Decision support for telephone triage of acute chest pain in out-of-hours primary care

Amy Manten


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Decision support for telephone triage of acute chest pain in out-of-hours primary care

Amy Manten

COLOFON

The work described in this thesis was performed at the department of General Practice, Amsterdam UMC, University of Amsterdam, the Netherlands, within the Amsterdam Public Health research institute, program Quality of Care, Amsterdam, the Netherlands, and Amsterdam Cardiovascular Sciences Research Institute, Amsterdam the Netherlands.

ISBN:	978-94-6537-525-0
Author:	Amy Manten
Printing:	Ridderprint | www.ridderprint.nl
Layout design:	Arina van Londen, Ridderprint | www.ridderprint.nl
Cover illustration:	Arina van Londen, Ridderprint | www.ridderprint.nl

The research presented in this thesis was funded by a grant from ZonMw-HGOG (project number: 839150004), a grant from the Amsterdam Cardiovascular Sciences Research Institute (ACS-2018-TRACE22254), and internal funding from the Department of General Practice of the Amsterdam University Medical Centers, location AMC, the Netherlands.

Publishing of this thesis was supported by SBOH, employer of GP trainees.

Decision support for telephone triage of acute chest pain in out-of-hours primary care

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. ir. P.P.C.C. Verbeek
ten overstaan van een door het College voor Promoties ingestelde commissie,
in het openbaar te verdedigen in de Agnietenkapel
op vrijdag 26 juni 2026, te 10.00 uur

door Amy Manten
geboren te Breukelen

Promotiecommissie

Promotores:	dr. R.E. Harskamp	AMC-UvA
	prof. dr. E.P. Moll van Charante	AMC-UvA
Copromotores:	dr. J.C.L. Himmelreich	AMC-UvA
Overige leden:	prof. dr. J.P.S. Henriques	AMC-UvA
	prof. dr. S. Repping	AMC-UvA
	dr. I.G.M. van Valkengoed	AMC-UvA
	prof. dr. J.W.L. Cals	Maastricht University
	prof. dr. F.M.A.C. Martens	Vrije Universiteit Amsterdam
	dr. Y.L. Basta	Flevoziekenhuis

Faculteit der Geneeskunde

TABLE OF CONTENTS

Appendices


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 1

General introduction

GENERAL INTRODUCTION

Chest pain is a common symptom in the general population, with a lifetime prevalence of 20-40%.[1,2] While the vast majority of chest pain episodes are benign and self-limiting, people often seek medical attention when symptoms raise concern for serious underlying conditions, particularly with the fear of having a heart attack. In the Netherlands, people seeking care can follow different pathways. In imminent life-threatening situations, they are urged to contact emergency services via the national 1-1-2 number. In all other cases, general practitioners (GPs) serve as first point of contact, providing care through local practices (i.e. during office hours) and regional out-of-hours primary care (OOH-PC) facilities (i.e. during evenings, nights, weekends and national holidays).

The exact distribution of patient flow across primary care and emergency services is not fully known. However, data on the overall workload in each setting provides useful context. Each year, a quarter of a million ambulances are dispatched for chest pain in the Netherlands.[17] In primary care, chest pain accounts for 0.7% to 3.0% of all daytime practice consultations, and consistently ranks among the top ten presenting complaints in OOH-PC as well.[1,4,5,18-21]

Given the sheer volume, subjecting all chest pain patients to an immediate clinical evaluation and diagnostic work-up is neither feasible nor necessary. Therefore, both primary care and emergency services rely on triage to determine the urgency for each patient.[23] Triage is primarily conducted by telephone, as patients are required to make initial contact that way. During triage calls, most Dutch OOH-PC facilities and approximately half of the ambulance dispatch centres use triage protocols from the Netherlands Triage Standard (NTS) – a five-level, symptom-based and semi-automated decision support tool introduced in 2011.[23-26] The NTS assigns patients with an urgency code, ranging from U0 (highest) to U5 (lowest), to determine who requires immediate care and who can safely wait (also see *Table 1*).

Balancing safety and efficiency

At present, over 2.5 million people (i.e. approximately 15% of Dutch residents) contact the OOH-PC facility at least once per year.[21,27] Although this demand has remained stable in recent years, the perceived workload has increased since the introduction of the NTS in 2011.[23,27,28] This rise may partly reflect demographic changes with subsequent intensification of care (e.g. population growth and ageing) and the growing expectation of 24/7 primary care availability. Furthermore, since the implementation of NTS protocols in the triage process, the proportion of high-urgency classifications (particularly U2) has increased, without accompanying changes in presenting complaints.[23,29-31] This pattern

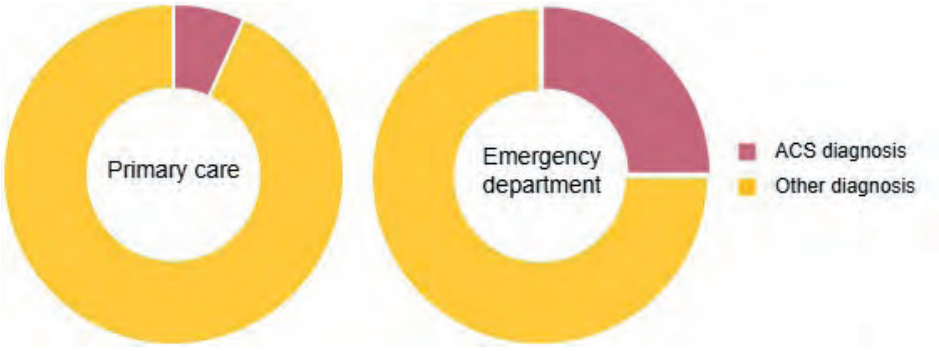
may suggest that growing risk aversion and accountability pressures within the healthcare system have led to a more defensive application of the NTS triage protocols and higher referral rates to secondary care.

Many GPs share this concern. They report that the NTS contributes to unnecessary consultations, and 80% believe telephone triage should be stricter to manage rising workloads.[28]

Moreover, these pressures raise questions not only about efficiency but also about patient safety. Triage assistants must constantly balance the need to respond quickly with the responsibility to accurately assess the patient's urgency. In chest pain, this task is particularly challenging. The symptom can result from a wide range of underlying causes that vary greatly in both etiology and clinical significance. While chest pain is the hallmark symptom of an acute coronary syndrome (ACS) – a spectrum of clinical conditions caused by myocardial ischemia – it may also signal other relevant urgent conditions.[12,16,32,33] Furthermore, in primary care populations, benign causes such as musculoskeletal pain are far more common (*Figure 1*).[4,5,18,34] Despite the relative rarity of ACS diagnosis, a national review of OOH-PC safety incidents reported that one-third of all incidents involved acute myocardial infarctions.[35]

Together, the dual challenges of safety and efficiency highlight the complexity of telephone triage for chest pain in OOH-PC, where decisions must be made quickly and access to ancillary diagnostic resources is limited.

Figure 1. Incidence of ACS across patient populations.



The figure illustrates the variation in the a priori risk of ACS across healthcare settings. Among patients presenting with chest pain, ACS may be present in 1.5-12.7% of cases in daytime primary care[3-5], and 25% in the emergency department.[11]
Abbreviations: ACS, acute coronary syndrome.

Textbox 1. General practitioners in the Netherlands

In the Netherlands, GPs play a central role in the healthcare system. The country counts approximately 14,000 GPs and nearly 5,000 primary care practices, serving a population of about 18 million.[13,14] Every citizen is registered with a primary care practice near their home. These practices maintain comprehensive and continuous patient records, including general practice visits, diagnostic results, hospital correspondence, and discharge letters. In addition, Dutch GPs act as gatekeepers to secondary and specialized care, ensuring that primary care retains its coordinating role within the healthcare system.

Dutch out-of-hours primary care

Dutch OOH-PC was substantially reorganized around the turn of the century. Before the year 2000, GPs provided out-of-hours care individually or through small rota groups. Increasing healthcare demands, high workloads, and a growing preference for working part-time led to a major reorganization. In the late 1990's, GPs began forming large, regional cooperatives to share responsibilities.[26,36-38] These cooperatives gradually established OOH-PC facilities to provide afterhours care to affiliated patients.[23,26,37,39] Today, over one hundred OOH-PC facilities operate across the Netherlands (*Figure 2*), with around 70% co-located with an emergency department.[23,26]

The transformation of Dutch OOH-PC mirrored developments in countries like the United Kingdom and Denmark, where small rota groups were similarly replaced by GP cooperatives.[40,41] This model later became dominant in several other European countries, including Belgium, Croatia, Germany, Norway, Slovakia, Spain and Switzerland.[42] Moreover, in most Western countries, GPs fulfill a comparable gatekeeping role, and a form of triage is typically implemented in the majority of OOH-PC models.[42,43]

Figure 2. OOH-PC facilities in the Netherlands (per December 2024).

Each dot on the map represents an OOH-PC facility. Green locations provide care during all afterhours (i.e. evenings, nights, weekends and national holidays). Operating hours of red locations are more restricted. The lines between the OOH-PC facilities represent the network of regional cooperatives in which the OOH-PC facilities are organized.
Source: the figure was adapted from the Dutch National Institute for Public Health and the Environment (RIVM) and originally based on the 'Benchmark huisartsenposten 2023 (InEen, 2024).[10]

Telephone triage of chest pain using the NTS

In the first decade after their establishment, Dutch OOH-PC facilities faced challenges related to urgency classification and task delegation to supporting staff. These issues, along with a need for standardization and improved communication with secondary care, prompted the development and implementation of the NTS in 2011.[24-26]

Development of the NTS

The NTS was adapted from the Manchester Triage System, which was originally developed in an emergency department setting in the United Kingdom in the mid-1990s and later adopted in several European countries, Australia and Brazil.[44-47] An expert panel tailored the system to the Dutch primary care setting using existing telephone triage guidelines.[24,48] The resulting system consists of 53 symptom-based protocols, each containing hierarchically structured questions that address the most critical symptoms first.[24] This design reflects the historical purpose of triage: to estimate clinical risk and allocate limited healthcare resources safely.[46] Modern triage protocols retain this focus on risk stratification. They aim to determine the urgency of care rather than to establish a diagnosis.[49,50] Because urgency assessment follows a structured approach, it can be delegated to trained non-physician staff. In turn, physicians monitor and supervise their work, and are responsible for diagnostic and treatment decisions.

Operating the NTS

Triage assistants, who are specifically trained for the role, manage incoming calls and operate the NTS system. They select the protocol that best fits the presenting complaint and enter patient responses. Each symptom-based protocol initiates with an assessment of vital functions, based on the ABCDE-method, including checks on breathing, consciousness and color.[51] It continues with a set of structured questions to assess specific symptom characteristics. It is not mandatory to report answers to all symptom-specific questions. Based on the available answers, the NTS continuously calculates an urgency level, linked to a recommended response time and clinical action (*Table 1*). Triage assistants then determine the appropriate follow-up, such as ambulance deployment, GP consultation, or self-care advice, thereby concluding the triage process.

Apart from the standardized NTS questions, assistants may also document additional details, nuances and contextual information in a free-text field. Although this information does not affect the urgency level generated by the system, it can support deviations from the recommended urgency level or action after consulting with the attending GP.

Table 1. NTS urgency levels with their definition and recommended response time and action.

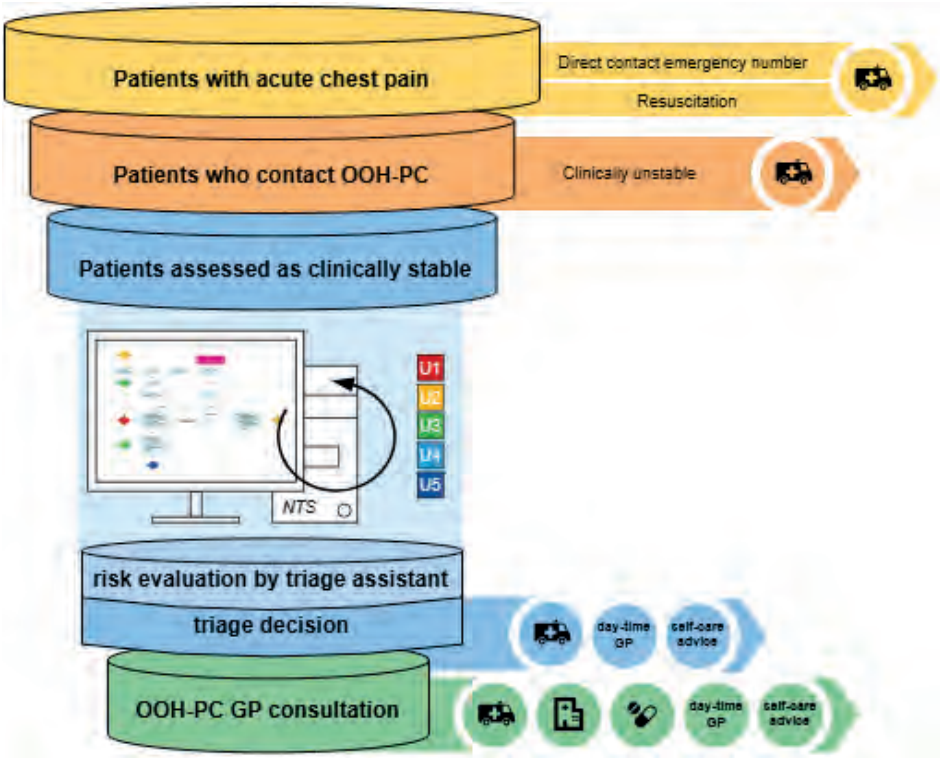
NTS urgency	Definition	Response time and action
U0 – Resuscitation*	Loss of vital functions	Immediate ambulance activation for resuscitation
U1 – Life threatening	Unstable vital functions	Immediately, care within 15 minutes
U2 – Emergent	Vital functions in danger or organ damage	Assessment as soon as possible, care within 1 hour
U3 – Urgent	Possible risk of damage	Assessment within 3 hours
U4 – Non-urgent	Marginal risk of damage	Care within 24 hours
U5 – Advice	No risk of damage	Advice, not time related

Notes: *U0 urgency levels are reserved to patients in need of resuscitation, in such cases, triage is not initiated and an ambulance is dispatched immediately. Abbreviations: NTS, Netherlands Triage Standard; U, urgency code.

NTS chest pain protocol

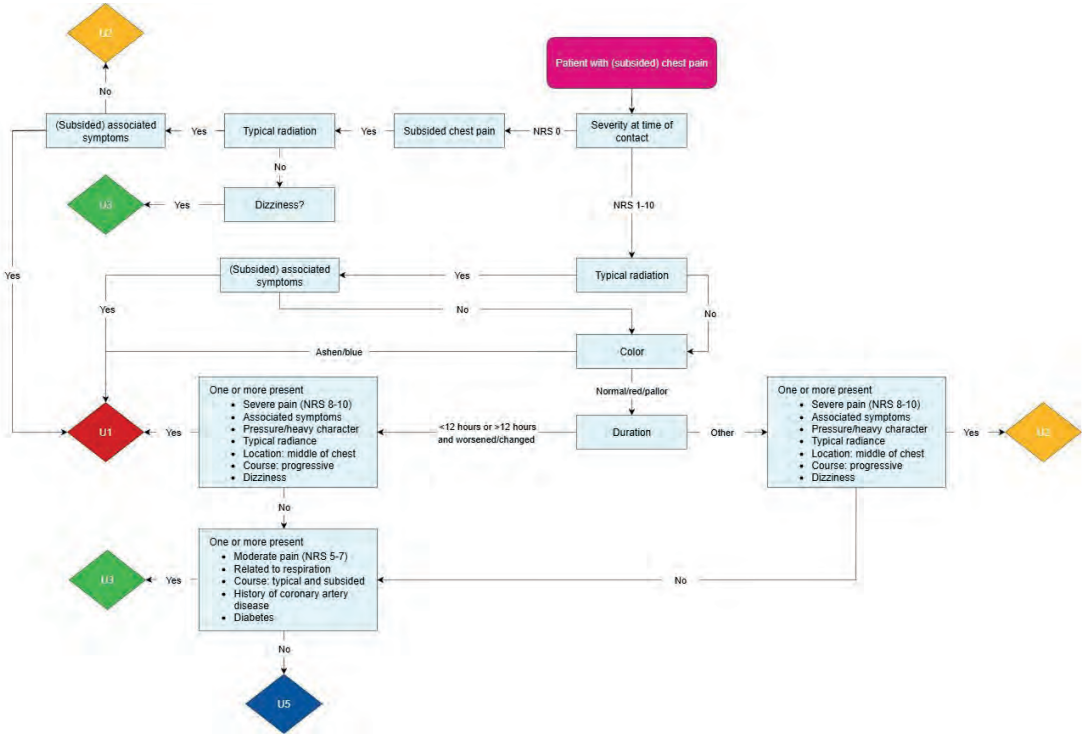
Figure 3 illustrates the flow of care for patients with chest pain in OOH-PC. The NTS protocol for chest pain includes questions addressing the type, duration, severity, course and location of the pain, as well as the presence of radiation and associated symptoms. *Figure 4* illustrates the hierarchical structure of these questions within the protocol.

Figure 3. Chest pain evaluation in Dutch OOH-PC.



The figure illustrates the care pathway for patients with acute chest pain in OOH-PC. The top tier represents all patients experiencing chest pain during afterhours. Those who contact emergency medical services are managed by the ambulance dispatch center and exit the pathway. The second tier consists of chest pain patients that contact an OOH-PC facility. Upon contact, triage assistants first assess vital functions and immediately request an ambulance if the patient is clinically unstable. Clinically stable patients (third tier) are assessed using the NTS chest pain protocol, which results in an urgency code (U1-U5). A detailed overview of the content and hierarchy of the NTS protocol is provided in Figure 4. Based on the assigned urgency, triage assistants determine the appropriate action: ambulance activation, face-to-face GP consultation, deferral to daytime primary care, or self-care advice. The bottom tier illustrates the patients that receive a face-to-face GP consultation (either on-site or through a home visit). Here, the GP decides on the eventual course of action after their assessment (e.g. referral to the hospital with or without ambulance transportation, prescribing medication, deferral to daytime primary care or self-care advice). Abbreviations: OOH-PC, out-of-hours primary care; U, urgency code; NTS, Netherlands Triage Standard; GP, general practitioner.

Figure 4. Decision tree of the NTS protocol for chest pain.



The figure illustrates the hierarchical structure of the NTS protocol for chest pain and corresponding urgency codes. The protocol contains multiple choice questions on the type, duration, severity, course, and location of the pain, as well as the presence of radiation and associated symptoms.
Source: the decision tree displayed here was translated from a version provided by researchers from the Julius Center, UMC Utrecht, and the Netherlands Triage Standard.

KNOWLEDGE GAPS IN TRIAGE OF CHEST PAIN IN OOH-PC

Now that we have outlined the background of Dutch OOH-PC services and the NTS protocol for chest pain, we can address the knowledge gaps in triage of acute chest pain in OOH-PC examined in this thesis.

Chest pain patient flow in pre-hospital care

In the Netherlands, patients with acute chest pain are not limited to seeking care through OOH-PC facilities, as they may also directly contact emergency services. These parallel pre-hospital care providers are not integrated and the distribution of patient volumes remains unclear.

