specific subgroups, rather than broad lipid-lowering strategies in heterogenic populations to help further refine our understanding how various lipid profiles may influence dementia risk. Ultimately, this thesis underscores the need for a nuanced approach when assessing the role of dyslipidaemia in dementia risk, taking into account individual patient characteristics and the broader metabolic and vascular context. These insights may enhance dementia risk stratification and inform the development of more targeted interventions for ageing

populations, encouraging clinicians to adopt a more personalised, context-sensitive strategy when interpreting lipid profiles in older adults.

General Conclusion

This thesis contributes several new pieces to the complex puzzle of dementia prevention.

Our findings suggest that traditionally adverse lipid profiles in older individuals are not necessarily associated with adverse outcomes, such as dementia and mortality, with factors like low BMI, high education, and lower disability levels potentially mitigating these risks. This indicates that a more nuanced interpretation of lipid profiles in older age is warranted. These insights could improve dementia risk prediction and guide the development of future targeted interventions for aging populations.

This thesis further adds to the growing body of evidence that specific AHM classes, particularly ARBs, are associated with a lower dementia risk compared to ACE inhibitors, without increasing the risk of mortality or other adverse outcomes. Although dihydropyridine CCBs and thiazide diuretics were also associated with lower dementia risk compared to ACE inhibitors, results were less consistent across subgroup and sensitivity analyses. Moreover, interviews with general practitioners suggested AHM prescription are likely to have been influenced by physicians preferences and treatment context. This confounding by indication is likely never to be fully eliminated in observational studies, underscoring the need for RCTs directly comparing AHM classes with dementia as a primary outcome. ARBs and ACE inhibitors, given their similar indications in hypertension management, are likely the most promising candidates for such studies. If future RCTs confirm these findings, preferentially prescribing ARBs over other equivalent AHM classes could offer a cost-effective, readily implementable, and safe approach to help reduce the global burden of Dementia.

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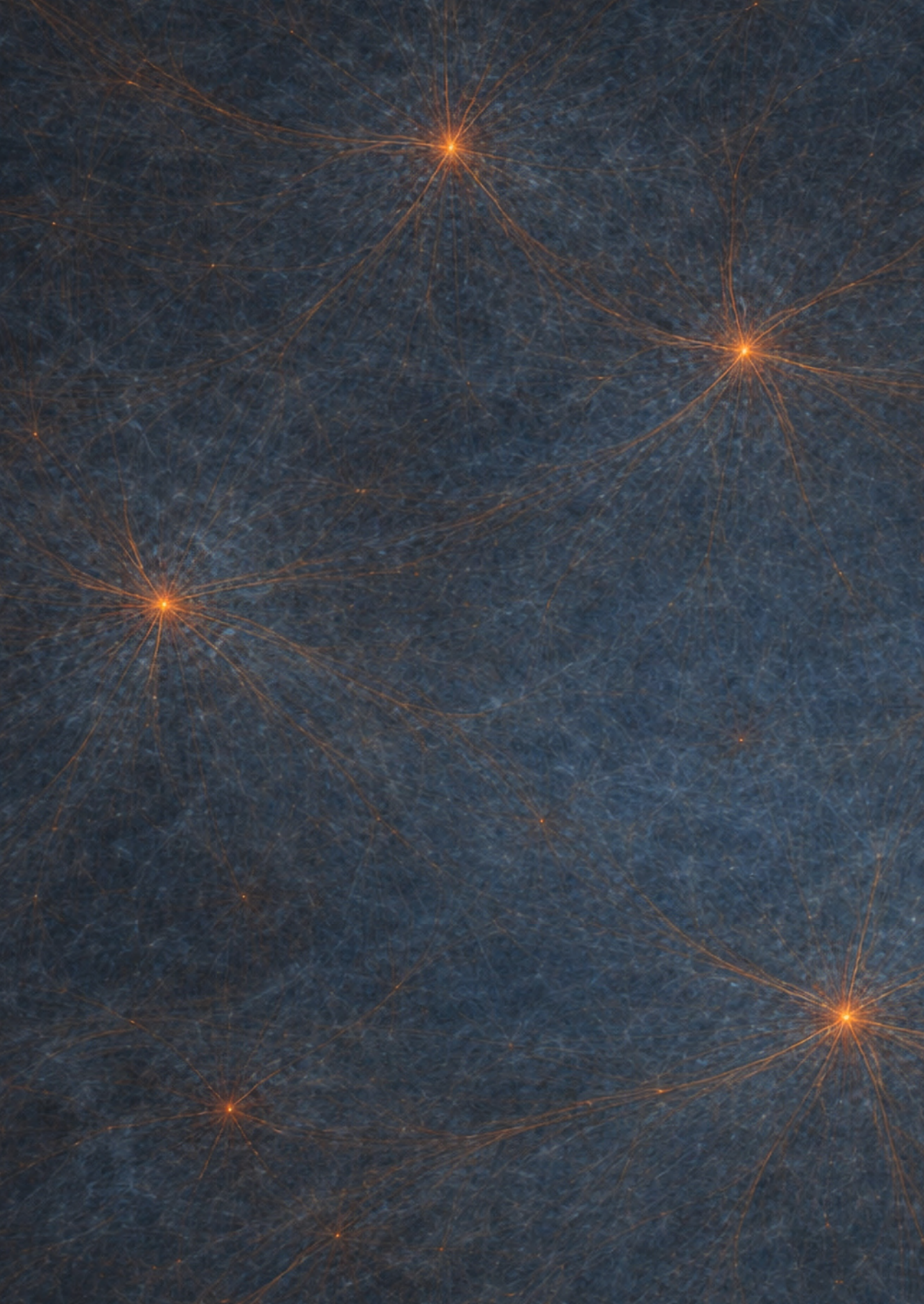