Understanding the flow of chest pain patients is necessary to assess the relative burden on OOH-PC, and to identify opportunities for improvement that support sustainable and coordinated pre-hospital care.

NTS validity

Before its implementation in 2011, the NTS was not validated against clinical outcomes. Since then, only one study has assessed its validity using proxy markers for urgency: high urgency levels were associated with more referrals to the emergency department and low urgency levels with telephone advice.[25] However, these findings do not provide insight into whether the assigned urgency levels accurately reflected the underlying clinical severity of the patient's condition.

At the outset of this thesis in 2019, despite its widespread use in Dutch OOH-PC, the diagnostic performance of the NTS in assessing chest pain remained unknown. This lack of validation underscores the need to examine how well the NTS distinguishes serious from non-serious cases of chest pain in OOH-PC, and how efficiently it allocates care.

Decision support tools for triage of chest pain

Numerous decision support tools have been developed to aid the in-person assessment of chest pain or suspected ACS. We hypothesize that incorporating (elements of) validated clinical decision rules may improve triage accuracy without compromising patient safety. However, many well-known tools, such as the HEART, TIMI and GRACE scores, were developed in an emergency department setting and rely on diagnostic information (e.g. ECG, troponin) not yet available in primary care settings.[52-54] In 2019, a systematic review assessed primary care-based clinical decision rules for chest pain and identified the Marburg Heart Score (MHS) and the INTERCHEST score as most

promising.[8] Both scores rely on elements that can be applied in a telephone triage context (see *Textbox 2*).

Furthermore, while this research was underway, advances in chest pain assessment in primary care continued. In this context, a new risk stratification tool for ruling out ACS in OOH-PC was developed, the Safety First Prediction Rule (see *Textbox 3*).

To date, the validity and added value of easy-to-apply clinical decision support tools for telephone triage of chest pain in OOH-PC (including the MHS, INTERCHEST and Safety First Prediction Rule) remain unestablished, leaving uncertainty about their potential role.

Textbox 2. The Marburg Heart Score (MHS) and INTERCHEST score

The MHS is a five-item, point-based score developed for ruling out coronary artery disease (CAD) in primary care patients presenting with chest pain.[6] Items include: (i) female ≥65 years or male ≥55 years, (ii) known CAD, cerebrovascular disease or peripheral vascular disease, (iii) pain worse with exercise, (iv) pain reproducible with palpation, and (v) patient assumes pain is cardiac. Internal and external validation studies for CAD have shown good discriminative ability, with C-statistics ranging from 0.84 to 0.90.[6-8]

The INTERCHEST score is similar in structure, consisting of six items and also developed to rule out CAD in primary care patients with chest pain.[22] Items include: (i) history of coronary artery disease, (ii) female ≥65 years or male ≥55 years, (iii) chest pain related to effort, (iv) pain reproducible by palpation, (v) physician initially suspected a serious condition, and (vi) chest discomfort feels like 'pressure'. The INTERCHEST score was derived using pooled individual patient data, including the original MHS cohort. Internal validation of the score demonstrated good discrimination, with a C-statistic of 0.84.[8,22]

Textbox 3. The Safety First Prediction Rule

In 2022, the Safety First Prediction Rule was developed specifically for ruling out ACS in an OOH-PC setting.[15] The rule consists of a multivariate model with seven predictors: (i) age, (ii) sex, (III) acute onset of chest pain (<12 hours), (iv) a pressing/heavy character, (v) radiation of pain, (vi) sweating, and (vii) calling at night (i.e. between 00:00 and 09:00). Internal validation showed good discrimination, with a C-statistic of 0.77.[15]

Clinical outcomes: ACS and beyond

As described earlier, chest pain can reflect a wide range of underlying conditions. Although only 1.5-3.6% of primary care patients with chest pain are ultimately diagnosed with an ACS, it is often the first diagnosis considered.[1,3,19] Rightly so – up to 90% of ACS patients present with chest pain as their main symptom.[33,55,56] Timely identification of ACS is critical. Missed diagnosis can delay treatment and could result in irreversible myocardial damage, an increased risk of complications (e.g. ventricular arrythmias, mechanical complications, heart failure), and increased mortality.[32,55,57-60]

Textbox 4. Pathophysiology and diagnosis of ACS

The pathophysiology of ACS results from myocardial ischemia caused by a sudden reduction or interruption of coronary blood flow. This causes an imbalance between oxygen supply and demand, usually triggered by atherosclerotic plaque rupture and subsequent thrombosis. It may also occur secondary to vasospasm, coronary microvascular disfunction or non-atherosclerotic coronary dissection.[12]

Clinically, ACS includes acute myocardial infarction and unstable angina.[12,16] ACS diagnosis requires identifying myocardial ischemia and subsequent myocardial injury, typically through elevated cardiac troponin values – a biomarker for cardiomyocyte injury – alongside other features: suggestive symptoms, ischemic changes on the electrocardiogram (ECG), imaging evidence of myocardial damage, or angiographic proof of a coronary thrombus.[16] Therefore, in order to establish or reject ACS diagnosis, patients with a sufficiently high clinical suspicion of ACS should be referred for further diagnostic testing.

Major events

While ACS is the most feared diagnosis, it represents only a proportion of urgent cases among patients with acute chest pain in primary care. Other life-threatening conditions, such as pulmonary embolism or aortic dissection, can present with similar symptoms and also require prompt recognition and treatment.[4,5,18,34] This clinical variety should be reflected in the outcome measures used to evaluate triage performance.

To capture the broader range of urgent outcomes, we used the composite outcome 'major event'. Major events are defined as a composite of urgent conditions linked to the initial complaint of chest pain, requiring hospital admittance and/or urgent in-hospital treatment. For example, with this definition, new onset atrial fibrillation requiring cardioversion qualifies as a major event, whereas recurrent, outpatient-managed atrial fibrillation does not. Furthermore, all-cause mortality is considered a major event.

The inclusion of major events as a clinical outcome allows for a more comprehensive evaluation of triage performance. It captures the full clinical spectrum of potentially serious causes of unselected chest pain and provides a more accurate measure of both the safety and efficiency of triage in an OOH-PC setting.

Sex differences and chest pain

The current NTS protocol for chest pain does not differentiate between women and men, nor does it account for sex-specific differences in symptom presentation, or consider sex as a predictive factor. Yet, prior research showed that male sex is associated with a higher likelihood of ACS diagnosis.[61] Because the triage process relies heavily on symptom characteristics, overlooking sex-related associations could reduce its accuracy and efficiency in identifying patients at risk.

Globally, numerous initiatives - such as the ESC's *Women at Heart* campaign – have drawn attention to the under-recognition of cardiovascular disease in women. These efforts aim to address gaps in knowledge, understanding, and general awareness.[62] Subsequent research on selected populations with myocardial ischemia reported sex differences in symptom presentation, treatment strategies, and clinical outcomes.[63-71] As a result, the view that women more often present with 'atypical' cardiac symptoms has become a dominant narrative in both public campaigns and clinical discussions. However, studies using systematic symptom reporting found more similarities than differences between men and women.[72-74]

Placing disproportionate emphasis on sex differences without robust evidence may inadvertently detract from the value of classical symptomatology. These findings underscore the need to investigate whether sex-specific differences in symptom presentation or triage performance exist among unselected patients with chest pain.

Textbox 5. Sex

In this thesis, *sex* refers to the differentiation between males and females based on biological characteristics (i.e. genetics, gonadal and genitals). These biological features are not entirely exclusive, as some individuals possess both.[9]

The term *gender*, which reflects social and personal identity rather than biology, is not addressed in this work.

AIM AND OUTLINE OF THIS THESIS

The overarching aim of this thesis is to improve the safety and efficiency of chest pain evaluation in Dutch OOH-PC by focusing on the process of telephone triage. To this end, we address the following research questions:

1. What is the relative volume of chest pain patients that access care through OOH-PC?
2. How does the current NTS triage standard perform in terms of safety and efficiency for ACS as well as a broad range of relevant clinical outcomes, and are there sex-specific differences?
3. Can easy-to-apply, additional decision support tools improve the efficiency and safety of telephone triage for chest pain in OOH-PC?

To address these research questions, we designed the TRiage of Acute Chest pain Evaluation in primary care (TRACE) project. TRACE consists of a retrospective and prospective cohort of patients with acute chest pain, who contacted a large regional OOH-PC facility in Alkmaar, the Netherlands.

Chapter 2 explores the flow of patients with chest pain in afterhours pre-hospital care and describes the relative burden on OOH-PC facilities and ambulance dispatch centers in two regions of the Dutch province of Noord-Holland.

Chapter 3 describes the rationale and design of the retrospective phase of the TRACE project, designed to evaluate the current standard for telephone triage for chest pain and to explore whether additional clinical support tools can enhance the overall efficiency.

Chapter 4 addresses the results of the retrospective phase of the TRACE project. It describes the case mix of patients presenting to OOH-PC with chest pain, and evaluates telephone triage performance for major events and ACS.

Chapter 5 evaluates sex differences in chest pain presentation, triage assessment and outcomes in Dutch OOH-PC.

Chapter 6 examines two validated clinical decision rules, the Marburg Heart Score (MHS) and INTERCHEST score, and compares their diagnostic performance to that of the current NTS protocol for chest pain in a retrospective sample of patients.

Chapter 7 compares the use of the MHS and INTERCHEST score to the current NTS protocol among patients contacting OOH-PC regarding chest pain, using a prospective study design.

Chapter 8 describes the external validation of the Safety First prediction model for triage of chest pain in OOH-PC.

Chapter 9 evaluates the availability and validity of clinical decision support tools for chest pain in primary care, including tools that rely on troponin testing.

Chapter 10 provides a general discussion of the thesis findings, reflecting on their contribution to the broader understanding of telephone triage for chest pain in OOH-PC. The chapter also addresses methodological considerations, and provides recommendations for clinical practice and future research.

Appendices

Summary

Nederlandse samenvatting

Authors and affiliations

List of publications & author's contribution

PhD Portfolio

Dankwoord

About the author

REFERENCES

1. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141–6. doi:10.3109/13814780903329528
2. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. *Fam Pract*. Apr 2006;23(2):167–74. doi:10.1093/fampra/cmi124
3. Haasenritter J, Biroga T, Keunecke C, et al. Causes of chest pain in primary care--a systematic review and meta-analysis. *Croat Med J*. Oct 2015;56(5):422–30. doi:10.3325/cmj.2015.56.422
4. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart*. Nov 2017;103(21):1727–1732. doi:10.1136/heartjnl-2016-310905
5. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340–347.
6. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212
7. Haasenritter J, Bösner S, Vaucher P, et al. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. *British Journal of General Practice*. 2012;62(599):e415–e421. doi:10.3399/bjgp12X649106
8. Harskamp RE, Laeven SC, Himmelreich JC, Lucassen WAM, van Weert H. Chest pain in general practice: a systematic review of prediction rules. *BMJ Open*. Feb 27 2019;9(2):e027081. doi:10.1136/bmjopen-2018-027081
9. WHO. Sexual health - definitions. World Health Organization.
10. OOH-PC locations in the Netherlands 2024. www.vzinfo.nl: Dutch National Institute for Public Health and the Environment (RIVM) 2024.
11. Stepinska J, Lettino M, Ahrens I, et al. Diagnosis and risk stratification of chest pain patients in the emergency department: focus on acute coronary syndromes. A position paper of the Acute Cardiovascular Care Association. *European Heart Journal: Acute Cardiovascular Care*. 2020;9(1):76–89.
12. Byrne RA, Rossello X, Coughlan J, et al. 2023 ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal: Acute Cardiovascular Care*. 2024;13(1):55–161.
13. Flinterman LE, Batenburg R, Kenens RJ, Duijkers B. Huisartsen en praktijken in kaart - Cijfers uit Nivel Beroepenregistraties in de Zorg 2023-2024. English title: General practitioners and practices - Figures from Nivel Occupational Registrations in Healthcare 2023-2024 Nivel; 2025.

14. Population counter (original title: Bevolkingsteller). Centraal Bureau voor de Statistiek. Accessed 12-06-2025, https://www.cbs.nl/nl-nl/visualisaties/dashboard-bevolking/bevolkingsteller

15. Wouters LT, Zwart DL, Erkelens DC, et al. Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study. *BMJ open*. 2022;12(10):e064402.

16. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138(20):e618–e651.

17. Implementation plan for pre-hospital triage of chest pain in ambulance care (Original title: Implementatieplan prehospitale traige bij pijn op de borst in de ambulancezorg). Ambulancezorg Nederland; 2025.

18. Frese T, Mahlmeister J, Heitzer M, Sandholzer H. Chest pain in general practice: Frequency, management, and results of encounter. *Journal of Family Medicine and Primary Care*. 2016;5(1)doi:10.4103/2249-4863.184625

19. McConaghy JR, Oza RS. Outpatient Diagnosis of Acute Chest Pain in Adults. *American Family Physician*. 2013;87(1)

20. Nilsson S, Scheike M, Engblom D, et al. Chest pain and ischaemic heart disease in primary care. *British Journal of General Practice*. 2003;53:378–382.

21. Ramerman L, Rijpkema C, Hek K, et al. Care through out-of-hours primary care. Nivel Care Registrations Primary Care: annual figures 2024 and trend figures 2020-2024. (Original Dutch title: "Zorg via de huisartsenspoedpost Nivel Zorgregistraties Eerste Lijn: jaarcijfers 2024 en trendcijfers 2020-2024") Utrecht: Nivel; 2025. p. 34.

22. International Working Group on Chest Pain in Primary Care (INTERCHEST), Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011

23. Smits M, Rutten M, Keizer E, Wensing M, Westert G, Giesen P. The Development and Performance of After-Hours Primary Care in the Netherlands: A Narrative Review. *Ann Intern Med*. May 16 2017;166(10):737–742. doi:10.7326/M16-2776

24. Domus Medica - Netherlands Triage Standard. 2014.

25. van Ierland Y, van Veen M, Huibers L, Giesen P, Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. *Fam Pract*. Jun 2011;28(3):334–41. doi:10.1093/fampra/cmq097

26. Giesen P, Smits M, Verstappen W, Kant J, Sluiter A, Rutten M. The impact of 20 years of out-of-hours GP services. . Original title: De opbrengst van 20 jaar huisartsenposten Huisarts & Wetenschap; 2021.

27. InEen. InEen Benchmark out-of-hours primary care 2023 (Original title: InEen Benchmark huisartsenspoedposten 2023). 2024. https://ineen.nl/ineen-benchmarks/ineen-benchmark-huisartsenspoedposten/

28. Keizer E, Maassen I, Smits M, Wensing M, Giesen P. Reducing the use of out-of-hours primary care services: a survey among Dutch general practitioners. *European Journal of General Practice*. 2016;22(3):189–195.

29. Jansen T, de Hoon S, Hek K, Verheij E. Developments at the out-of-hours primary care facility - changes in healthcare demand and health problems from 2013-2015. Original title: Ontwikkelingen op de huisartsenpost - veranderingen in zorgvraag en gezondheidsproblemen in 2013-2015 Nivel; 2017.

30. Jansen T, Ramerman L, Verheij R. Data of out-of-hours primary care - Triage: index complaints and urgency allocation. *Nivel Zorgregistraties Eerste Lijn* Geraadpleegd op 21–10–2020 2020;

31. Smits M, Verheij R. Changes in urgencies of out-of-hours primary care contacts 2013-2016 (Original title: Veranderingen in de urgentie van contacten met de huisartsenpost 2013-2016) *Nivel rapport*. 2017;

32. Auwerda A, Bouma M, Bruins Slot M, et al. NHG-Standaard Acuut coronair syndroom Nederlands Huisartsen Genootschap; 2022.

33. Harskamp RE, Fanaroff AC, Zhen SW, Sawe HR, Weber EJ. Recognising acute coronary syndrome. *BMJ*. 2022;377

34. Svavarsdóttir AE, Jónasson MR, Gudmudsson GH, Fjeldsted K. Chest pain in family practice. *Canadian Family Physician*. 1996;42:1122–1128.

35. Rutten M, Kant J, Giesen P. What can we learn from incidents at the out-of-hours primary care facility? . Original title: Wat kunnen we leren van calamiteiten op de huisartsenpost? : Huisarts en Wetenschap; 2018.

36. Uden Cv, Giesen PH, Metsemakers JF, Grol RP. Development of out-of-hours primary care by general practitioners (GPs) in The Netherlands: from small-call rotations to large-scale GP cooperatives. 2006;

37. Moll van Charante EP. *Dutch general pracitioners in a time of change: studies on out-of-hours and GP hospital care*. Universiteit van Amsterdam; 2007.

38. Moll van Charante EP, Delnoij DMJ, IJzermans CJ, Klazinga NS. From playmaker to pawn? The changing role and position of the Dutch general practitioner. . Original title: Van spelverdeler tot speelbal? De veranderende rol en positie van de Nederlandse huisarts Huisarts en Wetenschap; 2002.

39. Giesen P, van der Wilden-van Lier E, Schers H, Schreuder J, Busser G. Telephone advice and triage during out-of-hours primary care. . Original title: Telefonisch advies en triage tijdens de dienst Huisarts & Wetenschap; 2002.

40. Hallam L, Cragg D. Organisation of primary care services outside normal working hours. *BMJ*. 1994;309(6969):1621–1623.

41. Olesen F, Jolleys JV. Out of hours service: the Danish solution examined. *BMJ*. 1994;309(6969):1624–1626.

42. Steeman L, Uijen M, Plat E, Huibers L, Smits M, Giesen P. Out-of-hours primary care in 26 European countries: an overview of organizational models. *Family practice*. 2020;37(6):744–750.

43. Franks P, Clancy CM, Nutting PA. Gatekeeping revisited—protecting patients from overtreatment. Mass Medical Soc; 1992. p. 424–429.

44. Mackway-Jones K, Janet M, Windle J. *Emergency triage: Manchester Triage Group* John Wiley & Sons, Ltd. ; 2013.

45. Mackway-Jones K, Robertson C. Emergency triage. *BMJ-British Medical Journal-International Edition*. 1997;314(7086):1056.

46. Dippenaar E. Triage systems around the world: a historical evolution. *International Paramedic Practice*. 2019;9(3):61–66.

47. Nishi FA, Maia FdOM, de Souza Santos I. Assessing sensitivity and specificity of the Manchester Triage System in the evaluation of acute coronary syndrome in adult patients in emergency care: a systematic review. *JBI Evidence Synthesis*. 2017;15(6):1747–1761.

48. National guidelines for telephone triage and advice in primary care https://triagewijzer.nhg.org/

49. Blank L, Coster J, O'Cathain A, et al. The appropriateness of, and compliance with, telephone triage decisions: a systematic review and narrative synthesis. *Journal of advanced nursing*. 2012;68(12):2610–2621.

50. Christ M, Grossmann F, Winter D, Bingisser R, Platz E. Modern triage in the emergency department. *Deutsches Ärzteblatt International*. 2010;107(50):892.

51. Thim T, Krarup NHV, Grove EL, Rohde CV, Løfgren B. Initial assessment and treatment with the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. *International Journal of General Medicine*. 2012;5:117.

52. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. *Jama*. 2000;284(7):835–842.

53. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *bmj*. 2006;333(7578):1091.

54. Six A, Backus B, Kelder J. Chest pain in the emergency room: value of the HEART score. *Netherlands Heart Journal*. 2008;16(6):191–196.

55. Gulati M, Levy PD, Mukherjee D, et al. 2021 AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR guideline for the evaluation and diagnosis of chest pain: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Journal of Cardiovascular Computed Tomography*. 2022;16(1):54–122.

56. Brieger D, Eagle KA, Goodman SG, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. *Chest*. 2004;126(2):461–469.

57. Kalarus Z, Svendsen JH, Capodanno D, et al. Cardiac arrhythmias in the emergency settings of acute coronary syndrome and revascularization: an European Heart Rhythm Association (EHRA) consensus document, endorsed by the European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Acute Cardiovascular Care Association (ACCA). *EP Europace*. 2019;21(10):1603–1604.

58. Kwok CS, Mallen CD. Missed acute myocardial infarction: an underrecognized problem that contributes to poor patient outcomes. *Coronary Artery Disease*. 2021;32(4):345–349.

59. Wu J, Gale CP, Hall M, et al. Editor's Choice-Impact of initial hospital diagnosis on mortality for acute myocardial infarction: A national cohort study. *European Heart Journal: Acute Cardiovascular Care*. 2018;7(2):139–148.

60. Al-Khatib SM, Stebbins AL, Califf RM, et al. Sustained ventricular arrhythmias and mortality among patients with acute myocardial infarction: results from the GUSTO-III trial. *American heart journal*. 2003;145(3):515–521.

61. Haasenritter J, Stanze D, Widera G, et al. Does the patient with chest pain have a coronary heart disease? Diagnostic value of single symptoms and signs–a meta-analysis. *Croatian medical journal*. 2012;53(5):432–441.

62. Stramba-Badiale M, Fox KM, Priori SG, et al. Cardiovascular diseases in women: a statement from the policy conference of the European Society of Cardiology. *European heart journal*. 2006;27(8):994–1005.

63. Arora G, Bittner V. Chest pain characteristics and gender in the early diagnosis of acute myocardial infarction. *Curr Cardiol Rep*. Feb 2015;17(2):5. doi:10.1007/s11886-014-0557-5

64. Chiha J, Mitchell P, Gopinath B, Plant AJH, Kovoor P, Thiagalingam A. Gender differences in the severity and extent of coronary artery disease. *Int J Cardiol Heart Vasc*. 2015 July 30 2015;8:161–166. doi:10.1016/j.ijcha.2015.07.009

65. Dawson LP, Nehme E, Nehme Z, et al. Sex Differences in Epidemiology, Care, and Outcomes in Patients With Acute Chest Pain. *J Am Coll Cardiol*. Mar 14 2023;81(10):933–945. doi:10.1016/j.jacc.2022.12.025

66. Jones E, Eteiba W, Bairey Merz N. Cardiac Syndrome X and Microvascular Coronary Dysfunction. *Trends Cardiovasc Med*. 2012;22(6):161–168.

67. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. *Heart*. 2020;106:487–492.

68. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women. A Scientific Statement From the American Heart Association. *Circulation*. 2016;133:916–947.

69. Perdoncin E, Duvernoy C. Treatment of coronary artery disease in women. *Methodist DeBakey cardiovascular journal*. 2017;13(4):201.

70. Shaw JL, Merz CNB, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006 Feb 7 2006;47:S4–S20. doi:10.1016/j.jacc.2005.01.072

71. Shin JY, Martin R, Suls J. Meta-analytic evaluation of gender differences and symptom measurement strategies in acute coronary syndromes. *Heart Lung*. Jul–Aug 2010;39(4):283–95. doi:10.1016/j.hrtlng.2009.10.010

72. DeVon HA, Rosenfeld A, Steffen AD, Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *Journal of the American Heart Association*. 2014;3(2):e000586.

73. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. *European heart journal*. 2011;32(24):3107–3114.

74. van der Meer MG, Appelman Y, Rutten KH, et al. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open*. 2019;9(11):e031613.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 2

Comparing ambulance and out-of-hours primary care pathways for acute chest pain in the Netherlands

Amy Manten, Indra M.B. Melessen, Jelle C.L. Himmelreich, Eric P. Moll van Charante, Ralf E. Harskamp

Submitted to Netherlands Heart Journal

ABSTRACT

Background: Chest pain is a common reason for seeking out-of-hours care. In the Netherlands, both emergency medical services (EMS) and out-of-hours primary care (OOH-PC) assess these patients, yet how their workloads compare remains unclear.

Methods: We performed a retrospective observational study using aggregated routine care data from six OOH-PC cooperatives and two ambulance dispatch centers across two Dutch regions (approximately 1.2 million inhabitants). Annual data (2019-2024) included chest pain contacts, assigned urgency levels, and actions following contact. For the comparison between OOH-PC and EMS, EMS volumes were adjusted to reflect afterhours activity.

Results: In total, 32,675 chest pain contacts were reported in 2023-2024, 25,078 for OOH-PC and 7,687 for EMS dispatched ambulances. Per 1,000 inhabitants, OOH-PC managed 3.4 times as many contacts as EMS dispatched ambulances in 2023, and 3.2 times as many in 2024. Between 2019 and 2024, OOH-PC contacts increased from 6.3 to 10.3 contacts per 1,000 inhabitants, and EMS volumes rose from 2.7 to 4.4 per 1,000 inhabitants. OOH-PC contacts increasingly resulted in an ambulance request, while urgency levels remained stable. EMS-initiated ambulance dispatches showed a growing share of potentially unnecessary deployments, as these increasingly resulted in on-site assessment without subsequent hospital transport.

Conclusion: OOH-PC manages more acute chest pain contacts than EMS dispatches ambulances. Although demand increased for both services, the concurrent rise in ambulance requests from OOH-PC and the growing proportion of EMS dispatches not requiring transport may indicate inefficient resource allocation. Closer coordination and alignment of triage methods are needed to preserve pre-hospital capacity.

INTRODUCTION

Chest pain is a common reason for seeking out-of-hours care, with 20-40% of individuals presenting with this symptom over their lifetime.[1,2] It can stem from a wide range of underlying causes, including life-threatening conditions that require timely assessment at the appropriate level of care.[1,3]

In the Netherlands, pre-hospital care is provided by two parallel services: 24/7 emergency medical services (EMS) for life-threatening situations, and out-of-hours primary care (OOH-PC) for urgent complaints outside regular office hours. Both EMS and OOH-PC face rising workloads, often attributed to demographic changes and inappropriate use of out-of-hours resources.[4]

To reduce workloads, Dutch EMS and OOH-PC have launched national campaigns to educate patients on appropriate care use. However, more targeted interventions to increase cost-effectiveness and optimize pre-hospital care requires knowledge on the relative burden on pre-hospital care providers. We aim to explore the pre-hospital flow of patients with acute chest pain by comparing the relative volumes of EMS and OOH-PC contacts, and by examining temporal trends in chest pain-related contacts across these organizations using two regions in the Netherlands. By gaining a better understanding of how demand is distributed between EMS and OOH-PC, this study may help identify opportunities to improve coordination, align workflows, and use pre-hospital resources more efficiently.

METHODS

We reported our study in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) statement.[5]

Setting and design

We conducted an explorative retrospective observational study on chest pain-related contacts with pre-hospital care providers in two regions in the northwestern part of the Netherlands. Together, these regions represent approximately 1.2 million inhabitants, about 7% of the Dutch population. It covers 25 municipalities, including both urban and rural areas. We used routine care data from the six OOH-PC cooperatives and two ambulance dispatch centres involved in these regions (*Figure 1*).

Dutch inhabitants are affiliated with an OOH-PC facility and ambulance dispatch centre based on their home address. Some overlap exists between

adjacent regions, and ambulances may be dispatched to aid different regions when necessary.

OOH-PC

The six OOH-PC cooperatives operate across eight locations within the region. The catchment populations range from approximately 125,000 to 300,000 inhabitants. OOH-PC services are available outside regular office hours, that is, during evenings, nights, weekends and national holidays. Upon contact, urgencies are assessed through standardized, symptom-based triage protocols from the Netherlands Triage Standard (NTS).[6] Assigned urgency levels range from U1 to U5 and are linked to a recommended time-to-care (i.e. U1 life-threatening, immediate care; U2 emergent, care <60 minutes; U3 urgent, care <3 hours; U4 non-urgent, care <24 hours; and U5 no medical assessment necessary, not time related). Actions following triage are based on the urgency level and may include ambulance activation, GP consultation (via home-visit or on-site), or telephone advice.

EMS

We included two regional ambulance dispatch centres, serving 570,000 and 670,000 inhabitants, respectively. EMS operates 24/7 and incoming calls to the national emergency number (1-1-2) are initially handled by the ambulance control room, an integral part of regional dispatch centres. Here, contacts are triaged to determine their urgency and to decide whether ambulance deployment is needed. Urgent responses are classified as A0-A2, and routine or non-urgent transports as B1-B2.

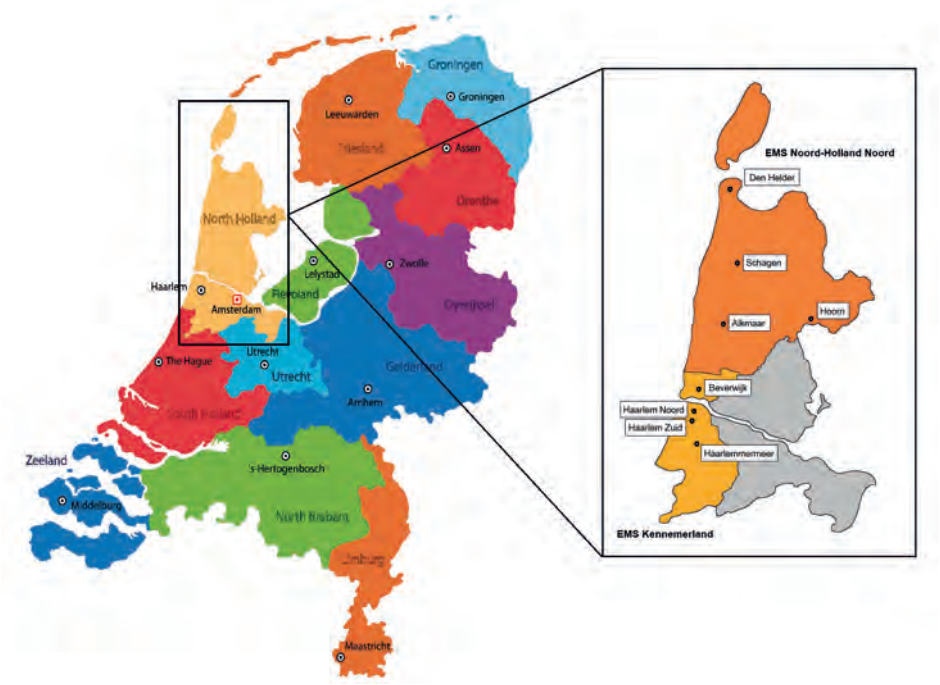
Data collection

We requested annual, aggregated data on chest pain-related contacts from the OOH-PC cooperatives and ambulance dispatch centres for the years 2019-2024. Contacts were identified using the standardized entry complaint linked to the call. No individual-level or traceable patient data were collected. There were no age restrictions.

For OOH-PC, five out of six cooperatives used the GP information system HealthConnected (Healthconnected Holding B.V., 2019). Authorized personnel provided written consent, after which the chief information security officer of HealthConnected extracted the data. One facility (Haarlemmermeer) used a different system (VIPlive SPOED, Topicus B.V.) and independently extracted data using the same query. OOH-PC data included the total number of chest pain contacts, stratified by urgency level and the action following triage.

Both ambulance dispatch centres used a Medical Priority Dispatch System, ProQA (Priority Dispatch Corporation, Salt Lake City, USA) for urgency assessment and reporting. Data managers of the respective centres extracted data on total ambulance dispatches, assigned urgency levels, and whether patients were transported to hospital or received on-site care. Records of EMS calls that did not lead to an ambulance dispatch were not available to the regional ambulance dispatch centres and were therefore not included. Furthermore, ambulance deployments requested by OOH-PC are coordinated by EMS but bypass the ProQA triage system and were therefore only included in the OOH-PC dataset.

Figure 1. Included regions.



The figure shows the area included in our study. It covers two regions within the province of North Holland in the Netherlands. The area is covered by two ambulance dispatch centres (EMS Noord-Holland Noord and EMS Kennemerland), and eight OOH-PC facilities which are organized in six primary care cooperatives. The catchment area includes approximately 1.2 million inhabitants, of whom 50.4% are female, 51,6% are aged 25-65 years, and 51.1% are of non-Western ethnicity (e.g. Moroccan, Turkish, Surinamese, Netherlands Antillean).

Statistical analysis

We used aggregated data of the calendar years with complete records to compare the relative volume of care provided by OOH-PC and EMS. To improve comparability, we adjusted for hours in which both services were operational using a calculated ratio (i.e. adjusting ambulance data for afterhours). Furthermore, we explored the proportion of chest pain contacts that potentially involved both services (i.e. ambulance deployments requested by OOH-PC).

Secondary, we used all available data to describe time trends in chest pain related contacts at the included OOH-PC and ambulance dispatch centres separately.

In our results, the number of contacts (OOH-PC) or ambulance dispatches (EMS) are displayed per 1,000 inhabitants in the respective catchment areas.

RESULTS

We received aggregated data from all six primary care cooperatives and both regional ambulance dispatch centres. Data availability varied across the requested years, but was complete for 2023 and 2024.

In those years, OOH-PC handled 10.0 and 10.3 chest pain-related contacts per 1,000 inhabitants, respectively. The distribution of urgency levels and subsequent actions following triage were comparable between 2023 and 2024. Overall, 60.0-61.2% of the total chest pain contacts were assessed as high urgency (i.e. U1 or U2), and 36% resulted in the request of an ambulance dispatch. Approximately 40% of total contacts were followed by a face-to-face GP consultation (*Table 1*).

Together, the two ambulance regions dispatched 4.0 ambulances per 1,000 inhabitants in 2023, and 4.4 per 1,000 in 2024. After adjusting the ambulance data for OOH-PC operating hours, 3.0 and 3.2 ambulance dispatches per 1,000 inhabitants remained, respectively. The vast majority of ambulance dispatches were classified as urgent (A0-A2), yet 41% of cases only required on-site care and did not result in hospital transport (*Table 1*).

When comparing workloads, OOH-PC handled 2.4 times more chest pain related contacts than EMS dispatched ambulances in 2023, and 2.3 times as many in 2024. After correcting for afterhours, these ratios increased to 3.4 in 2023 and 3.2 in 2024.

Figure 2 illustrates the difference in workload after this correction. Furthermore, the figure includes an exploration of shared workload, represented by the

number of ambulance deployments requested by OOH-PC. When this shared workload is taken into account (i.e. OOH-PC-requested ambulances are considered a burden on both OOH-PC and EMS), the difference in workloads decreased to a ratio of 1.5 for both years. Corresponding data on EMS contacts that were deferred to OOH-PC were not available and could not be included.

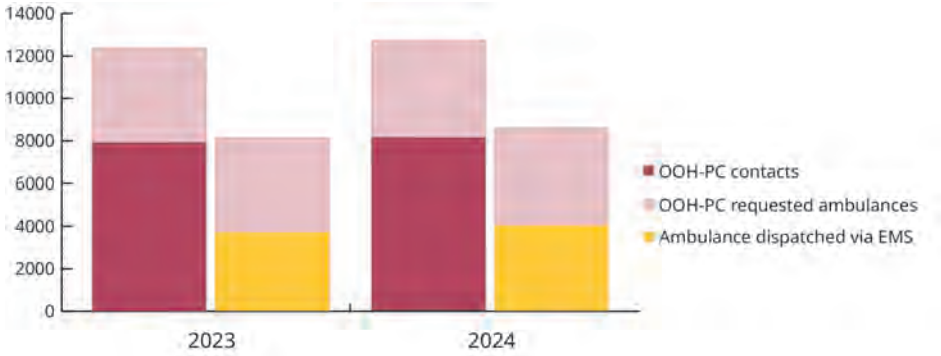
Table 1. Care provided by OOH-PC and EMS in 2023 and 2024.

	2023	2024
OOH-PC		
Total contacts (/1,000 inhabitants)	12,316 (10.0)	12,672 (10.3)
Urgency (%)		
U1	4712 (38.3)	4773 (37.7)
U2	2822 (22.9)	2831 (22.3)
U3	3431 (27.9)	3607 (28.5)
U4	225 (1.8)	245 (1.9)
U5	1126 (9.1)	1216 (9.6)
Action following triage (%)		
Ambulance dispatch requested by OOH-PC	4447 (36.1)	4584 (36.2)
GP consultation	5235 (42.5)	5538 (43.7)
Telephone advice	2436 (19.8)	2546 (20.1)
Other	198 (1.6)	4 (0.03)
EMS		
Total ambulance dispatches (/1,000 inhabitants)	4,971 (4.0)	5,426 (4.4)
Afterhours (/1,000 inhabitants)	3,679 (3.0)	4,008 (3.2)
Urgency (%)		
A0/A1	4834 (97.2)	5266 (97.1)
A2	135 (2.7)	156 (2.9)
B1/B2	0 (0.0)	2 (0.04)
Unknown	2 (0.04)	2 (0.04)
Action		
Transportation to hospital	2941 (59.2)	3200 (59.0)
On-site care	2030 (40.8)	2226 (41.0)

The top part of the table illustrates the volume of chest pain-related care provided by the OOH-PC facilities. The total number of contacts are displayed per 1,000 inhabitants in the combined catchment area (i.e. 1,229,700 inhabitants). Urgency codes and actions following triage are displayed as a number and its percentage. The bottom section of the table illustrates the volume of chest pain-related ambulance dispatches by EMS, both before and after correction for OOH-PC operating hours (evening, nights, weekends and national holidays). The correction was performed using a calculated ratio. The number of

ambulance dispatches are displayed per 1,000 inhabitants in the catchment area of the two ambulance dispatch centres combined (i.e. 1,240,000 inhabitants). Urgency levels and actions after the arrival of the ambulance are displayed as a number and its percentage. Urgency levels are defined as follows: A0 – direct dispatch of nearest ambulance with priority, A1 – direct dispatch, A2 – dispatch as soon as possible, and B1/B2 - routine care. Abbreviations: OOH-PC, out-of-hours primary care; EMS, emergency medical services.

Figure 2. OOH-PC and EMS workloads in 2023 and 2024.