Appendices

THESIS SUMMARY

The growing global prevalence of dementia, coupled with the absence of a cure in the foreseeable future, highlights the urgent need for affordable and widely accessible preventive strategies. In this thesis, we investigated two modifiable risk factors for dementia that are candidates for such strategies: hypertension and dyslipidaemia. In the first part of the thesis, we explored potential differences between antihypertensive medication (AHM) classes and dementia risk. In the second, we examined how various lipid profiles were associated with dementia risk in older adults.

In Chapter II, using data from the Prevention of Dementia by Intensive Vascular Care (PreDIVA) trial and its observational extension (POE), we examined whether previously reported associations between specific antihypertensive medication (AHM) classes and a reduced risk of dementia persisted over extended follow-up. We included more than 1,900 community-dwelling older adults who used AHMs and found that the lower dementia risk associated with angiotensin receptor blockers (ARBs), dihydropyridine calcium channel blockers (CCBs), and Angiotensin II (Ang II)–stimulating AHMs, which was evident over a 7-year follow-up, was no longer statistically significant after 12 years. Nonetheless, risk estimates for these AHM classes remained up to 25% lower compared with the use of other AHM.

In Chapter III, we analysed routine-care data from over 133,000 community-dwelling adults, comprising more than 5,800 dementia cases, 96,000 cardiovascular diagnoses, and over 8 million individual AHM prescriptions during a median follow-up of 7.6 years. Using these extensive longitudinal data, we employed a detailed time-dependent model to compare AHM subclasses with angiotensin-converting enzyme (ACE) inhibitors, and Ang II–stimulating with Ang II–inhibiting AHMs. Use of ARBs, CCBs, and Ang II–stimulating AHMs as a group were all associated with a 12–23% lower risk of dementia, without excess mortality explaining these results. Findings were robust in extensive subgroup and sensitivity analyses.

In Chapter IV, we extended the analyses of Chapter III using the same longitudinal routine-care data, focusing on physicians' primary motivations for initiating antihypertensive therapy, namely the prevention of stroke, myocardial infarction, and mortality, alongside dementia as primary endpoints. We further refined our populations, selecting individuals treated for primary, uncomplicated hypertension to ensure that all AHM classes were truly guideline-equivalent. The results indicated that ARBs and thiazide diuretics were associated with 14% and 29% lower risks of major adverse events, respectively, compared with ACE inhibitors.

In Chapter V, we conducted interviews with 18 Dutch general practitioners (GPs) to explore their prescribing preferences, beliefs, and decision-making processes for managing primary hypertension. Our findings revealed discrepancies between guideline recommendations and everyday clinical practice. GPs, contrary to guideline recommendations, did not consider different AHM classes to be fully interchangeable. Furthermore, they expressed concern about the growing incentive to initiate treatment with combination therapy. Incorporating GPs' perspectives into guideline development may lead to more practical, tailored recommendations that improve adherence and patient outcomes in real-world care.

In the second part of this thesis, we studied the complex relationship between dyslipidaemia and dementia risk.