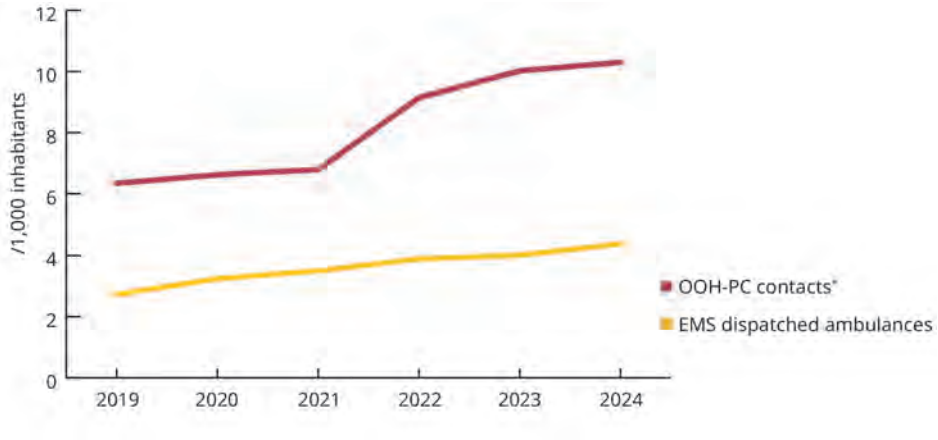
In this graph, the columns on the left illustrate the volume of chest pain-related contacts with OOH-PC for 2023 and 2024, respectively. The top of these columns are made up of the ambulance dispatches requested by OOH-PC.
The columns on the right show the total ambulances dispatched after contact with EMS (corrected for afterhours), with those requested by OOH-PC added on top. This combination is used to represent the shared workload between services.
Abbreviations: OOH-PC, out-of-hours primary care; EMS, emergency medical services.

Temporal trends

Figure 3 shows temporal trends in pre-hospital care volumes between 2019 and 2024. OOH-PC contacts increased from 6.3 contacts per 1,000 inhabitants in 2019 to 10.3 in 2024, an increase of 63%. Similarly, EMS volumes rose with 60%, showing an increase in dispatched ambulances from 2.7 to 4.4 per 1,000 inhabitants.

Supplemental tables 1 and 2 provide detailed information on OOH-PC and EMS data respectively, stratified by year and facility/region. These temporal trends expressed similar results as observed between 2023 and 2024, with a rise in OOH-PC contacts that led to an ambulance dispatch (+9.8% between 2019 and 2024), and an increase in the proportion of EMS-initiated ambulances in which on-site care sufficed (+8.8% between 2019 and 2024).

Figure 3. Temporal trends in pre-hospital care volumes (2019-2024).



The graph shows temporal trends in OOH-PC contacts and dispatched ambulances for chest pain between 2019 and 2024, expressed per 1,000 inhabitants of the respective catchment areas. In this graph, EMS data was not adjusted for afterhours. Notes: *OOH-PC data for 2019-2021 were available for one OOH-PC cooperative, for four cooperatives in 2022, and for all six in 2023-2024. Yearly contact rates per 1,000 inhabitants were calculated using the catchment areas of the OOH-PC facilities with available data. Abbreviations: OOH-PC, out-of-hours primary care; EMS, emergency medical services.

DISCUSSION

Our study explored out-of-hours pre-hospital care for acute chest pain in the Netherlands and found that OOH-PC managed substantially more patient contacts than EMS dispatched ambulances. Over time, the demand increased for both services.

Our findings align with national reports indicating a growing pressure on the acute care chain. For ambulance services, these reports show a steady increase in the total number ambulance dispatches and a rising proportion of cases not resulting in hospital transport (i.e. potentially unnecessary dispatches).[7-9] In our data, EMS also handled an increasing number of these potentially low-urgency cases, as the proportion of dispatches without transportation rose from 32.2% in 2019 to 41.0% in 2024. At the same time, in OOH-PC, temporal trends showed an increase in requested ambulances, while urgency levels remained stable. These patterns indicate suboptimal resource use, particularly in acute symptoms such as chest pain, where pre-hospital assessments tend to be defensive while only a minority of patients have an urgent underlying condition.[10,11] Nevertheless, a broader trend of rising demand on pre-hospital care services is evident. Previous studies have linked this increase to several factors, including demographic shifts (e.g. population growth and ageing),

societal expectations for 24/7 access, limited daytime primary care availability, and potential limitations in triage accuracy.[4,12-14] Together, these factors underline the need for closer collaboration and better-aligned triage methods to sustain pre-hospital care capacity, improve efficiency, and reduce costs.

Over recent years, Dutch OOH-PC and EMS have become more coordinated. A key development was the introduction of a seven-category ambulance urgency classification (2023-2025), replacing the former three-level system (A1, A2, B). The new classification differentiates emergency care into A0 (nearest ambulance, highest priority), A1 (immediate dispatch), and A2 (dispatch as soon as possible). Routine care is divided into B1 (high-complexity) , and B2 (medium or low-complexity), while C1 (deferral) and C2 (self-care advice) cover less urgent cases.[15] This structure more closely resembles OOH-PC's five-level urgency system and may support better alignment in urgency assessment across services.

Further improvements in pre-hospital efficiency may be achieved by regulating patient inflow or by adjusting care capacity. National campaigns have already aimed to guide the public on appropriate care use, although evidence for their impact on reducing or redirecting acute care demand remains limited.[16] Additional strategies include stricter or improved triage protocols, incorporation of decision support tools (including AI-based systems), and expanding daytime primary care availability.[4,17] More structural approaches, such as deploying GPs alongside ambulance crews or establishing shared call centres, may also improve coordination.[18] However, these models require substantial organizational changes and evidence for their value remains limited.[19]

Future research

Our study provides an explorative evaluation of pre-hospital patient flows for chest pain, but more detailed analyses are needed to fully compare volumes of care provided by OOH-PC and EMS. Furthermore, in order to regulate care delivery, we need to understand how patients decide which service to contact first. Perceived urgency, familiarity with the healthcare system, and possible financial considerations may all play a role.[14,20] Exploring these factors could inform strategies to guide patients to the most appropriate entry point and reduce pressure on both OOH-PC and EMS.

Strengths and limitations

We conducted explorative analyses on the relative burden of chest pain-related contacts in Dutch pre-hospital care using routine care data. By linking

information from both OOH-PC and EMS, this study provides new insights into pre-hospital care pathways and highlights opportunities to optimize appropriate care delivery. Data were obtained from services in two Dutch regions that are broadly representative of the national population. Furthermore, reporting chest pain-related contacts and ambulance deployments per 1,000 inhabitants enhances comparability and generalizability of our findings.

Our study also has several limitations. First, data availability varied across OOH-PC cooperatives, which restricted comparative analyses to 2023 and 2024. This also reduced the precision of the time-trend analyses, as data for 2019-2021 were available for only one facility with a relatively low workload, which may have led to an overestimation of the increase in total OOH-PC contacts. Second, the datasets were not fully compatible: EMS records only included dispatched ambulances, and contacts without dispatch were unavailable, likely underestimating the relative workload of EMS. Additionally, EMS operates 24/7, while OOH-PC is limited to evenings, nights, weekends and national holidays. To improve comparability, we adjusted EMS volumes using a calculated ratio based on overlapping operating hours. However, this correction did not account for hourly variation in caseload, as no such temporal data were available. Finally, the study relied on aggregated data, which precluded analyses of patient characteristics, repeated contacts, and clinical outcomes.

CONCLUSION

In two Dutch regions, OOH-PC managed more acute chest pain contacts than EMS-dispatched ambulances. While both services experienced increasing demand, the concurrent rise in OOH-PC ambulance requests and the growing proportion of EMS dispatches not requiring transport may indicate inefficient resource allocation. These findings underscore the need for enhanced inter-service coordination and harmonized triage protocols to optimize pre-hospital resource utilization and preserve system capacity under increasing demand.

REFERENCES

1. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141–6. doi:10.3109/13814780903329528
2. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. *Fam Pract*. Apr 2006;23(2):167–74. doi:10.1093/fampra/cmi124
3. Carret MLV, Fassa ACG, Domingues MR. Inappropriate use of emergency services: a systematic review of prevalence and associated factors. *Cadernos de saude publica*. 2009;25:7–28.
4. Keizer E, Maassen I, Smits M, Wensing M, Giesen P. Reducing the use of out-of-hours primary care services: a survey among Dutch general practitioners. *European Journal of General Practice*. 2016;22(3):189–195.
5. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Ann Intern Med* 2007 Oct 16 2007;147(8):574–7. doi:10.7326/0003-4819-147-8-200710160-00010.
6. Domus Medica - Netherlands Triage Standard. 2014.
7. Ambulancezorg Nederland - Sectorkompas. Vol. 2019-2023. https://www.ambulancezorg.nl/sectorkompas
8. Ambulancezorg Nederland. Insights into the rise in ambulance deployments (Original title: Inzicht in de toename van het aantal ambulance-inzetten). 2017.
9. Smits M, Francissen O, Weerts M, Janssen K, van Grunsven P, Giesen P. Spoedritten ambulance vaak eerstelijnszorg. *Ned Tijdschr Geneeskd*. 2014;158(A7863)
10. Smits M, Verheij R. Changes in urgencies of out-of-hours primary care contacts 2013-2016 (Original title: Veranderingen in de urgentie van contacten met de huisartsenpost 2013-2016) *Nivel rapport*. 2017;
11. Zeilstra R, Giesen P. Chest pain: general practitioner or ambulance? (Original title: Pijn op de borst: huisarts of ambulance?) *Huisarts & Wetenschap*. 2017;60(10)
12. Bakker E, Verhage V, Tuinstra J, Bouma J. Ambulance rides without transport of the patient (Original title: Ambulanceritten zonder vervoer van de patiënt). *Tijdschrift voor Gezondheidswetenschappen*. 2014;3:119–124.
13. Brown E, Sindelar J. The emergent problem of ambulance misuse. *Annals of emergency medicine*. 1993;22(4):646–650.
14. Kommer GJ, Gijsen R, van Gils P. Trendanalysis emergency ambulance care (Original title: Trendanalyse spoedeisende ambulancezorg) 2015.

15. Ambulancezorg Nederland. Optimal utilization: improved urgency classification in ambulance services (Original title: optimale inzet: verbeterde urgentie-indeling ambulancezorg). Accessed 12-08-2025, https://www.ambulancezorg.nl/themas/kwaliteit-van-zorg/urgentie-indeling

16. Ramerman L, Rijpkema C, Verheij R. Application of the Netherlands Triage Standard in out-of-hours primary care (Original title: Toepassing van de Nederlandse Triage Standaard op de huisartsenspoedpost) Effects of revisions to the traige standard and the Urgent=Urgent campaign on urgency allocation (Original secondary title: Effecten van wijzigingen in de triagestandaard en Spoed=Spoed op de urgentietoekenning) Nivel 2024.

17. Berchet C. Emergency care services: trends, drivers and interventions to manage the demand. 2015.

18. Turner J, O'Cathain A, Knowles E, Nicholl J. Impact of the urgent care telephone service NHS 111 pilot sites: a controlled before and after study. *Bmj Open*. 2013;3(11):e003451.

19. Hedqvist A-T, Ljungholm L, Svensson A, et al. Collaboration between ambulance services and primary care: a scoping review protocol. *BMJ open*. 2025;15(1):e094516.

20. Thuresson M, Jarlöv MB, Lindahl B, Svensson L, Zedigh C, Herlitz J. Factors that influence the use of ambulance in acute coronary syndrome. *American heart journal*. 2008;156(1):170–176.

SUPPLEMENTARY MATERIAL

Supplemental Table 1. OOH-PC data stratified by year and facility.

2019	**Total** (%)	OOH-PC1 (%)	OOH-PC2 (%)	OOH-PC3 (%)	OOH-PC4 (%)	OOH-PC5 (%)	OOH-PC6 (%)
Total contacts	1,014	n/a	n/a	n/a	n/a	n/a	1,014
Urgency level							
U1	322 (31.8)						322 (31.8)
U2	282 (27.8)						282 (27.8)
U3	323 (31.9)						323 (31.9)
U4	28 (2.8)						28 (2.8)
U5	59 (5.8)						59 (5.8)
Action following triage							
Ambulance	268 (26.4)						268 (26.4)
GP consult (home visit)	56 (5.5)						56 (5.5)
GP consult (on-site)	482 (47.5)						482 (47.5)
Telephone advice	208 (20.5)						208 (20.5)
2020	**Total** (%)	OOH-PC1 (%)	OOH-PC2 (%)	OOH-PC3 (%)	OOH-PC4 (%)	OOH-PC5 (%)	OOH-PC6 (%)
Total contacts	1,059	n/a	n/a	n/a	n/a	n/a	1,059
Urgency level							
U1	391 (36.9)						391 (36.9)
U2	229 (21.6)						229 (21.6)
U3	326 (30.8)						326 (30.8)
U4	26 (2.5)						26 (2.5)
U5	87 (8.2)						87 (8.2)

continues

continued

Action following triage							
Ambulance	296 (28.0)						296 (28.0)
GP consult (home visit)	52 (4.9)						52 (4.9)
GP consult (on-site)	384 (36.3)						384 (36.3)
Telephone advice	327 (30.9)						327 (30.9)
2021	**Total** (%)	OOH-PC1 (%)	OOH-PC2 (%)	OOH-PC3 (%)	OOH-PC4 (%)	OOH-PC5 (%)	OOH-PC6 (%)
Total contacts	1,086	n/a	n/a	n/a	n/a	n/a	1,086
Urgency level							
U1	441 (40.6)						441 (40.6)
U2	202 (18.6)						202 (18.6)
U3	303 (27.9)						303 (27.9)
U4	26 (2.4)						26 (2.4)
U5	114 (10.5)						114 (10.5)
Action following triage							
Ambulance	318 (29.3)						318 (29.3)
GP consult (home visit)	36 (3.3)						36 (3.3)
GP consult (on-site)	374 (34.4)						374 (34.4)
Telephone advice	358 (33.0)						358 (33.0)
2022	**Total** (%)	OOH-PC1 (%)	OOH-PC2 (%)	OOH-PC3 (%)	OOH-PC4 (%)	OOH-PC5 (%)	OOH-PC6 (%)
Total contacts	7,887	1,671	n/a	2,903	n/a	2,243	1,070
Urgency level							
U1	3,004 (38.1)	708 (42.4)		1,062 (36.6)		793 (35.4)	441 (41.2)
U2	1,855 (23.5)	408 (24.4)		751 (25.9)		536 (23.9)	160 (15.0)

continues

continued

U3	2,181 (27.7)	474 (28.4)		791 (27.2)		563 (25.1)	353 (33.0)
U4	144 (1.8)	28 (1.7)		38 (1.3)		50 (2.2)	28 (2.6)
U5	703 (8.9)	53 (3.2)		261 (9.0)		301 (13.4)	88 (8.2)
Action following triage							
Ambulance	2,765 (35.1)	665 (39.8)		1,001 (34.5)		758 (33.8)	341 (31.9)
GP consult (home visit)	384 (4.9)	66 (3.9)		174 (6.0)		109 (4.9)	35 (3.3)
GP consult (on-site)	2,971 (37.7)	617 (36.9)		1,152 (19.8)		859 (38.3)	343 (32.1)
Telephone advice	1,767 (22.4)	323 (19.3)		576 (19.8)		517 (23.0)	351 (32.8)
2023	**Total** (%)	OOH-PC1 (%)	OOH-PC2 (%)	OOH-PC3 (%)	OOH-PC4 (%)	OOH-PC5 (%)	OOH-PC6 (%)
Total contacts	12,316	1,722	2,438	2,815	1,310	2,684	1,347)
Urgency level							
U1	4,712 (38.3)	765 (44.4)	971 (39.8)	1,085 (38.5)	575 (43.9)	862 (32.1)	454 (33.7)
U2	2,822 (22.9)	378 (22.0)	551 (22.6)	711 (25.3)	288 (22.0)	696 (25.9)	198 (14.7)
U3	3,431 (27.9)	482 (28.0)	630 (25.8)	775 (27.5)	295 (22.5)	688 (25.6)	561 (41.6)
U4	225 (1.8)	29 (1.7)	43 (1.8)	29 (1.0)	25 (1.9)	68 (2.5)	31 (2.3)
U5	1,126 (9.1)	68 (3.9)	243 (10.0)	215 (7.6)	127 (9.7)	370 (13.8)	103 (7.6)
Action following triage							
Ambulance	4,447 (36.1)	732 (42.5)	933 (38.3)	1015 (36.1)	535 (40.8)	819 (30.5)	413 (30.7)
GP consult (home visit)	529 (4.3)	66 (3.8)	99 (4.1)	159 (5.6)	35 (2.7)	138 (5.1)	32 (2.4)
GP consult (on-site)	4,706 (38.2)	620 (36.0)	899 (36.9)	1157 (41.1)	524 (40.0)	1099 (40.9)	407 (30.2)
Telephone advice	2,436 (19.8)	304 (17.7)	507 (20.8)	484 (17.2)	216 (16.5)	628 (23.4)	297 (22.0)
Unknown	198 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	198 (14.7)

continues

continued

2024	**Total** (%)	OOH-PC1 (%)	OOH-PC2 (%)	OOH-PC3 (%)	OOH-PC4 (%)	OOH-PC5 (%)	OOH-PC6 (%)
Total contacts	12,672	1,866	2,553	2,803	1,521	2,868	1,061
Urgency level							
U1	4,773 (37.7)	705 (37.8)	1,039 (40.7)	1,010 (36.0)	693 (45.6)	900 (31.4)	426 (40.2)
U2	2,831 (22.3)	417 (22.3)	500 (19.6)	720 (25.7)	305 (20.1)	704 (24.5)	185 (17.4)
U3	3,607 (28.5)	633 (33.9)	730 (28.6)	819 (29.2)	368 (24.2)	733 (25.6)	324 (30.5)
U4	245 (1.9)	26 (1.4)	48 (1.9)	37 (1.3)	29 (1.9)	90 (3.1)	15 (1.4)
U5	1,216 (9.6)	85 (4.6)	236 (9.2)	217 (7.7)	126 (8.3)	441 (15.4)	111 (10.5)
Action following triage							
Ambulance	4,584 (36.2)	705 (37.8)	1,008 (39.5)	933 (33.3)	669 (44.0)	888 (31.0)	381 (35.9)
GP consult (home visit)	498 (3.9)	64 (3.4)	103 (4.0)	142 (5.1)	40 (2.6)	129 (4.5)	20 (1.9)
GP consult (on-site)	5,040 (39.8)	747 (40.0)	941 (36.9)	1,219 (43.5)	577 (37.9)	1,169 (40.8)	387 (36.5)
Telephone advice	2,546 (20.1)	346 (18.5)	501 (19.6)	509 (18.2)	235 (15.5)	682 (23.8)	273 (25.7)
Other*	4 (0.03)	4 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The table provides detailed information on the chest pain-related contacts to OOH-PC, assigned urgency levels, and actions following triage, stratified by year and facility. OOH-PC facilities are numbered in the table and correspond to the following primary care cooperatives and facilities: 1) Huisartsen Spoedpost Kop van Noord-Holland (includes locations Schagen and Den Helder), 2) Huisartsenspoedpost West-Friesland (Hoorn), 3)Huisartsenorganisatie Noord-Kennemerland (Alkmaar), 4) SpoedEisende Medische Dienst (Beverwijk), 5) Huisartsenspoedpost Haarlem (includes locations Haarlem Noord and Haarlem Zuid), and 6) Huisartsenspoedpost Haarlemmermeer (Haarlemmermeer). Notes: * Patients were invited for face-to-face triage at the OOH-PC facility. Abbreviations: OOH-PC, out-of-hours primary care; GP, general practitioner.

Supplemental Table 2. EMS data stratified by year and region.