In Chapter VI, we examined the association between various lipid markers and dementia risk in a cohort of over 3,300 older adults from the PreDIVA trial. Contrary to the established understanding of dyslipidaemia in cardiovascular disease, adverse lipid profiles, characterised by high total cholesterol (TC), high low-density lipoprotein cholesterol (LDL-C), and low high-density lipoprotein cholesterol (HDL-C), were associated with a *lower* risk of dementia. Sensitivity analyses suggested that low body mass index (BMI) and higher education levels may attenuate adverse outcomes associated with dyslipidaemia. These findings highlight the need for a different interpretative approach to lipid profiles in older adults, one that could improve dementia risk prediction and guide future intervention studies to move beyond cholesterol lowering alone, exploring whether maintaining or even supporting certain lipid levels in late life might help reduce dementia risk

In Chapter VII, in response to a research letter regarding our publication in Chapter VI, we showed that the apparent beneficial associations of adverse lipid profiles with lower dementia risk were primarily observed in individuals with the least disability, while the use of oral antidiabetic drugs did not affect these findings. This suggests that functional status may modulate the relationship between lipid profiles and dementia risk, with higher lipid levels potentially reflecting better overall physiological reserve in healthier older adults rather than a direct protective effect.

Taken together, the findings on dyslipidaemia from the observational data presented in this thesis add nuance to current understanding, indicating that the clinical relevance of lipid profiles may be age-dependent, requiring more careful interpretation in older adults and warranting further investigation. The studies on hypertension demonstrated that the choice of antihypertensive class seems to matter, with ARBs in

particular consistently associated with lower risks of dementia, mortality, and major adverse cardiovascular events compared with ACE inhibitors. While guidelines regard these agents as equivalent, our interviews indicate that such equivalence is not uniformly acknowledged among GPs, reflecting potential divergences between evidence and clinical practice. A randomized controlled trial directly comparing ARBs with ACE inhibitors for dementia risk would provide definitive evidence on whether choosing one otherwise guideline-equivalent option over the other truly reduces dementia risk. Insights from this thesis may inform the design of such trials and contribute to the development of safe, cost-effective preventive strategies aimed at lowering the global burden of dementia.

SAMENVATTING VAN HET PROEFSCHRIFT

De wereldwijde toename van dementie, gecombineerd de verwachting dat er in de voorziene toekomst geen genezing gevonden zal worden, maakt duidelijk dat er behoefte is aan preventiestrategieën die zowel betaalbaar als breed toepasbaar zijn. In dit proefschrift onderzochten we twee beïnvloedbare risicofactoren voor dementie die hiervoor in aanmerking komen: hoge bloeddruk (hypertensie) en ongunstige vetwaarden in het bloed (dyslipidemie). Het eerste deel van het proefschrift richtte zich op mogelijke verschillen tussen soorten bloeddrukmedicijnen en hoe deze samenhangen met het risico op dementie. In het tweede deel keken we naar de samenhang tussen verschillende lipidenprofielen en het risico op dementie bij ouderen.

In Hoofdstuk II onderzochten we, met gegevens uit de PreDIVA-studie en de observationele uitbreiding daarvan (POE), of eerdere bevindingen over specifieke soorten bloeddrukmedicijnen ook op de lange termijn bleven gelden. We includeerden meer dan 1.900 zelfstandig wonende ouderen die bloeddrukmedicatie gebruikten. Het lagere risico op dementie dat we eerder zagen bij gebruik van angiotensine-receptorblokkers (ARBs), dihydropyridine-calciumantagonisten en de overkoepelende groep bloeddrukmedicijnen die Angiotensine II (Ang II) stimuleren, was na zeven jaar duidelijk zichtbaar, maar na twaalf jaar niet langer statistisch significant. Toch bleven de schattingen wijzen op een tot 25% lager risico bij deze medicijnen vergeleken met andere soorten bloeddrukmedicatie.

In Hoofdstuk III bekeken we zorggegevens uit de dagelijkse praktijk van meer dan 133.000 zelfstandig wonende volwassenen. Onder hen waren meer dan 5.800 mensen met dementie en 96.000 met een hart- of vaatziekte, en er waren ruim 8 miljoen afzonderlijke recepten voor bloeddrukmedicatie. De deelnemers werden gemiddeld 7,6 jaar gevolgd. Met deze gegevens vergeleken we verschillende soorten bloeddrukmedicatie. Zo keken we zowel naar individuele middelen ten opzichte van ACE-remmers als naar Ang II–stimulerende medicijnen als groep ten opzichte van Ang II–remmende medicijnen. We zagen dat het gebruik van ARBs, dihydropyridine-calciumantagonisten en Ang II–stimulerende medicijnen geassocieerd was met een 12–23% lager risico op dementie, vergeleken met ACE-remmers en Ang II–remmende medicijnen. Dit verschil werd niet verklaard door sterfte. De bevindingen bleken bovendien betrouwbaar in verschillende subgroepen en bij aanvullende analyses.

In Hoofdstuk IV bouwden we voort op de resultaten van Hoofdstuk III, opnieuw gebruikmakend van dezelfde gegevens uit de dagelijkse praktijk. Dit keer keken we niet alleen naar dementie, maar ook naar beroerte, hartinfarct en sterfte, omdat

dit de belangrijkste redenen zijn voor artsen om bloeddrukmedicatie voor te schrijven. Bovendien selecteerden we alleen mensen die behandeld werden voor primaire, ongecompliceerde hoge bloeddruk, zodat alle soorten bloeddrukmedicatie volgens de richtlijnen vergelijkbaar waren. De resultaten lieten zien dat het gebruik van ARBs en thiazidediuretica geassocieerd was met respectievelijk 14% en 29% lager risico op ongewenste uitkomsten vergeleken met ACE-remmers.

In Hoofdstuk V interviewden we 18 Nederlandse huisartsen over hun voorkeuren bij het voorschrijven, hun opvattingen en hun beslissingsprocessen bij de behandeling van primaire hoge bloeddruk. Uit de interviews bleek dat er verschillen zijn tussen wat de richtlijnen adviseren en wat in de dagelijkse praktijk gebeurt. Huisartsen zagen, in tegenstelling tot de richtlijnen, verschillende soorten bloeddrukmedicatie vaak niet als volledig uitwisselbaar. Daarnaast maakten ze zich zorgen over de steeds vaker aanbevolen start met combinatietherapie. Door het perspectief van huisartsen mee te nemen bij het opstellen van richtlijnen, kunnen aanbevelingen praktischer en beter toepasbaar worden, wat de naleving en de resultaten in de dagelijkse zorg kan verbeteren.

Het tweede deel van dit proefschrift richt zich op de complexe samenhang tussen ongunstige vetwaarden in het bloed (dyslipidemie) en het risico op dementie.

In Hoofdstuk VI keken we naar verschillende vetwaarden in het bloed en het risico op dementie bij meer dan 3.300 oudere volwassenen uit de PreDIVA-studie. Opvallend was dat oudere mensen met vetwaarden die meestal als ongunstig worden gezien soms juist een lager dementierisico hadden, vooral bij mensen met een laag gewicht en een hogere opleiding. Deze bevindingen laten zien dat lipidenprofielen bij ouderen anders geïnterpreteerd moeten worden, wat kan helpen om het risico op dementie beter in te schatten en toekomstige studies naar interventies te sturen, bijvoorbeeld door te onderzoeken of het behouden of zelfs ondersteunen van bepaalde vetwaarden op latere leeftijd het risico op dementie kan verlagen.

In Hoofdstuk VII, geschreven naar aanleiding van een onderzoeksbrief over onze publicatie in Hoofdstuk VI, zagen we dat het lagere risico op dementie dat samenhing met ongunstige vetwaarden in het bloed vooral voorkwam bij mensen met weinig beperkingen in hun dagelijks functioneren. Het gebruik van medicijnen tegen suikerziekten had hier geen invloed op. Dit suggereert dat de fysieke en cognitieve gesteldheid van een oudere persoon de samenhang tussen vetwaarden en dementierisico kan beïnvloeden. Hogere vetwaarden zouden in gezondere ouderen mogelijk een betere algemene lichamelijke reserve aangeven, in plaats van een direct beschermend effect tegen dementie.

Concluderend laten de bevindingen over dyslipidemie zien dat de betekenis van lipidenprofielen in de praktijk waarschijnlijk afhangt van de leeftijd en daarom bij ouderen zorgvuldig geïnterpreteerd moet worden. De vier studies over hoge bloeddruk tonen dat de keuze van bloeddrukmedicatie mogelijk belangrijk is. Vooral ARBs waren consistent geassocieerd met een lager risico op dementie, sterfte en ernstige hart- en vaatproblemen in vergelijking met ACE-remmers. Hoewel de richtlijnen deze medicijnen als gelijkwaardig beschouwen, bleek uit onze interviews dat huisartsen hier niet altijd hetzelfde over denken, wat kan wijzen op verschillen tussen wetenschappelijke kennis en dagelijkse praktijk. Een gerandomiseerde studie waarin ACE-remmers en ARBs rechtstreeks worden vergeleken met dementie als belangrijkste uitkomst, zou duidelijk kunnen maken of het verkiezen van de een boven de ander het risico op dementie daadwerkelijk verlaagt. De inzichten uit dit proefschrift kunnen helpen bij het opzetten van dergelijke studies en zo bijdragen aan de ontwikkeling van veilige, betaalbare preventiestrategieën die de wereldwijde last van dementie kunnen verminderen.