2018	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	2991	1719	1272
Transport to hospital	2060 (68.9)	1234 (71.8)	826 (64.9)
On-site care	931 (31.1)	485 (28.2)	446 (35.1)
Urgency level			
A0/A1	2882 (96.4)	1660 (96.6)	1222 (96.1)
A2	106 (3.5)	58 (3.4)	48 (3.8)
B1/B2	2 (0.1)	1 (0.1)	1 (0.1)
Unknown	1 (0.03)	0 (0.0)	1 (0.1)
2019	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	3385	1759	1626
Transport to hospital	2296 (67.8)	1248 (70.9)	1048 (64.5)
On-site care	1089 (32.2)	511 (29.1)	578 (35.5)
Urgency level			
A0/A1	3241 (95.7)	1685 (95.8)	1556 (95.7)
A2	141 (4.2)	73 (4.2)	68 (4.2)
B1/B2	1 (0.03)	1 (0.1)	0 (0.0)
Unknown	2 (0.1)	0 (0.0)	2 (0.1)
2020	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	4014	2118	1896
Transport to hospital	2604 (64.9)	1418 (66.9)	1186 (62.6)
On-site care	1410 (35.1)	700 (33.1)	710 (37.4)
Urgency level			
A0/A1	3912 (97.5)	2016 (95.2)	1896 (100.0)
A2	201 (2.5)	102 (4.8)	0 (0.0)
B1/B2	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)
2021	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	4337	2297	2040
Transport to hospital	2667 (61.5)	1484 (64.6)	1183 (58.0)
On-site care	1670 (38.5)	813 (35.4)	857 (42.0)
Urgency level			
A0/A1	4096 (94.4)	2166 (94.3)	1930 (94.6)
A2	238 (5.5)	130 (5.7)	108 (5.3)
B1/B2	1 (0.02)	1 (0.04)	0 (0.0)
Unknown	2 (0.05)	0 (0.0)	2 (0.1)

continues

continued

2022	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	4828	2582	2246
Transport to hospital	2938 (60.9)	1627 (63.0)	1311 (58.4)
On-site care	1890 (39.1)	955 (37.0)	935 (41.6)
Urgency level			
A0/A1	4597 (95.2)	2446 (94.7)	2151 (95.8)
A2	226 (4.7)	133 (5.2)	93 (4.1)
B1/B2	4 (0.1)	3 (0.1)	1 (0.04)
Unknown	1 (0.02)	0 (0.0)	1 (0.04)
2023	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	4971	2684	2287
Transport to hospital	2941 (59.2)	1644 (61.3)	1297 (56.7)
On-site care	2030 (40.8)	1040 (38.7)	990 (43.3)
Urgency level			
A0/A1	4834 (97.2)	2606 (97.1)	2228 (97.4)
A2	135 (2.7)	78 (2.9)	57 (2.5)
B1/B2	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	2 (0.04)	0 (0.0)	2 (0.1)
2024	**Total** (%)	EMS1 (%)	EMS2 (%)
Total dispatches	5426	2949	2477
Transport to hospital	3200 (59.0)	1813 (61.5)	1387 (56.0)
On-site care	2226 (41.0)	1136 (38.5)	1090 (44.0)
Urgency level			
A0/A1	5266 (97.1)	2867 (97.2)	2399 (96.9)
A2	156 (2.9)	82 (2.8)	74 (3.0)
B1/B2	2 (0.04)	0 (0.0)	2 (0.1)
Unknown	2 (0.04)	0 (0.0)	2 (0.1)

The table provides detailed information on chest pain-related ambulance dispatches by EMS, their urgency levels, and whether the patient was transported to the hospital or received on-site care only, stratified by year and region. EMS regions are numbered in the table and correspond to the following regional ambulance dispatch centres: 1) EMS Noord-Holland Noord, and 2) EMS Kennemerland. Urgency levels are defined as follows: A0 – direct dispatch of nearest ambulance with priority, A1 – direct dispatch, A2 – dispatch as soon as possible, and B1/B2 - routine care. Abbreviations: EMS, emergency medical services.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 3

Rationale and design of a cohort study evaluating triage of acute chest pain in out-of-hours primary care in the Netherlands (TRACE)

Amy Manten*, Cuny J.J. Cuijpers*, Remco P. Rietveld, Emma Groot, Freek van de Graaf, Sandra Voerman, Jelle C.L. Himmelreich, Wim A.M. Lucassen, Henk C.P.M. van Weert, Ralf E. Harskamp.

*Contributed equally

Published in Primary Health Care Research & Development, 2020

PMID: 32383424

DOI: 10.1017/S1463423620000122

ABSTRACT

The aims of the study are (1) to evaluate the performance of current triage for chest pain; (2) to describe the case mix of patients undergoing triage for chest pain; and (3) to identify opportunities to improve performance of current Dutch triage system for chest pain.

Chest pain is a common symptom, and identifying patients with chest pain that require urgent care can be quite challenging. Making the correct assessment is even harder during telephone triage. Temporal trends show that the referral threshold has lowered over time, resulting in overcrowding of first-responders and emergency services. While various stakeholders advocate for a more efficient triage system, careful evaluation of the performance of the current triage in primary care is lacking.

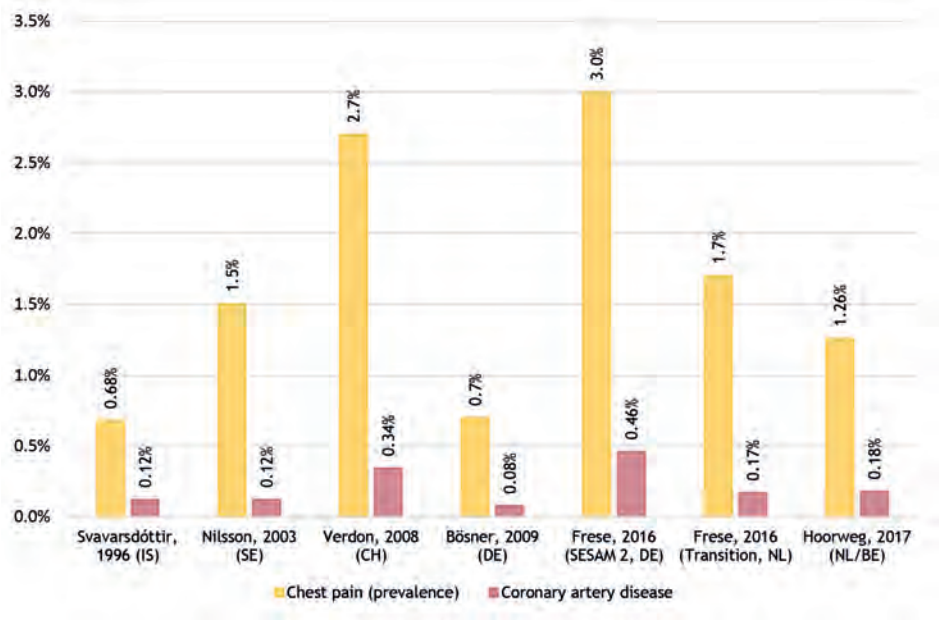
TRiage of Acute Chest pain Evaluation in primary care (TRACE) is a large cohort study designed to describe the current Dutch triage system for chest pain and subsequently evaluate triage performance in regard to clinical outcomes. The study consists of consecutive patients who contacted the out-of-hours primary care facility with chest pain in the region of Alkmaar, the Netherlands, in 2017, with follow-up for clinical outcomes out to August 2019. The primary outcome of interest is 'major event', which is defined as the occurrence of death from any cause, acute coronary syndrome, urgent coronary revascularization, or other high-risk diagnoses in which delay is inadmissible and hospitalization is necessary. We will evaluate the performance of the triage system by assessing the ability of the triage system to correctly classify patients regarding urgency (accuracy), the proportion of safe actions following triage (safety) as well as rightfully deployed ambulances (efficacy).

TRACE is designed to describe the current Dutch triage system for chest pain in primary care and to subsequently evaluate triage performance in regard to clinical outcomes.

BACKGROUND AND RATIONALE

Chest pain is a common symptom with a lifetime prevalence of 20-40%, and in primary care about 1 in every 50 consultations is related to chest pain.[1-11] A minority of these cases have an underlying heart condition, with a pre-consultation probability that varies from 1.5 to 10% (*Figure 1*).[1,2,4,6,7,9-13] Early detection of these disease states is warranted as adequate treatment prevents complications, such as heart failure, ventricular arrhythmias, as well as death itself.[14,15] Unfortunately symptoms may not always be as straightforward, and this can be particularly challenging for out-of-hours primary care facilities where initial triage occurs mainly over the telephone. Triage protocols have therefore been put in place in order to adequately and quickly identify urgent cases, while simultaneously preventing iatrogenic harm by exposure to unnecessary ambulance activation, hospital admissions, diagnostic evaluation, and/or treatment in non-urgent cases.[5,6,8] The inability to perform physical examination and the absence of clinical risk scores typically used in clinical settings complicates telephone triage even further.

Figure 1. The prevalence of chest pain and the occurrence of coronary artery disease.



The yellow charts show the prevalence of chest pain among patients in primary care for each study. The occurrence of coronary artery disease among patients presenting with chest pain is illustrated by the pink charts.

The health care system in the Netherlands is designed to provide equal access to all citizens. Every Dutch citizen is enlisted with a local primary care physician's (PCP) office, which keeps an electronic patient record file with all health care information (including correspondence from other health care facilities) for each of its patients. PCPs across the country are organized into regional, large-scale PCP cooperatives. The responsibilities of these cooperatives include the after-hours acute primary care services of the affiliated PCPs in that region through out-of-hours care facilities.[16] Most out-of-hours care facilities use the Dutch triage guideline [Nederlandse Triage Standaard (NTS)].[17] The NTS for chest pain ('pijn thorax') is derived from extrapolating hospital triage questions and consensus of expert opinion. These triage questions have never been cross-validated with clinical outcomes in a primary care population with undifferentiated chest pain.[15] Additionally, we have poor understanding of the initial presentation of patients with chest pain in out-of-hours primary care, as prior research has exclusively focused on either office hours primary care or emergency departments.[7,8,10] As a result, the diagnostic value of the NTS in out-of-hours primary care has been largely criticized by PCPs as well as ambulance services.[18] Triage inefficiency has been named as a main factor leading to frequent consultations for non-urgent cases and a high rate of unnecessary ambulance deployments, but other factors also play(ed) a role (i.e., organizational and cultural changes, financial and legal incentives).[16,18,19] Additionally, prior research has concluded that the urgency is underestimated in 19% of cases, potentially leading to unsafe situations.[16,18-22]

As such, we decided to conduct the TRiage of Acute Chest pain Evaluation (TRACE in primary care) study, designed to validate and optimize current triage decision-making in primary care by evaluating the current triage of chest pain in relationship to predicting major event. The first objective is to evaluate the performance of the current triage protocol/system for chest pain. The second objective is to describe symptom presentation, patient characteristics, triage decisions, final diagnoses, and clinical outcomes in patients presenting with chest pain in out-of-hours primary care. Finally, we explore opportunities to further improve triage safety and efficacy.

METHODS

The TRACE study involves an retrospective, observational cohort of consecutive patients who contacted a Dutch primary care out-of-hours facility with symptoms of chest pain. We reported our study protocol using the 'Strengthening the reporting of observational studies in epidemiology' checklist.[23]

Study population

TRACE involves a partnership with Huisartsenorganisatie Noord-Kennermerland (HONK). The HONK organization is the primary care cooperative of the surrounding region of Alkmaar, the Netherlands (*Figure 2*), comprising approximately 240,000 individuals. In the Alkmaar region, the majority of the inhabitants are of Dutch or European ancestry, with 12.8% being of non-Western/non-Caucasian descent. Of those, the largest minorities are Turkish (2.9%), Moroccan (2.0%), Surinamese (1.5%) and Antillean (1.2%).[24] The out-of-hours primary care facility in Alkmaar is responsible for the after-hours primary care services to patients of the 98 affiliated primary care day practices. In the Netherlands, all inhabitants are registered at one primary care practice in their area of residence. TRACE will include all patients who telephonically and/or physically contacted the out-of-hours primary care facility in Alkmaar with a complaint of chest pain between 1 January 2017 and 31 December 2017. Patients aged 18 years and over at the time of initial contact with a primary or secondary complaint of chest pain will be eligible for inclusion. For patients who reach out to the HONK with chest pain on multiple occasions during the inclusion window, only the first encounter will be included.

Figure 2. Regional coverage of the HONK network.

The regional coverage of the HONK network in the province of Noord-Holland, north of Amsterdam. Each pin on the map represents an affiliated primary care practice.

Inclusion procedure

All patients who contacted the HONK with chest pain in 2017 will receive information regarding the TRACE study by mail. The envelope includes an information leaflet and a form with the request to withdraw from participation ('opt out'). Data of patients who opt-out will not be used in any form for this study. Moreover, we will also not collect data on patients with unstable vital signs (U0 urgency), or when follow-up data cannot be collected (e.g., individuals who were not administered with a PCP at the time of initial contact, such as visitors/tourists, asylum seekers). All PCPs affiliated with the HONK will also be informed of the conduct of the study. We will also telephone PCP offices to schedule an appointment to complete follow-up information and to obtain current vital status information.

Triage system used at the out-of-hours facility

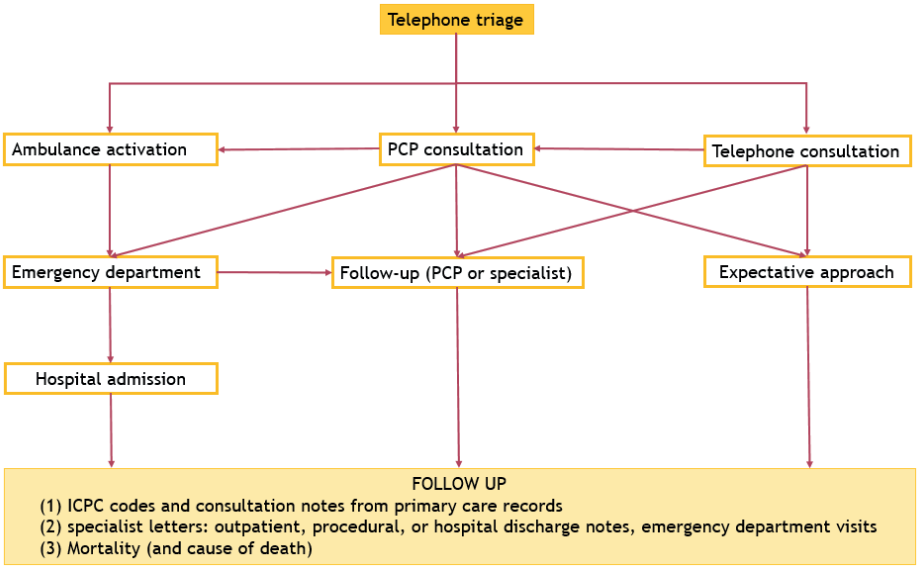
To assure nationwide consistency, primary care cooperatives use a standardized, software-based triage system, which relies on algorithms developed, maintained and exploited by the NTS.[17] The out-of-hours facilities are directly accessible for patients, but the preferred route of contact is by telephone. During a telephone contact, initial triage is carried out by trained triage nurses and supervised by on-site PCPs.[16] Triage nurses start by ensuring the hemodynamic status of a patient, and when unstable vital signs are present, the highest urgency level is activated, resulting in immediate ambulance deployment. In the vast majority of patients these vital signs are stable and triage for chest pain follows, and questions include chest pain characteristics, that is, the type of pain, duration, severity, course, localization and whether the patient experienced radiation of the pain or symptoms of sweating, nausea, or vomiting. Additionally, triage nurses can explore the medical history, medication use or the presence of accompanying symptoms, such as dyspnea or dizziness. Based on the answers to the standardized questions, an algorithm will generate an urgency category varying from urgency level 0 to 5 (U0-U5) as shown in *Table 1.* Possible actions following telephone triage include ambulance deployment, consultation by a PCP (at the center or a home visit) or telephone advice, as shown in *Figure 3*. The urgency classification determines the course of action and its time frame (see *Table 1*). When triage nurses suspect that a different urgency level would be more fitting to the patients' symptom, they can overrule the suggested urgency after consulting the attending physician.

Table 1. Urgency classification according to NTS.

Urgency codes	Definitions	In time
U0	No vital signs	Immediate - resuscitation
U1	Life threatening	As soon as possible - ambulance
U2	Emergent	Care <60 minutes
U3	Urgent	Care within several hours
U4	Non-urgent	Care within 24 hours
U5	Advice	Next workday - advice

Abbreviations: NTS, Nederlandse Triage Standaard.

Figure 3. Flowchart of telephone triage and actions after triage.



This figure depicts the actions that can be taken after telephone triage of chest pain.

Data collection

Data collection for TRACE will consist of two parts: the first part involves collection of baseline data and the second involves collection of follow-up and clinical outcomes data. Collection of follow-up data will be performed once data entry for baseline characteristics has been completed. We will enter all data into Castor Electronic Data Capture (Castor EDC)[25], a cloud-based electronic data capturing platform in which the data of each participant can be registered within an electronic case report form (eCRF). Castor EDC includes an audit trail. We will pseudonymize all patient data before data entry.

Baseline data

We will regard the information available at the time of the index (telephone) consultation of the out-of-hours facility as baseline data. This information will consist of demographics, telephone triage outcome in terms of ascribed urgency, and the management that followed triage, as recorded by the HONK. We will counter inter-observer variability of entered data by developing agreements on data registering of each variable, as well as by an internal audit of data by three researchers (A.M., W.A.L., R.E.H.). For cross-validation purposes, we will also retrieve information from PCPs' offices regarding baseline characteristics and medication use (at time of baseline consultation).

Follow-up data

For data on clinical outcomes we will use information derived from electronic patient records, including correspondence regarding hospital visits and outpatient consultations. Relevant documentation, such as specialist letters regarding follow-up of chest pain, will be pseudonymized and uploaded into the eCRF. This follow-up information will include both final diagnosis in relation to the index consultation and other relevant outcomes during the entirety of the follow-up period. We will gather follow-up data of all patients up to 12-30 months after index telephone triage. Our research team will schedule appointments with the practice to allow our researchers to visit the practice to collect follow-up data. In small primary care practices with few participants, and limited work space, we will contact the PCP to discuss the method of data entry. In these practices, PCPs will either allow one of the researchers to visit the practice for data collection, or the PCP will receive a personal token to log in to our eCRF and process the information of these patients themselves. We believe that via this approach we are sensitive towards the logistical challenges (i.e., providing a work station) that our study may impose on small practices. Still, as our team provides flexibility in our data collection visits, we anticipate that the vast majority will opt for our research team to collect follow-up information. Collection of follow-up data will be concluded in August 2019.

Final diagnosis: major and non-major events

We will evaluate triage performance by comparing the initial triage management at the HONK with the final diagnosis and clinical outcomes as retrieved from the patient records at the PCPs' offices. In order to do so, we will establish the final diagnosis for each patient and evaluate whether this diagnosis should be identified as a 'major event'. Subsequently, we will review the necessity of ambulance activation in hindsight when regarding the final diagnosis.