PHD PORTFOLIO

PhD period: February 2020 – September 2025

Courses

Year	Course	ECTS
2020-25	Weekly PhD education	6.0
2020-25	Dep. Of General Practice Meetings: *Journal Club, Research meeting, and Early-Career Researchers meeting*	5.0
2020	The Amsterdam World of Science	0.7
2020	AMC Graduate School – Scientific Writing in English	1.5
2020	AMC Graduate School – Qualitative Health Research	1.9
2022	E-BROK – AMC	1.5

Conferences, Presentations & Lecturing

2020	Alzheimer's Association International Conference (AAIC) - Amsterdam (online due to covid-19 restrictions), attendance	0.8
2021	ePoster with pre-recorded oral presentation & attendance at the Alzheimer's Association International Conference (AAIC) - Denver (online due to covid-19 restrictions)	1.2
2022	Annual Amsterdam Public Health (APH) meeting 2022, attendance	0.3
2022	ZonMw. & SBOH HGOG research meeting, attendance	0.3
2022	15th European Public Health Conference – Berlin, attendance	0.3
2022	2023 European Forum on Prevention and Primary Care – Porto, attendance	0.8
2023	Oral presentation at the Academic General Practitioners Network Amsterdam (AHNA) research evening - "General practitioners and electronic health records data"	0.6
2023	Oral presentation at the Zaans Medisch Centrum (ZMC) research night	0.8
2023	NHG-Wetenschapsdag – Groningen, attendance	0.3
2023	Annual Amsterdam Public Health (APH) meeting 2024, attendance	0.3
2024	AIOTO-day & NHG-Wetenschapsdag – Rotterdam, attendance	0.7
2024	Academic General Practitioners Network Amsterdam (AHNA) research evening, attendance	0.2
2024	Lecture 'Evidence Based Medicine' for General Practitioners in training at University of Amsterdam/Academic Medical Centre	0.8
2024	Oral presentation *"Antihypertensive Medication and Risk of Dementia"* & attendance at Alzheimer Nederland & ZonMw 1st Annual Dutch Dementia Researchers Congres DEMPACT	1.0
2024	Poster presentation & attendance at the Annual Amsterdam Public Health (APH) meeting 2024	0.8

2025	Attendance at the AIOTO-day and Oral Presentation *"Antihypertensive medication classes and risk of incident dementia in primary care patients: a longitudinal cohort study in the Netherlands"* & attendance *at the* NHG Wetenschapsdag – Amsterdam	1.2

Peer Reviewing & other publications

Year	Conference	ECTS
2024	Peer Review - BMC Public Health (two review rounds)	0.4
2024	Peer review – JAMDA	0.2
2024	Article Request for the journal of Dutch Academic General Practitioners *'Huisarts en Wetenschap'*	1.6
2025	Article Request for the journal of Dutch Practice Nurses *'Tijdschrift voor Praktijkondersteuners'*	0.8

LIST OF PUBLICATIONS & AUTHOR CONTRIBUTIONS

Articles included in this thesis

Schroevers JL*, Eggink E*, Hoevenaar-Blom MP, Van Dalen JW, Van Middelaar T, Van Gool WA, Richard E, Moll Van Charante EP. Antihypertensive medication classes and the risk of dementia over a decade of follow-up. J Hypertens. 2023 Feb 1;41(2):262-270. doi: 10.1097/HJH.0000000000003324. Epub 2022 Nov 18. PMID: 36394298; PMCID: PMC9799049. *Contributed equally

Authors contributions: JLS, EE, and MHB conceived the study. All other authors were involved in further refining the study design. JLS, EE, MHB, and JWvD performed statistical analyses. JLS and EE provided the manuscript. All other authors provided input during the review and editing process. All authors read and approved the final version of the article.

Schroevers JL, Hoevenaar-Blom MP, Busschers WB, Hollander M, Van Gool WA, Richard E, Van Dalen JW*, Moll van Charante EP*. Antihypertensive medication classes and risk of incident dementia in primary care patients: a longitudinal cohort study in the Netherlands. Lancet Reg Health Eur. 2024 May 15;42:100927. doi: 10.1016/j.lanepe.2024.100927. Erratum in: Lancet Reg Health Eur. 2024 Nov 16;47:101132. doi: 10.1016/j.lanepe.2024.101132. PMID: 38800111; PMCID: PMC11126814. *Contributed equally

Author contributions: EMvC and JLS conceived the study and collected the data. All other authors, excluding MH, were involved in further refining the study design. MH curated data from the Utrecht GPRN. JLS and JWvD performed statistical analyses. MHB and WB were performed statistical validation. JLS and JWvD provided the manuscript. with input from all other authors during the review and editing process. All other authors provided input during the review and editing process. All authors read and approved the final version of the article.

Schroevers JL, Hoevenaar-Blom MP, Richard E, Van Gool WA, Moll van Charante EP, Van van Dalen JW. The Risk of Major Cardiovascular Events, Dementia, and Mortality Differs Between Antihypertensive Medication Classes: A Longitudinal Cohort Study in the Netherlands. Submitted for Publication to *The Lancet Neurology*.

Author contributions: JLS, JWvD, and EMvC conceived the study. All other authors were involved in further refining the study design. JLS and JWvD performed statistical analyses . MHB performed statistical validation. JLS and JWvD provided the

manuscript. All other authors provided input during the review and editing process. All authors read and approved the final version of the article.

Schroevers JL*, Witvliet MP*, Moll van Charante EP. General practitioners' perspectives, preferences, and practices in prescribing antihypertensive medication in primary, uncomplicated hypertension. Fam Pract. 2025 Aug 14;42(5):cmaf059. doi: 10.1093/fampra/cmaf059. PMID: 40810544; PMCID: PMC12351541. *Contributed equally

Author contributions: Author's contribution: JLS, MPW and EMvC conceived the study. JLS and MPW carried out data collection and data analysis. JLS, MPW, and EMvC constructed the narrative of the data. The first draft of the manuscript was written by JLS and MPW. EMvC provided input during the review and editing process. All authors read and approved the final version of the article.

Schroevers JL, Richard E, Hoevenaar-Blom MP, van den Born BH, van Gool WA, Moll van Charante EP, van Dalen JW. Adverse Lipid Profiles Are Associated with Lower Dementia Risk in Older People. J Am Med Dir Assoc. 2024 Sep;25(9):105132. doi: 10.1016/j.jamda.2024.105132. Epub 2024 Jul 6. PMID: 38977201.

Author contributions: JWvD and JLS conceived the study. All other authors were involved in further refining the study design. JWvD performed statistical analyses. JLS and JWvD provided the manuscript. All other authors provided input during the review and editing process. All authors read and approved the final version of the article.

Schroevers JL, van Dalen JW; Co-authors of the original publication. Response to Comment on "Adverse Lipid Profiles are Associated With Lower Dementia Risk in Older People". J Am Med Dir Assoc. 2025 Feb;26(2):105377. doi: 10.1016/j.jamda.2024.105377. Epub 2024 Dec 3. PMID: 39642911.

Author contributions: JLS and JWvD wrote the response. JLS & JWvD performed statistical analyses. JLS provided the manuscript. JWvD provided input during the review and editing process. Both authors read and approved the final version of the article.

Articles not included in this thesis

Schroevers JL, Ursem SR. ACE-remmer of angiotensine receptor blokker bij albuminurie bij DM2? Huisarts en wetenschap. 2024 Nov; 67, 11, p. 24-25 2 p.

Author contributions: JLS and SU conceived the study. JLS and SU executed the search. JLS and SU provided the manuscript. Both authors read and approved the final version of the article.

Schroevers JL, Ursem SR. ACE-remmer of ARB tegen nierschade bij DM2? Accepted for publication in Tijdschrift for Praktijkondersteuners.

Author contributions: JLS and SU conceived the study. JLS and SU executed the search. JLS provided the manuscript. Both authors read and approved the final version of the article.

DANKWOORD

Op de voorzijde van dit proefschrift prijkt mijn naam, maar zoals het veelgebruikte cliché luidt: alleen was het mij natuurlijk nooit gelukt. Dit laatste, vaak best (door menigeen enig) gelezen hoofdstuk draag ik op aan iedereen die mij de afgelopen zes jaar, op welke manier dan ook, heeft bijgestaan. Zij die mij goed kennen, weten dat plannen en organiseren niet tot mijn kernkwaliteiten behoren. Mochten er dus namen ontbreken, weet dat dit niet intentioneel bedoeld is; dit dankwoord is ook aan jullie gericht.

Zonder data, geen onderzoek. Daarom wil ik mijn dank uitspreken aan studiedeelnemers, zorgmedewerkers en alle anderen die betrokken zijn geweest bij de totstandkoming van de onderzoeksgegevens van PreDIVA, POE en de academische huisartsennetwerken. Ook wil ik de achttien huisartsen bedanken die, ondanks een steeds groter wordende werkdruk, de tijd namen om deel te nemen aan onze interviews.