First we will determine final diagnosis. In primary care, diagnoses are registered as International Classification of Primary Care (ICPC) codes. We will use the ICPC codes that are registered in the patient records at the time of clinical follow-up. We anticipate to encounter a number of cases in which the registered ICPC code does not match with final diagnosis based on information from electronic health records. In case of doubt about the validity of the registered ICPC code, the necessity of revision of the ICPC code based on the full patient file (including information on diagnostic work-up and correspondence by specialists) will be decided on by discussion among the research group and, in case of disagreement, by an independent expert who is blinded for initial management. The (mis-classified) ICPC code will be adjusted to the more fitting code in the eCRF according to this final judgement. Such changes will be recorded in data logs.

Second, final diagnoses will be classified as either 'major' or 'non-major'. This distinction, as shown in *Table 2*, will be based on whether patients suffered from an acute coronary syndrome (ACS), a Major Adverse Cardiovascular Event (MACE), or other urgent clinical outcome. We defined MACE as the occurrence of all mortality, myocardial infarction/unstable angina or coronary revascularization, as used in the HEART score.[26] Data on mortality are obtained from various sources, including the HONK database (linkage) and from electronic health records from the daytime PCPs. The occurrence of ACS and coronary revascularization is based on source documentation, based on a specialist and/or hospital discharge letter. Clinical outcomes other than ACS or MACE will be classified as major event when they fulfill all of the following three criteria: (1) ambulance activation was justifiable in hindsight, (2) the patient was hospitalized, and (3) final diagnosis can be linked to the initial complaint of chest pain. Major events are separated further into events occurring within 6 weeks and events occurring later than 6 weeks following initial contact. This division is based on the assumption that most major events associated with initial contact would manifest within a period of 6 weeks. Major event occurring later than 6 weeks for instance include patients who suffered from cardiac ischemia later on or participants who died within the follow-up period. We decided to include a longer follow-up period as it may counter some of the effects of verification bias, as patients initially not referred to a specialist, may have been referred/diagnosed at a later stage.

Table 2. Distribution of major and non-major events

	Final diagnosis	Management
Major event	ACS	
	MACE	
	Pulmonary embolism	
	Thoracic aortic aneurysm	
	Severe/acute congestive heart failure	Hospitalization
	Severe peri(myo)carditis	Hospitalization
	(Tension) pneumothorax	Hospitalization/drain
	Severe pneumonia	Hospitalization
	Symptomatic atrial fibrillation	First onset/hospitalization/ ECV or converted through medication.
	Aortic valve stenosis	Symptomatic
	Inflammatory processes such as appendicitis, pancreatitis, cholecystitis	Hospitalization
	Other, such as: exacerbation of COPD or hypertensive crisis	
Non-major event	Mild congestive heart failure	Outpatient treatment
	Mild peri(myo)carditis	Outpatient treatment
	Mild pneumothorax	Outpatient treatment
	Mild pneumonia	Outpatient treatment
	Atrial fibrillation	Recurrence/paroxysmal
	Pericarditis	Outpatient treatment
	Hypertension	Outpatient treatment
	Angina pectoris	Stable, outpatient treatment
	Skeletomuscular	
	Traumatic	
	Gastric/esophagus problems	
	Mild respiratory problems (such as viral infections)	
	Mental health/panic attack/anxiety disorder	

Abbreviations: ACS, acute coronary syndrome; MACE, major adverse cardiovascular event; ECV, Electrical Cardioversion; COPD, chronic obstructive pulmonary disease.

Triage performance

We will assess the performance of the current triage system by its 'accuracy', 'safety', and 'efficacy' regarding the ability to differentiate major from non-major events. We will define 'accuracy' as the overall probability that a patient is correctly classified by the triage system regarding the urgency of the final diagnosis. We will define correct classification as ambulance activation at initial consultation for a participant with a major event and no ambulance activation for a participant with a non-major event. We will determine 'safety' as one minus the false negative rate (i.e., the proportion of cases falsely assessed as non-major divided by the total number of included triage cases). The triage system's safety therefore ranges from 0 to 1, where a safety close or equal to 1 indicates a low proportion of cases with a 'missed' major event. 'Efficacy' refers to the proportion of ambulance deployments that involved an major event (true positives) divided by the total number of ambulance activations.

Additionally, we will also compare the urgency levels overruled by triage nurse (and PCP) versus not overruled and what effect this overruling has on safety, efficacy and accuracy. The action of overruling of the triage nurse is documented in the HONK database.

Statistical analysis

We will perform descriptive analyses on symptom presentation, patient characteristics, triage decisions, final diagnosis, and clinical outcomes. We will display discrete variables as number and percentages and continuous variables as means ± standard deviations or median and interquartile range for non-Gaussian distributions. We will compare continuous variables using Student's t-test and proportions using the Fisher's exact test or Pearson's chi-square test. We will use two-tailed tests.

We will evaluate the current NTS triage performance using safety, efficacy, and accuracy regarding major events and ambulance activity. We will perform a stratified analysis of triage performance comparing the sole use of (computer/algorithm-based) NTS telephone triage recommendation or the actual every-day use which integrates overruling of the triage nurse or physician.

We will evaluate diagnostic accuracy of the triage questions by their sensitivity, specificity and predictive values regarding the outcomes (1) major event and (2) MACE. We will also assess discrimination (C-statistics) and calibration (assessing calibration plots, and performing modified Hosmer-Lemeshow tests) of triage questions. We anticipate to include 1,500-2,000 patients with chest pain over a 1-year observation period based on prior the site's telephone consultation history. Of those, we estimate that approximately 10% of cases will involve a major event that requires immediate referral. Based on the rule

of thumb that one variable would require at least 10 cases of the primary outcome, this would provide us with sufficient power to allow for the analysis of 15-20 variables.

We will conduct all analyses using IBM SPSS Statistics for Windows, Version 25 (IBM Corp., Released 2017, Armonk, NY, USA). We will evaluate statistical significance in all analyses at the 0.05 level.

Ethical approval

The study proposal of TRACE was assessed by the Medical Ethical Committee (METC) (institutional review board) of the Amsterdam University Medical Centers, location Academic Medical Center (AMC). Given the observational design of the study, the METC exempted TRACE for full evaluation, as provided in writing on 13 February 2018 (reference number W18_035#18.053). All patients who sought telephone contact with chest pain in the year 2017 will receive a letter from the HONK with information about the TRACE study. They will also be provided with the possibility to withdraw from the study cohort through an attached 'opt-out-form' and return envelope, in case of objection. These actions have been reviewed by internal legal consultation and data protection representatives, and are (for the current study) within the boundaries of the new General Data Protection Regulation installed in May 2018 and the Dutch law on Medical Research in Humans. A summary of the study protocol has been published on Netherland trial register of the Dutch Cochrane group (Trial NL7581, https://www.trialregister.nl/trial/7581).

DISCUSSION

Chest pain provides a challenge for telephone triage, particularly for atypical symptoms and/or supposedly low-risk patients. This study will provide new insights as we will apply the actual clinical outcome as the reference, instead of 'expert opinion' which is the current basis of the NTS triage system. Critical evaluation of our current triage system using clinical follow-up data may provide us with the opportunity to further refine triage in order to maximize safety and efficacy. The available data would allow us to identify additional predictors for adverse clinical outcomes that could be taken into account when developing future updates of the current NTS triage system. While the Dutch healthcare system has unique features, the findings of TRACE will in general still be applicable in other countries with a strong primary care presence in acute/urgent care.

Prior and ongoing studies

A comparable study evaluating the optimization of telephone triage is currently conducted by Erkelens *et al.*[27] in the region of Utrecht, the Netherlands. This study uses the telephone triage audio recordings of patients with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care. Instead of initial management, Erkelens *et al.* focus on the diagnostic accuracy of the allocated urgency level after telephone triage. The results of this study are likely to complement TRACE in attaining a complete picture of current triage standards in the Netherlands.

Strengths and limitations

The TRACE study reflects real-world care of a contemporary cohort, with a patient population that is reflective of a Western European population. Use of primary care and affiliated resources in the Alkmaar region is comparable with the Dutch average, as is the use of medications, and chronic medical conditions (https://www.waarstaatjegemeente.nl/dashboard/Zorggebruik/). Moreover, since consecutive patients will be enrolled over the course of a year, we minimize possible selection or seasonal bias. Another strength is the robust follow-up and documentation of both cardiac life-threatening diagnoses (ACS/MACE) and other significant clinical outcomes. Furthermore, the urgency of the final diagnosis will be evaluated manually for each participant instead of relying solely on ICPC code registering. A limitation of our study is verification bias. We will only have follow-up documentation available of patients who were sent to secondary care for further evaluation. In other words, we only have partial verification, where only those triaged to secondary care (either immediately due to telephone triage or indirectly after PCP evaluation) will receive complete evaluation for rule out of major events. The magnitude of verification bias depends on the number of cases referred. We try to minimize this effect by having an extended follow-up, to allow for delayed-type/missed events to be captured. The use of extended follow-up using routine medical care data also introduces information bias, of which loss to follow-up is one of importance. Another form of bias that may play is confusion bias. With this form of bias, other (temporal) factors that are related to the ultimate outcome (i.e., age or sex), but not related to (or known at time of) triage, can modulate the effects of triage. Also, we run the potential for data manipulation errors, as the follow-up data of some practices (with <20 participants) will be entered by the PCPs themselves, instead of by our research team. Lastly, while the findings of our study may be reflective of a Dutch urgent primary care setting, it uncertain how these findings extrapolate to countries with health care systems where primary care plays a less prominent role in urgent care.

CONCLUSION

TRACE is designed to evaluate telephone triage of patients presenting with chest pain in out-of-hours primary care. The study will focus on various aspects of telephone triage, including symptom presentation, triage decision-making, and triage performance. The main goal will be to provide insight in our current triage decisions and to create recommendations to enhance the safety and efficacy.

REFERENCES

1. Svavarsdóttir AE, Jónasson MR, Gudmudsson GH, Fjeldsted K. Chest pain in family practice. *Canadian Family Physician*. 1996;42:1122–1128.
2. Nilsson S, Scheike M, Engblom D, et al. Chest pain and ischaemic heart disease in primary care. *British Journal of General Practice*. 2003;53:378–382.
3. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. *Fam Pract*. Apr 2006;23(2):167–74. doi:10.1093/fampra/cmi124
4. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340–347.
5. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141–6. doi:10.3109/13814780903329528
6. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212
7. McConaghy JR, Oza RS. Outpatient Diagnosis of Acute Chest Pain in Adults. *American Family Physician*. 2013;87(1)
8. Frese T, Mahlmeister J, Heitzer M, Sandholzer H. Chest pain in general practice: Frequency, management, and results of encounter. *Journal of Family Medicine and Primary Care*. 2016;5(1)doi:10.4103/2249-4863.184625
9. Aerts M, Minalu G, Bösner S, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011
10. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart*. Nov 2017;103(21):1727–1732. doi:10.1136/heartjnl-2016-310905
11. Harskamp R, van Peet P, Bont J, Ligthart S, Lucassen W, van Weert H. The conundrum of acute chest pain in general practice: a nationwide survey in The Netherlands. *BJGP Open*. Dec 2018;2(4):bjgpopen18X101619. doi:10.3399/bjgpopen18X101619
12. Haasenritter J, Biroga T, Keunecke C, et al. Causes of chest pain in primary care--a systematic review and meta-analysis. *Croat Med J*. Oct 2015;56(5):422–30. doi:10.3325/cmj.2015.56.422
13. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC Cardiovasc Disord*. Jun 11 2015;15:48. doi:10.1186/s12872-015-0049-6
14. Deakin CD. Does telephone triage of emergency (999) calls using advanced medical priority dispatch (AMPDS) with Department of Health (DH) call prioritisation effectively identify patients with an acute coronary syndrome? An audit of 42 657 emergency calls to Hampshire Ambulance Service NHS Trust. *Emergency Medicine Journal*. 2006;23(3):232–235. doi:10.1136/emj.2004.022962

15. van Ierland Y, van Veen M, Huibers L, Giesen P, Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. *Fam Pract*. Jun 2011;28(3):334–41. doi:10.1093/fampra/cmq097

16. Smits M, Rutten M, Keizer E, Wensing M, Westert G, Giesen P. The Development and Performance of After-Hours Primary Care in the Netherlands: A Narrative Review. *Ann Intern Med*. May 16 2017;166(10):737–742. doi:10.7326/M16-2776

17. Nederlandse Triage Standaard, Domus Medica. 2014.

18. Keizer E, Maassen I, Smits M, Giesen P. Verminderen van zorgconsumptie op huisartsenposten. *Huisarts & Wetenschap*. 2014;57(10):510–4.

19. Smits M, Verheij R. Veranderingen in de urgentie van contacten met de huisartsenpost 2013-2016. *Nivel rapport*. 2017;

20. Giesen P, Ferwerda R, Tijssen R, et al. Safety of telephone triage in general practitioner cooperatives: do triage nurses correctly estimate urgency? *Qual Saf Health Care*. Jun 2007;16(3):181–4. doi:10.1136/qshc.2006.018846

21. Ambulancezorg Nederland. Inzicht in de toename van het aantal ambulance-inzetten. 2017.

22. Zeilstra R, Giesen P. Pijn op de borst: huisarts of ambulance? *Huisarts & Wetenschap*. 2017;60(10)

23. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. Oct 20 2007;370(9596):1453–7. doi:10.1016/S0140-6736(07)61602-X

24. Centraal Bureau voor de Statistiek. *Ethniciteit per gemeente*. 2013. https://www.volksgezondheidenzorg.info/onderwerp/bevolking/regionaal-internationaal/etniciteit#!node-overige-niet-westerse-allochtonen-gemeente

25. Castor Electronic Data Capture, Ciwit BV. 2016. http://castoredc.com

26. Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *European Heart Journal: Acute Cardiovascular Care*. 2017;7(2):111–119. doi:10.1177/2048872617710788

27. Erkelens DC, Wouters LT, Zwart DL, et al. Optimisation of telephone triage of callers with symptoms suggestive of acute cardiovascular disease in out-of-hours primary care: observational design of the Safety First study. *BMJ Open*. Jul 1 2019;9(7):e027477. doi:10.1136/bmjopen-2018-027477


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 4

Evaluation of telephone triage among chest pain patients in out-of-hours primary care in the Netherlands (TRACE)

Amy Manten, Remco P. Rietveld, Lukas De Clercq, Inge van Hulst, Wim A.M. Lucassen, Eric P. Moll van Charante, Ralf E. Harskamp.

Published in Family Practice, 2022

PMID: 35849343

DOI: 10.1093/fampra/cmac077

ABSTRACT

Background: Telephone triage is fully integrated in Dutch out-of-hours primary care (OOH-PC). Patients presenting with chest pain are initially assessed according to a standardized protocol ('Netherlands Triage Standard' [NTS]). Nevertheless, little is known about its (diagnostic) performance, nor on the impact of subsequent clinical judgements made by triage assistants and general practitioners (GPs).

Objective: To evaluate the performance of the current NTS chest pain protocol.

Methods: Observational, retrospective cohort study of adult patients with chest pain who contacted a regional OOH-PC facility in the Netherlands, in 2017. The clinical outcome measure involved the occurrence of a 'major event', which is a composite of all-cause mortality and urgent cardiovascular and noncardiovascular conditions, occurring ≤6 weeks of initial contact. We assessed the performance using diagnostic and discriminatory properties.

Results: In total, 1,803 patients were included, median age was 54.0 and 57.5% were female. Major events occurred in 16.2% of patients with complete follow-up, including 99 (6.7%) cases of acute coronary syndrome and 22 (1.5%) fatal events. NTS urgency assessment showed moderate discriminatory abilities for predicting major events (c-statistic 0.66). Overall, NTS performance showed a sensitivity and specificity of 83.0% and 42.4% with a 17.0% underestimated major event rate. Triage assistants' revisions hardly improved urgency allocation. Further consideration of the clinical course following OOH-PC contact did generate a more pronounced improvement with a sensitivity of 89.4% and specificity of 61.9%.

Conclusion: Performance of telephone triage of chest pain appears moderate at best, with acceptable safety yet limited efficiency, even after including further work-up by GPs.

BACKGROUND

Chest pain is a common symptom among patients reaching out to primary care. It accounts for approximately 0.7-2.7% of daytime general practice consultations and is consistently present in the top 10 of main complaints in out-of-hours primary care (OOH-PC) settings.[2-7] When it comes to chest pain, acute coronary syndrome (ACS) is usually the first diagnosis that comes to mind. Understandably so, since missing an ACS may have serious consequences for the patient.[8] However, the spectrum of possible underlying conditions reaches far beyond ACS and includes several serious diagnoses that should not be overlooked (e.g. pulmonary embolism, aortic dissection, and sepsis).[2,6,7,9] Timely detection of these cases is vital in order to start adequate treatment to prevent complications, and even death.[8]

In several countries with general practitioner (GP) involvement in urgent care, telephone triage protocols are in place to aid adequate assessment of patients.[10] In the Netherlands, triage is performed using standardized, symptom-based questions, which is integrated in software developed by the 'Netherlands Triage Standard' (NTS).[11] In essence, the NTS protocols were developed by an expert panel using a modified version of the Manchester Triage System[12], in combination with existing telephone triage protocols used in daytime primary care.[13] However, the specific protocol for assessing chest pain was not validated before its instalment and a survey among Dutch GPs showed that 83.9% believed that the current system performs too defensively, contributing to overcrowding of out-of-hours care services.[14] Furthermore, a nation-wide increase in the number of ambulance deployments was seen, partly induced by increased usage of ambulance services through OOH-PC.[15]

Despite its common use and clinical relevance, research efforts on evaluating the performance of triage systems for chest pain are limited, and the influence of OOH-PC personnel (i.e. triage assistants, attending GP) on triage decision-making is often neglected. Thus far, 1 prior study evaluated the NTS for chest pain and found that urgencies were underestimated in a quarter of cases.[16] We aim to build upon this knowledge through an elaborate assessment of the several layers of decision-making in a large stand-alone OOH-PC facility.

METHODS

Study design

Our study 'TRiage of Acute Chest pain Evaluation in primary care (TRACE)' is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[17] A detailed description of study

design and methods was published previously.[18] In short, we performed an observational, retrospective cohort study of consecutive, adult patients with chest pain who contacted the OOH-PC facility in Alkmaar, the Netherlands, between 1 January and 31 December 2017. At the outset of the TRACE study, eligible patients received information by mail and were provided the opportunity to opt-out of sharing data.[18,19] Patients who bypassed OOH-PC, and immediately contacted the national emergency number, were not included.

Background and setting

In the Netherlands, the main organizational structure for OOH-PC consists of regional GP cooperatives that provide care to patients of affiliated GPs. The designated out-of-hours facility in Alkmaar provides care to 240,000 individuals, living in both rural and urban areas.

The flow of care in Dutch OOH-PC consists of multiple interacting layers, illustrated in *Figure 1*. In short, when patients contact the facility, triage assistants use the NTS decision support tool to triage a patient's urgency. Each complaint-specific NTS protocol starts by ensuring patient's vital signs using the ABCDE-method.[1] In patients assessed as 'unsafe' (i.e. hemodynamically threatened/unstable), ambulance services are immediately activated. In all others, the NTS protocol for chest pain continues with 7 standardized questions regarding the symptom characteristics (type, duration, severity, course, location, radiation, and associated symptoms). The supporting NTS algorithm uses the available answers (minimum of 1) to continuously calculate a recommended urgency level (NTS urgency). Urgencies vary from U1 (life threatening) to U5 (no harm) and are linked, but not restricted to a subsequent recommendation of time-until-care. Triage assistants who operate the NTS may have considerable influence on the system in multiple ways: (i) triage assistants conduct the conversation and may gather additional information not covered by the protocol (e.g. paralanguage, 'gut-feeling'), (ii) in case of disagreement with the NTS tool, they may overrule the recommended urgency level, and (iii) they ultimately decide on the most fitting course of action (e.g. ambulance, GP consultation, and self-care advice).