Aan mijn (co)promotores, **prof. dr. Eric Moll van Charante**, **prof. dr. Edo Richard**, **dr. Marieke Hoevenaar-Blom** en **dr. Jan Willem van Dalen**. Groot was mijn verbazing, ruim zes jaar geleden, dat jullie dit onderzoeksavontuur met mij, relatief bleu als het aankwam op academische ervaring, aan durfden te gaan. Immens is mijn bewondering voor jullie expertise, jullie gedrevenheid, maar vooral voor de menselijkheid waarmee jullie mij de afgelopen zes jaar hebben begeleid. Ik moet ervoor waken niet nu al te verzanden in clichés, maar zonder jullie steun had ik dit promotietraject nooit tot een succesvol einde kunnen brengen.

Eric, vanaf ons eerste gesprek wist jij mij te enthousiasmeren en mij welkom te laten voelen. Jouw dagen lijken uit minstens veertig uur te bestaan en jouw weken uit acht dagen: als echtgenoot, vader en mantelzorgende zoon, maar ook als kinderboekenschrijver, cellist, zanger, huisarts en onderzoeker. Ik weet zeker dat ik nog rollen vergeet die jij, stuk voor stuk, vol overgave vervult. Toch lukt het jou altijd uitgebreid tijd te nemen wanneer ik weer eens een beroep op je deed. Wanneer ik vol trots op een zaterdagavond laat een manuscript van tientallen pagina's met minstens zoveel tabellen over jouw digitale schutting wierp, kreeg ik die bijna altijd diezelfde avond nog terug, met uitgebreide suggesties en aanvullingen ('ter overweging'), met oog voor detail tot ver achter de komma.

Edo, waar Eric een groot oog voor detail had, hield jij altijd het grote plaatje in beeld. *Less is more* is de les die jij mij keer op keer probeerde bij te brengen. En hoewel de introductie, discussie en dankwoord van dit proefschrift deze les niet helemaal eer

aandoen, was dit proefschrift zonder jou misschien wel twee keer zo lang geweest (zonder dat er echt meer in had gestaan). Ik heb genoten en geleerd van je humor, van je vlijmscherpe, kritische blik en van jouw ijzersterke voordrachten, waarbij je moeiteloos zowel expert en leek aan jouw lippen vast wist te laten klampen, zonder dat er ook maar één dia aan te pas hoefde te komen.

En hoewel de niet zelden grotendeels tegenstrijdig lijkende suggesties op mijn manuscripten soms frustrerend konden zijn, vullen jullie elkaar feilloos aan. Ik hoop dat nog vele promovendi mogen genieten van *Beun en de Haas B.V.* c.q. *Peppi en Kokki Unltd*.

Marieke, ik ben jouw eerste promovendus, maar daar heb ik in positieve zin weinig van gemerkt: het begeleiden en onderwijzen staat jou op het lijf geschreven. Jij was altijd bereikbaar: voor een wandeling wanneer ik weer eens diep in het onderzoeksmoeras was weggezakt, voor een wazige foto van mijn beeldscherm waarop in rode letters een foutmelding in mijn R-console (in de door mij gehate *Dr. Dre-omgeving*) stond te lezen, en voor paniekmomentjes wanneer de inhoud van data weer anders bleek te zijn dan ik had verwacht. Dan stuurde je altijd: *'even bellen?'*, en dan was de paniek snel verdwenen. Dank ook voor het bewaken van de wetenschappelijke integriteit, wanneer Jan Willem en ik weer kwamen opdraven met een iets te creatieve oplossing voor een statistisch probleem.

Jan Willem, ik weet niet of ik moet beginnen bij het Romeinse Rijk, *Total War*, kip, cola of Fanta, *South Park* of de Thierry-rap. Ik heb geen woorden voor hoe jij bizarre hersenspinsels in sneltreinvaart afwisselt met briljante ad-hocoplossingen voor de ingewikkeldste problemen. Ik ben dankbaar voor de sessies in Café De Jaren, waar ik voor de vorm ook achter mijn laptop zat, terwijl jij, pratend over bovenstaande onderwerpen, aan de lopende band R-loopjes uit je mouw schudde en je de eigenlijk onontginbare ruwe data toch wist te cultiveren tot een vruchtbaar geheel. Deze bijdrage en het daarop resulterende artikel markeerden het kantelpunt van gedemoraliseerd, klaar om voor het eerst in mijn leven op te geven, naar de vastberadenheid om de klus te klaren.

Ik kan deze sectie niet afsluiten zonder **Pim** te noemen. Nestor van onze onderzoeksgroep. Als de rest van onze onderzoeksgroep vastliep, kwam jij met een simpele, maar doeltreffende, pragmatische oplossing. Dank voor je grappige anekdotes, voor je immer bemoedigende woorden en jouw tact hoe om te gaan met overenthousiaste reviewers. Jouw bijdrage is groter dan dit korte dankwoord doet vermoeden.

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Maarten, tijdens de champagnetrips, etentjes en borrels probeerde je mij tevergeefs te behoeden voor te veel hooi op mijn vork. Hopelijk begrijp je dat ik straks, met een extra titel op zak, een promotie verwacht binnen Studio 2 Stripes.

Aan de Rosépiraten, **Arthur**, **Boris, Imre**, **Jasper**, (kleine) **Jochem**, **Kilian**, **Martijn**, **Paul, Perry** en **Roeland**. Er gaat geen dag voorbij dat ik jullie niet spreek en bijna geen week dat wij elkaar niet zien. Dank voor een onuitputtelijke bron van gezelligheid: varend op Gerben over de Amsterdamse grachten, zeilend op het Wad, of gewoon met een biertje in de hand, thuis of in de kroeg.

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Wouter en **Sake**, wie keihard werkt, moet minstens zo hard ontspannen. Vooral met dat laatste weten wij middels een feestje hier en daar wel raad mee.

Patrick en de JWZB-ers: camp on!

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ker niet om 7:55 in het AMC dient te verschijnen, deze les zat ik vijf kwartier lang alleen, op een donkere afdeling uit. **Melanie** (mijn Salmari partner in crime), **Melina** en **Hanna**, jullie lieten mij meteen thuis voelen in de onderzoeksgroep. **Patrick**, met jou bracht ik menig 'pauzepotje' door in de *Warzone*, waarbij we op wetenschappelijke wijze vaak de overwinning binnenhaalden. Hoewel dit misschien de nodige vertraging met zich meebracht, zorgde het er wel voor dat ik niet gek werd tijdens het maandenlange thuiswerken in de covidpandemie. **Joshua**, jij was altijd te verleiden tot het boevenpad, van de verbindingsdag in Amsterdam tot in de Bellboy in Berlijn. **Josephine**, een groots in energie, vrolijkheid en onbevlogenheid. Aan alle drie, ik heb genoten van onze 'snoepreisjes' in Berlijn en Porto. **Anne-Roos**, als laatste aangesloten, maar binnen mum van tijd (de gezelligste) leider van onze onderzoeksgroep en van de jonge huisartsonderzoekers (als neuroloog in spé?!). **Amy**, ik zou willen dat ik tien procent van jouw assertiviteit en planningsvermogen had. **Emma**, ik ben vereerd dat ik je Nederlands kroegjargon mocht bijbrengen. **Mink**, de aanjager van elk borrelinitiatief. **Indra**, koningin van het even inchecken bij je collega's. **Julie**, te kort medeonderzoeker, maar gelukkig snel collega-huisarts. **Julien**, dank voor je heerlijke lessen in eigenzinnigheid. **Dorien en Marthe**, jullie waren een fijn klankbord voor de uitdagingen van het aiotho-schap. **Eda**, jij zorgde voor continuïteit en bovenal verbinding binnen onze groep. **Ralf**, dank voor alle aanmoediging.

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Aan mijn kat, **Caesar Raspoetin II**, die eigenlijk alleen nog naar de naam **Couscous** luistert. Jij maakte elke thuiswerkdag een feest door de hele dag op mijn bureau liggend mee te turen naar de eindeloze stroom tabellen.

De laatste woorden van dit dankwoord, en daarmee van dit proefschrift, zijn voor mijn grote liefde, **Britt**. Jij vult mij feilloos aan, neemt mijn zorgen weg nog voordat ik ze zelf herken, en overspoelt mij al bijna negen jaar met liefde. Juist die liefde heeft mij door de momenten gedragen waarin ik bomen noch bos meer kon onderscheiden. Onze reizen, en natuurlijk Couscous, zijn mijn toevlucht en veilige haven. Vol enthousiasme kijk ik uit naar alles wat de toekomst voor ons in petto heeft.

BIOGRAPHICAL NOTE

Jakob Laurens Schroevers was born on 30 September 1992 in Amsterdam, the Netherlands. In 2011, he completed his secondary education at the Murmellius Gymnasium in Alkmaar and commenced the study of Medicine at the Vrije Universiteit Amsterdam. After obtaining his medical degree in 2018, he worked as a physician in the Departments of Cardiology and Pulmonology at the Onze Lieve Vrouwe Gasthuis in Amsterdam.

In 2020, he embarked upon a combined programme of general practice training and doctoral research at the Academic Medical Centre, later incorporated into Amsterdam UMC. He qualified as a General Practitioner in December 2025.