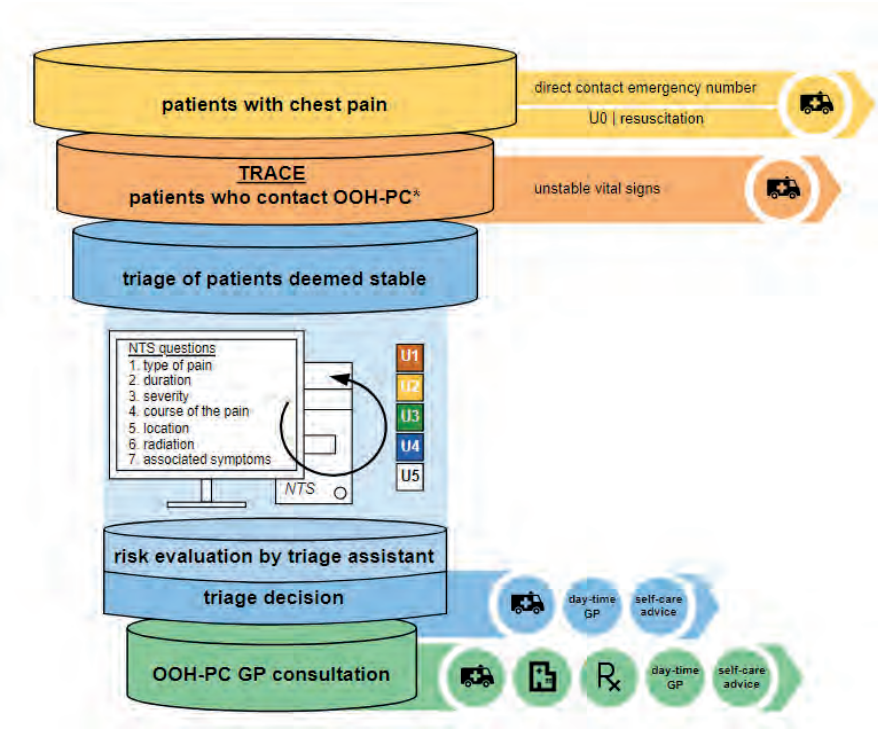
The attending GP forms another layer of the system and holds final responsibility. In this role, GPs may be consulted by the triage assistant, but also conduct face-to-face patient consultations at the OOH-PC facility or at the patient's home.

Data collection

Data collection consisted of 2 phases. In the first phase, digital triage registries were accessed from the OOH-PC facility and entered into a secure electronic

data-capturing platform (Castor EDC, Ciwit BV, Amsterdam, the Netherlands)[20] after deidentification. These registries included information on triage assessment: symptom characteristics, urgency levels, course of action, and GP assessment (in case of GP involvement). In the second phase, researchers visited daytime GP's offices to collect available information regarding patient characteristics (e.g. medical history and medication use) and clinical outcomes. Interobserver variability between researchers was restricted by the use of Standard Operating Procedures (SOPs) on data registering and by an internal audit.

Figure 1. Chest pain evaluation in Dutch out-of-hours primary care.



The figure illustrates the flow of care for chest pain patients in OOH-PC. Our study population corresponds to the second tier in the figure 'patients who contact OOH-PC'. Patients from the top tier bypassed the triage system and were not included in our study. The first step of triage is to identify, and filter out, patients that are hemodynamically unstable using the ABCDE method[1]. Further triage of the remaining, hemodynamically stable patients (third tier), follows the NTS protocol for chest pain evaluation, composed of 7 standardized questions. The supporting algorithm uses the answers (minimum of 1) to continuously calculate an urgency level (NTS urgency). These urgency codes are linked to a recommended time-until-care (U1 – as soon as possible, U2 – care <60 minutes, U3 – care within several hours, U4 – care within 24 hours, and U5 – next workday). Triage assistants can accept the recommended urgency or revise it and ultimately decide on the most appropriate course of action (i.e. the course of action is often associated with, but

not restricted to a certain urgency code). Patients who are further assessed face-to-face by a GP are represented in the bottom tier. Notes: *Contact occurs through telephone contact, and occasionally, in person ('self-referrals').

Definition of clinical outcomes

The main clinical outcome of interest was the occurrence of a major event within 6 weeks of initial contact. Major events were defined as a composite of all-cause mortality, and both cardiovascular and non-cardiovascular urgent conditions that were linked to the initial complaint of chest pain, and required hospital admittance or urgent in-hospital treatment (*Supplement 1*). ACS was included as a major event and was also assessed separately as a secondary outcome. We deliberately chose to consider ACS as a secondary, not primary outcome, to maintain the broad perspective of unselected chest pain.

The occurrence of clinical outcomes was based on the final diagnosis, registered as International Classification of Primary Care (ICPC) codes in the daytime GP's patient record file. The validity of these diagnoses was examined using information from the GP's file (including all relevant consultation notes and correspondence from hospital-based specialists or emergency departments), and cross-validated by an independent panel of expert GPs.

Analysing triage performance

We evaluated the performance of triage according to the separate layers of OOH-PC decision-making. First, triage was evaluated using NTS software derived urgency levels (*NTS urgency*) regarding the occurrence of a major event (and separately for ACS). Second, these were compared with *final urgencies*, which are the eventual urgency codes after possible up- and downscaling by the triage assistant. We assessed the discriminatory ability using *c*-statistics, and assessed the agreement between predicted and observed major events (and ACS) using calibration plots.

Diagnostic test properties (sensitivity, specificity, positive and negative predictive values) were assessed after dichotomizing the urgencies into a high (U1-U2; care <60 minutes) and low level (U3-U5; care >60 minutes).

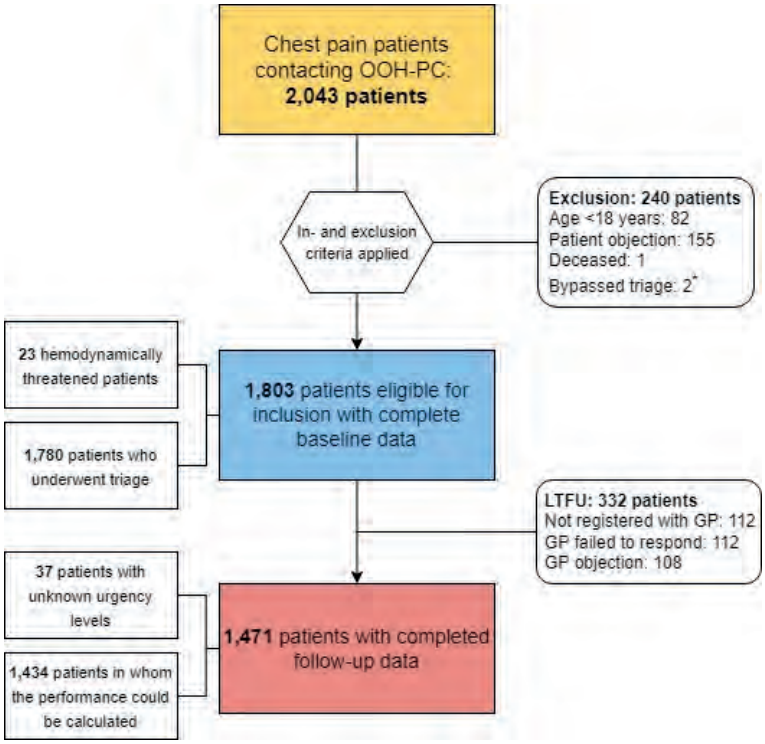
Third, we looked beyond urgency assessment and evaluated the performance of overall OOH-PC decision-making. Here, we used '*urgent referral*' as a reference standard, indicating whether patients were urgently referred to the hospital/emergency department (i.e. directly following initial triage or following subsequent GP consultation). Thus, forming a composite of the eventual course of action following OOH-PC contact.

RESULTS

A total of 2,043 consecutive patients with chest pain reached out to the OOH-PC facility. Of those, 1,803 patients met our inclusion criteria (*Figure 2*) and the vast majority of patients (1,738 [96.4%]) contacted the facility by telephone.

Supplement 2 displays the characteristics of the study population. Overall, the median age was 54.0 years [IQR: 37.0-70.0] and 1,038 (57.6%) were female. Most patients had at least 1 preexisting medical condition (69.9%) and/or used chronic medication (59.8%). A history of cardiovascular disease (CVD) was present in 363 (20.1%).

Figure 2. Flowchart of inclusion and exclusion of patients.



A total of 2,043 patients contacted the OOH-PC facility regarding chest pain in 2017. After exclusions, baseline information was completed for 1,803 patients. Upon contact, 23 patients were deemed hemodynamically unstable, resulting in discontinuation of triage and immediate action (i.e. activation of ambulance services). In total, follow-up data could be obtained for 1,471 patients. The allocated urgency levels were available for 1,434 patients. Notes: *Two patients bypassed the triage system entirely and were excluded from the dataset.

Clinical outcomes

Follow-up data on outcomes could be obtained from 1,471 patients (81.6%). A mentionable number of lost to follow-up was caused by GPs who expressed liability concerns (4 practices representing 108 patients).

In most patients, chest pain was caused by musculoskeletal conditions (674 [45.8%]). A total of 238 (16.2%) patients suffered from a major event within 6 weeks after initial contact, and majority of the major events were caused by cardiovascular disease (184 [77.3%]), including ACS (*n*=99), atrial fibrillation (n=38), and pulmonary embolisms (*n*=10) (*Supplement 3*). Of the remaining group (*n*=54, 22.7%), most could be ascribed to respiratory (*n*=23) and abdominal conditions (*n*=17). In total, 22 (1.5%) patients died in the first 6 weeks following contact. Patients with a major event were older, more often male, and more often known with a preexisting medical condition, including prior CVD (*Table 1*).

Of the 99 (6.7%) patients that suffered an ACS, 24 (24.2%) were diagnosed with ST-elevation myocardial infarction, 44 (44.4%) with non-ST-elevation myocardial infarction, 19 (19.2%) with unstable angina pectoris, and 12 (12.1%) cases were not further specified. Differences in patient characteristics between patients with and without an ACS were similar to those with or without major events.

Table 1. Patient characteristics of 1,471 patients with chest pain that contacted the out-of-hours primary care facility in 2017.

	Total (*n*=1,471)	**Major event** (*n*=238)	**Non-major** (*n*=1,233)	***p***
Age	55.0 (38.0-71.0)	71.0 (61.0-80.3)	51.0 (35.0-68.0)	<0.001
Sex (female)*	849 (57.7%)	109 (45.8%)	740 (60.0%)	<0.001
Pre-existing medical condition (any)	1093 (74.3%)	212 (89.1%)	881 (71.5%)	<0.001
History of cardiovascular disease	329 (22.4%)	100 (42.0%)	229 (18.6%)	<0.001
Prior CAD†	270 (18.4%)	84 (35.3%)	186 (15.1%)	<0.001
Prior stroke/TIA	102 (6.9%)	28 (11.8%)	74 (6.0%)	0.027
Prior peripheral arterial disease	38 (2.6%)	14 (5.9%)	24 (1.9%)	0.005
Cardiovascular risk factors (any)	841 (57.2%)	186 (78.2%)	655 (53.1%)	<0.001
Smoking (current)	265 (18.0%)	37 (15.5%)	228 (18.5%)	0.08
Hypertension	461 (31.3%)	124 (52.1%)	337 (27.3%)	<0.001
Hypercholesterolemia	243 (16.5%)	70 (29.4%)	173 (14.0%)	<0.001
Diabetes mellitus	181 (12.3%)	55 (23.1%)	126 (10.2%)	<0.001
Chronic use of medication (any)	945 (64.2%)	195 (81.9%)	750 (60.8%)	<0.001

The table lists the patient characteristics for the group of patients in whom follow-up data could be completed (n=1,471) and a division based on the occurrence of a major event. Continuous variables are presented as medians (IQR) due to a non-normal distribution. All categorical variables are presented as frequencies (%). Abbreviation: TIA, transient ischemic attack. Notes: *The patient sample included 1 transgender patient who transitioned from male to female gender, the sex of this patient was referred to as 'other'. †Prior coronary artery disease (CAD) was defined as a history of either acute or stable coronary syndromes.

Performance

1. NTS urgency assessment. Urgency codes were registered and available for 1,434 of the 1,471 patients with completed follow-up. c-Statistics were 0.66 [95%-CI: 0.62-0.69] for predicting major events and 0.69 [95%-CI: 0.65-0.72] for predicting an ACS. Calibration was adequate when comparing observed versus predicted major events or ACS. Next, we assessed the diagnostic properties of the NTS tool derived urgencies by dichotomizing them into a high (i.e. either U1 or U2; corresponding to a recommended time-until-care <1 h) and low level (i.e. U3-U5; care >1 h), resulting in 886 (61.8%) patients for whom the NTS tool yielded a high urgency. The corresponding diagnostic properties are listed in *Table 2*. The NTS adequately classified the urgency in 83.0% of patients with a major event and 85.7% of patients with an ACS (sensitivity), underestimating 40 (17.0%) major events and 14 (14.3%) ACS. The specificity

was 42.4% for predicting a major event and 40.0% for predicting ACS, with 691 and 802 unnecessary referrals (false positive rate), respectively.

2. Final urgency assessment. Triage assistants revised the recommended urgency levels in 271 (18.9%) cases, downscaling 160 (11.2%) and upscaling 86 (6.0%) urgencies. *c*-Statistics of the resulting final urgencies were 0.69 [95%-CI: 0.65-0.72] and 0.71 [95%-CI: 0.66-0.76] for predicting major events and ACS, respectively, with adequate calibration. Dichotomizing the final urgencies into a high (U1/U2) and low level (U3-U5) showed that triage assistants revisions of the urgency codes changed the composition of these groups only slightly (44 (3.1%) patients shifted from high to low and 50 (3.5%) patients shifted from low to high). This resulted in a high final urgency level for 892 (62.2%) patients. The diagnostic properties listed in *Table 2* further illustrate that the urgency revisions by the triage assistants marginally improved triage safety with only 4 (major events) and 1 (ACS) fewer underestimated cases.

3. Course of action. In 588 (32.6%) of the 1,803 patients that sought contact with the OOH-PC facility, triage assistants decided on activation of ambulance services directly following triage. This group included the 23 (1.3%) patients that were deemed hemodynamically unstable. When we combine urgency assessment with the course of action, we saw that 52.5% of the 892 patients with a high final urgency level received immediate ambulance activation (93.1% of the patients with an U1 [431/436] and 8.6% of U2 [37/429]). We further extended the evaluation of the course of action by assessing whether patients were urgently referred. Thus, either directly following triage or after subsequent GP consultation. Eventually, 89.4% of the major events and 94.9% of the patients with an ACS were urgently referred, while 25 and 5 patients with a major event or ACS were not (*Table 2*).

Table 2. Performance of the Dutch triage system on major events and acute coronary syndrome among 1,434 patients (2017).

	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Major event									
NTS urgency	195	691	40	508	83.0 [77.6-87.6]	42.4 [39.6-45.2]	22.0 [20.7-23.3]	92.7 [90.5-94.4]	49.0 [46.4-51.7]
Final urgency	199	693	36	506	84.7 [79.4-89.0]	42.2 [39.4-45.1]	22.3 [21.1-23.6]	93.4 [91.2-95.0]	49.2 [46.5-51.8]
Urgent referrals	210	457	25	742	89.4 [84.7-93.0]	61.9 [59.1-64.6]	31.5 [29.7-33.3]	96.7 [95.3-97.7]	66.4 [63.9-68.8]
ACS									
NTS urgency	84	802	14	534	85.7 [77.2-92.0]	40.0 [37.3-42.7]	9.5 [8.7-10.3]	97.5 [95.9-98.4]	43.1 [40.5-45.7]
Final urgency	85	807	13	529	86.7 [78.4-92.7]	39.6 [37.0-42.3]	9.5 [8.8-10.3]	97.6 [96.1-98.6]	42.8 [40.2-45.4]
Urgent referrals	93	574	5	762	94.9 [88.5-98.3]	57.0 [54.3-59.7]	13.9 [13.0-14.9]	99.4 [98.5-99.7]	59.6 [57.0-62.2]

The table illustrates the performance of the triage system in out-of-hours primary care in the Netherlands, regarding the occurrence of a major event and acute coronary syndrome. Diagnostic properties are presented as percentages [95%-CI]. 'NTS urgency' reflects the initial urgency recommendation provided by the NTS algorithm, while 'Final urgency' represents the concluding urgency levels after triage assistants' revisions. 'Urgent referrals' represent the course of action after contact with the OOH-PC facility. Abbreviations: ACS, acute coronary syndrome; FN, false negative; FP, false positive; NPV, negative predictive value; PPV, positive predictive value; TN, true negative; TP, true positive.

DISCUSSION

In this study, we assessed the performance of chest pain evaluation in a Dutch OOH-PC facility by assessing the current triage protocol (NTS), and the influence of OOH-PC personnel on its performance. The NTS tool itself showed moderate discriminatory and diagnostic properties for predicting both major events and ACS. Using it as an independent tool would lead to inappropriate urgency levels in a substantial proportion of patients, causing both large numbers of unnecessary referrals and underestimated urgencies. Triage assistants' revisions hardly improved urgency allocation. Final decision-making on the course of action (urgent referral or not) was more substantially improved by the combination of triage assistants and GPs, although the resulting performance remained moderate at best.

Strengths and limitations

Our study provides a representative reflection of OOH-PC in the Netherlands and may also be applicable in many other developed countries with a similar health care system. For the TRACE project, we enrolled consecutive patients who presented to the facility during the course of a full year, decreasing the chance of selection and seasonal bias. Furthermore, by using GPs' patient record files for the collection of follow-up data, we were able to examine patients' medical status and their clinical course following contact more thoroughly. Finally, we defined *major events* as our main clinical outcome to better match the variety of urgent underlying conditions that may cause chest pain, including but not restricted to ACS as one of the possible causes.

The most important limitation of our study is due to its retrospective design; observing the clinical course of patients with chest pain in which only those referred to hospital care underwent further diagnostic work-up (differential verification bias). However, we applied a follow-up period of 6 weeks to detect initially not-referred major events, which appeared to be sufficient. A mentionable amount of lost to follow-up was caused by GPs who expressed liability concerns due to the recent implementation of the European privacy regulations (GDPR).

How our findings fit with existing literature

The organizational structure of OOH-PC differs between and within countries. Nevertheless, in most European countries implementation of telephone triage has received considerable attention over the past decade.[10] A systematic review concluded that the use of telephone triage is safe in 97% when assessing a broad spectrum of patients and 89% among a high-risk population.[21,22]

The NTS's complaint-specific protocols were not separately validated prior to their introduction in OOH-PC and research focused on triaging chest pain is scarce.

Currently, TRACE is one of 2 ongoing studies evaluating triage of chest pain in Dutch OOH-PC. This provides a unique opportunity to compare results and explore possible regional differences. Wouters *et al.*[16] assessed the accuracy of NTS urgency allocation among patients with chest pain and found that 59.7% of their patient group was assigned with a high urgency level (U1-U2), compared with 61.8% in our sample. Despite slight differences in the definition of clinical endpoints (ACS and other life-threatening events), performance of the NTS algorithm was similar, with a sensitivity and specificity of 73% and 43%, respectively (TRACE: 83.0% and 42.4%). Differences stand out as well, with findings by Wouters *et al.* showing a higher number of underestimated cases (27% versus 17.0% in our study) and greater improvement of triage safety after including triage assistants' own revisions. As described in our results, a more pronounced improvement of safety would occur when we look beyond urgency assessment and consider the course of action following triage or GP-consultation. Here, triage assistants and/or GPs may compensate inappropriate urgencies through the management action that follows (e.g. ambulance deployment or urgent referral despite a low urgency).

Giesen *et al.*[23] performed a more general evaluation of triage assistants' accuracy in 2006. Results of this study showed that triage assistants underestimated urgencies in 19% of 352 contacts and a significant correlation was found between specific training on the use of the NTS guidelines and correct urgency estimation.

This implies that the way triage assistants operate the NTS triage tool may contribute to its performance as well. A second study by Wouters *et al.*[24] qualitatively explored the behavior of triage assistants in their urgency assessment. They found that triage assistants use symptom characteristics and paralanguage (vocal but not worded elements) to create a mental image of the clinical status of the patient. When their assessment was inconsistent with the NTS recommendation, triage assistants used several strategies to make their final decision. One of those strategies was to overrule the given urgency. Another coping strategy was to tinker the NTS responses to make the final recommendation align with the assistant's own assessment (e.g. up- or downgrading pain severity or exploring additional symptoms that might alter the calculated urgency). This may affect the way we ought to interpret our data, since we relied on a written depiction of the triage process, impeding our insight of the dynamics.

While chest pain can be caused by a variety of conditions, including several urgent diagnoses, the structure of the current NTS protocol appears to be

quite ACS-focused. This is also reflected by available research, in which data focused on the ACS prevalence in prehospital settings is more abundant. Here, the prevalence varies from 1.5 to 3.6% in primary care settings[2,9,25], rising to 9.4% among patients visiting the emergency department.[26]

An online survey among Dutch GPs conducted by our research group in 2018 investigated the missed ACS diagnosis rate GPs are willing to accept.[27] Results showed that GPs wish to keep a maximum referral threshold of 50 unnecessary referrals for each ACS diagnosis, and that GPs would accept a 0.1-1.0% missed diagnosis rate in clinical practice. Extrapolating this to our own results, we see that for each diagnosed ACS, 8 patients received a false-positive high urgency code and 6 patients were unnecessarily referred. The missed diagnosis rate amounted to 5.1% of ACS patients. Thus, despite GPs criticism on triage efficiency, triage results in an (more than) acceptable amount of unnecessary referrals, although the missed ACS rate exceeded the desired threshold.

Implications for further research

This study was primarily focused on the performance of telephone triage of patients with chest pain in OOH-PC. Our results illustrate that while urgency assessment is commonly used as a risk-stratification tool, this is often insufficient for a safe and efficient distinction between patients with and without a major event. Further research should focus on ways to improve chest pain evaluation in OOH-PC without overlooking the influence of healthcare professionals operating the system. Improvement might be sought in the content or procedure of the triage process, or by examining ways to improve risk stratification, for instance by using clinical decision rules during triage or GP consultation.[28]

CONCLUSION

The urgency assessment during telephone triage of chest pain in OOH-PC is often inaccurate, particularly when relying on the NTS tool alone. Further exploration of ways to improve telephone triage and OOH-PC decision-making is warranted.

REFERENCES

1. Thim T, Krarup NHV, Grove EL, Rohde CV, Løfgren B. Initial assessment and treatment with the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. *International Journal of General Medicine*. 2012;5:117.
2. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141–6. doi:10.3109/13814780903329528
3. Jansen T, Ramerman L, Verheij R. Data of out-of-hours primary care - Triage: index complaints and urgency allocation. *Nivel Zorgregistraties Eerste Lijn* Geraadpleegd op 21–10–2020 2020;
4. Nilsson S, Scheike M, Engblom D, et al. Chest pain and ischaemic heart disease in primary care. *British Journal of General Practice*. 2003;53:378–382.
5. Smits M, Verheij R. Changes in urgencies of out-of-hours primary care contacts 2013-2016 (Original title: Veranderingen in de urgentie van contacten met de huisartsenpost 2013-2016) *Nivel rapport*. 2017;
6. Svavarsdóttir AE, Jónasson MR, Gudmudsson GH, Fjeldsted K. Chest pain in family practice. *Canadian Family Physician*. 1996;42:1122–1128.
7. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340–347.
8. Harskamp RE, Fanaroff AC, Zhen SW, Sawe HR, Weber EJ. Recognising acute coronary syndrome. *BMJ*. 2022;377
9. Haasenritter J, Biroga T, Keunecke C, et al. Causes of chest pain in primary care - a systematic review and meta-analysis. *Croat Med J*. Oct 2015;56(5):422–30. doi:10.3325/cmj.2015.56.422
10. Steeman L, Uijen M, Plat E, Huibers L, Smits M, Giesen P. Out-of-hours primary care in 26 European countries: an overview of organizational models. *Family practice*. 2020;37(6):744–750.
11. Domus Medica - Netherlands Triage Standard. 2014.
12. Mackway-Jones K, Robertson C. Emergency triage. *BMJ-British Medical Journal-International Edition*. 1997;314(7086):1056.
13. National guidelines for telephone triage and advice in Family Practice. https://onderwerpen.nhg.org/spoedzorg/triagewijzer/
14. Keizer E, Maassen I, Smits M, Wensing M, Giesen P. Reducing the use of out-of-hours primary care services: a survey among Dutch general practitioners. *European Journal of General Practice*. 2016;22(3):189–195.
15. Jansen T, de Hoon S, Zwaanswijk M, Verheij R. Between ambulance and general practitioner *Nivel rapport*. 2016;
16. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA, Zwart DL. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open heart*. 2020;7(2):e001376.

17. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Ann Intern Med* 2007 Oct 16 2007;147(8):574–7. doi:10.7326/0003-4819-147-8-200710160-00010.

18. Manten A, Cuijpers CJJ, Rietveld RP, et al. Rationale and design of an observational cohort study of triage of acute chest pain in out-of-hours primary care in The Netherlans (TRACE). *Primary Health Care Research and Development*.

19. Ploem C, Harskamp RE, van Dijk N, et al. Privacy legislation and scientific research. . *Huisarts & Wetenschap*. 8 januari 2020 2020;

20. Castor Electronic Data Capture, Ciwit BV. 2016. http://castoredc.com

21. Huibers L, Smits M, Renaud V, Giesen P, Wensing M. Safety of telephone triage in out-of-hours care: a systematic review. *Scand J Prim Health Care*. Dec 2011;29(4):198–209. doi:10.3109/02813432.2011.629150

22. Lake R, Georgiou A, Li J, et al. The quality, safety and governance of telephone triage and advice services - an overview of evidence from systematic reviews. *BMC Health Serv Res*. Aug 30 2017;17(1):614. doi:10.1186/s12913-017-2564-x

23. Giesen P, Ferwerda R, Tijssen R, et al. Safety of telephone triage in general practitioner cooperatives: do triage nurses correctly estimate urgency? *Qual Saf Health Care*. Jun 2007;16(3):181–4. doi:10.1136/qshc.2006.018846

24. Wouters LT, Zwart DL, Erkelens DC, et al. Tinkering and overruling the computer decision support system: working strategies of telephone triage nurses who assess the urgency of callers suspected of having an acute cardiac event. *Journal of clinical nursing*. 2020;29(7-8):1175–1186.

25. McConaghy JR, Oza RS. Outpatient Diagnosis of Acute Chest Pain in Adults. *American Family Physician*. 2013;87(1)

26. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC Cardiovasc Disord*. Jun 11 2015;15:48. doi:10.1186/s12872-015-0049-6

27. Harskamp R, van Peet P, Bont J, Ligthart S, Lucassen W, van Weert H. The conundrum of acute chest pain in general practice: a nationwide survey in The Netherlands. *BJGP Open*. Dec 2018;2(4):bjgpopen18X101619. doi:10.3399/bjgpopen18X101619

28. Harskamp RE, Laeven SC, Himmelreich JC, Lucassen WAM, van Weert H. Chest pain in general practice: a systematic review of prediction rules. *BMJ Open*. Feb 27 2019;9(2):e027081. doi:10.1136/bmjopen-2018-027081

SUPPLEMENTAL MATERIAL

Supplement 1. Definition of major and non-major events.

	Final diagnosis	Conditional management
Major event	Death from any cause	
	Acute coronary syndrome	
	Urgent coronary revascularization	
	Pulmonary embolism	
	Thoracic aortic aneurysm (dissection or ruptured)	
	Severe/Acute congestive heart failure	Hospitalization
	Severe peri(myo)carditis	Hospitalization
	Symptomatic atrial fibrillation	Hospitalization (cardioversion or converted through medication)
	Aortic valve stenosis	Hospitalization
	(Tension) pneumothorax	Hospitalization
	Severe pneumonia	Hospitalization
	CVA/TIA	
	Inflammatory processes such as appendicitis, pancreatitis, cholecystitis	Hospitalization
	Other, such as: exacerbation COPD or hypertensive crisis	Hospitalization
	Traumatic event (with significant impact)	Hospitalization
Non-major event	Stable angina pectoris	Outpatient treatment
	Mild congestive heart failure	Outpatient treatment
	Mild peri(myo)carditis	Outpatient treatment
	Atrial fibrillation (recurrent/paroxysmal)	Outpatient treatment
	Hypertension	Outpatient treatment
	Mild pneumothorax	Outpatient treatment
	Mild pneumonia	Outpatient treatment
	Mild respiratory problems (such as viral infections)	
	Gastric/esophagus problems	
	Musculoskeletal	
	Traumatic (mild trauma)	Outpatient treatment
	Mental health/Panic attack/Anxiety disorder	

The table specifies the subdivision between major and non-major events, and states the conditional managements for some of these diagnoses in the right column. *Abbreviations:* COPD, chronic pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Supplement 2. Patient characteristics of the study population (n=1,803).

	Total (*n*=1,803)
Age	54.0 (37.0-70.0)
Sex (female)*	1038 (57.6%)
Pre-existing medical condition (any)	1260 (69.9%)
History of cardiovascular disease	363 (20.1%)
Prior CAD†	296 (16.4%)
Prior stroke/TIA	111 (6.2%)
Prior peripheral arterial disease	40 (2.2%)
Cardiovascular risk factors (any)	938 (52.1%)
Smoking (current)	288 (16.0%)
Hypertension	490 (27.1%)
Hypercholesterolemia	251 (13.9%)
Diabetes mellitus	199 (11.0%)
Chronic use of medication (any)	1079 (59.8%)

The table lists the patient characteristics for the total group of baseline patients. Continuous variables are presented as medians (IQR) due to a non-normal distribution. All categorical variables are presented as frequencies (%). Notes: *The patient sample included 1 transgender patient who transitioned from male to female gender, the sex of this patient was referred to as 'other'. †Prior coronary artery disease (CAD) was defined as a history of either acute or stable coronary syndromes.

Supplement 3. Final diagnoses among patients with a major event.

	Total (*n*=238)
Cardiovascular	**184 (77.3%)**
Acute coronary syndrome	99 (41.6%)
Chronic coronary syndrome *(e.g. stable angina, ischemic disease without angina)*	8 (3.4%)
Atrial fibrillation	38 (16.0%)
Congestive heart failure	13 (5.5%)
Peri(myo)carditis	3 (1.3%)
Aortic aneurysm or dissection	3 (1.3%)
Pulmonary embolism	10 (4.2%)
Cerebrovascular disease *(CVA and TIA)*	2 (0.8%)
Hypertension	2 (0.8%)
Other cardiovascular (*tachycardias, valvular disorders, unspecified complaints)*	6 (2.5%)
Musculoskeletal	**8 (3.4%)**
Respiratory	**23 (9.7%)**
Pneumonia	15 (6.3%)
Pneumothorax	2 (0.8%)
Chronic pulmonary diseases *(e.g. asthma, COPD)*	3 (1.3%)
Respiratory complaints other	3 (1.3%)
Abdominal	**17 (7.1%)**
Stomach and esophageal related complaints/diseases *(e.g. heartburn, reflux disease, nausea, indigestion, epigastric pain)*	2 (0.8%)
Inflammatory & biliary *(appendicitis, chronic enteritis, pancreatitis, cholecystitis w/o cholelithiasis)*	9 (3.8%)
Urological infection or calculi	4 (1.7%)
Other unspecified	2 (0.8%)
Psychological and mental health (*intoxication*)	**1 (0.4%)**
Other *(thyroid disease, diabetes related, fever, anaphylaxis)*	**5 (2.1%)**

The table shows the subdivision of final diagnoses among the patients with a major event. Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 5

Sex differences in chest pain presentation, triage assessment, and outcomes in urgent primary care: findings from the TRACE cohort study

Amy Manten, Bryn Hummel, Renee Bolijn, Remco P. Rietveld, Irene G.M. van Valkengoed, Eric P. Moll van Charante, Ralf E. Harskamp

Published in Primary Health Care Research & Development, 2025

PMID: 40605786

DOI: 10.1017/S1463423625100182

ABSTRACT

Aim: To evaluate sex differences in the triage and assessment of chest pain in Dutch out-of-hours primary care (OOH-PC).

Background: Prior research illustrated differences between women and men with confirmed cardiac ischemia. However, information on sex differences among patients with undifferentiated chest pain is limited and current protocols used to assess chest pain in urgent primary care in the Netherlands do not account for potential sex differences.

Methods: A retrospective cohort study of consecutive patients who contacted a large OOH-PC facility in the Netherlands in 2017 regarding chest pain. We performed descriptive analyses on sex differences in patient and symptom characteristics, triage assessment, and subsequent clinical outcomes, including acute coronary syndrome (ACS).

Findings: A total of 1,802 patients were included, the median age was 54 years and 57.6% were female. Compared to men, women less often had a history of cardiovascular disease (CVD) (16.0% vs 25.8%, p<0.001) or cardiovascular risk factors (49.3% vs 56.0%, p=0.005). Symptom characteristics were comparable between sexes. While triage urgencies were more frequently altered in women, the resulting triage urgencies were comparable, including ambulance activation rates (31.1% and 33.5%, respectively, p=0.33). Musculoskeletal causes were the most common in both sexes; but women were less likely to have an underlying cardiovascular condition (21.1% vs 29.6%, p<0.001), including ACS (5.4% vs 8.5%, p=0.019).

Conclusion: Women more frequently sought urgent primary care for chest pain than men. Despite a lower overall risk for cardiovascular events in women, triage assessment and ambulance activation rates were similar to those in men, indicating a potentially less efficient and overly conservative triage approach for women.

INTRODUCTION

Chest pain is a common medical complaint in primary care. During office-hours, 0.7-2.7% of all general practitioner (GP) consultations are related to chest pain, of which the majority usually concerns female patients.[1-5] In out-of-hours primary care (OOH-PC) settings, chest pain is among the top 10 of chief complaints.[6] Chest pain often presents a diagnostic dilemma, as the majority of patients suffer from non-life-threatening conditions, while severe underlying cardiovascular conditions, including acute coronary syndrome (ACS), are only present in approximately one out of every 8-12 patients.[3,7,8]

To aid adequate patient assessment in OOH-PC, triage protocols are in place, which rely on a number of patient and symptom characteristics. Remarkably, the patient's sex is not included in the Dutch triage protocols. This is relevant since prior studies on selected populations with proven cardiac ischemia showed more atypical symptom presentations, increased delay in diagnosis and treatment, and subsequent poorer outcomes in women.[9-17] However, information on sex-related differences in triage assessment of patients with undifferentiated chest pain is limited, and the applicability of the triage protocols in women and men separately is insufficiently examined.

Considering the broad range of possible underlying causes of chest pain and the importance of safe and efficient risk stratification in both women and men presenting with chest pain, we aimed to assess sex differences throughout the current Dutch triage protocol for chest pain in urgent primary care. We evaluated differences in patient- and symptom characteristics, triage assessment, and subsequent clinical outcomes in adult women and men who contacted an OOH-PC facility with a chief complaint of chest pain.

METHODS

We reported our study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline.[18] The study protocol was approved by our institution's Medical Ethical Committee and registered in the Dutch Trial Register (TRACE NL7581).[19]

This analysis is part of the "TRiage of Acute Chest pain Evaluation in primary care" (TRACE) cohort study.[20] In short, we performed a retrospective, observational cohort study of patients who contacted the OOH-PC facility in Alkmaar, the Netherlands, in 2017, with chest pain as the main reason for contact. At the outset of the study, all patients received information by mail and were provided with the opportunity to opt-out from sharing data. A more

elaborate description of TRACE study methods was published previously[20] and can also be found at https://www.amstelheart.nl.

Background and healthcare setting

In the Netherlands, all citizens are registered with a local GP's office that holds an electronic patient record file. When offices are closed, urgent primary care is handled through regional OOH-PC facilities.[21] The facility in Alkmaar is responsible for OOH-PC services for 98 affiliated GPs, representing a community of approximately 240,000 individuals living in both urban and rural areas.

To handle the high demand for care, OOH-PC facilities operate a (telephone) triage system, executed by trained triage assistants following standardised computer-based protocols by the Netherlands Triage Standard (NTS).[22] After a short check of the patient's hemodynamic status (mainly by assessing consciousness and breathing), the protocol for chest pain continues with 7 hierarchically structured questions regarding the characteristics of the complaint (i.e. type, duration, severity, course, location, pain radiance, and associated symptoms).[22,23] Based on the answers, the NTS algorithm calculates an urgency category, varying from urgency level 1 to 5, linked to a recommended 'time-until-care' (i.e. U1 – most urgent, immediate care, U5 – non-urgent, care within 24 hours). Triage assistants include their own assessment of the patient's condition and may overrule the proposed urgency code after consulting the attending physician. Possible responses following telephone triage include ambulance activation, consultation by a GP (either at the OOH-PC facility or at the patient's home), telephone advice, and deferral to the own GP during office hours.

Study population and size

We enrolled consecutive women and men contacting the OOH-PC facility with chest pain between January 1st 2017 and December 31st 2017. We excluded patients who objected to participate in the study, patients aged <18 years, patients who bypassed the triage process, and patients who had already died and for whom the OOH-PC was requested for a visit for formal death confirmation (*Figure 1*). Patients who directly contacted emergency services (i.e. ambulance services) were not enrolled.

Data collection and outcomes of interest

Data from the digital triage registry were linked to information from the GP's patient record file. After de-identification, data were entered into a secure

electronic data capturing platform (Castor EDC, Ciwit BV, Amsterdam, The Netherlands).[24] Gathered data include patient demographics (i.e. age and sex, defined as either male or female), medical history (with specific attention for cardiovascular risk factors and sex-specific risk factors), triage results and clinical outcomes. We aimed our main focus on cardiovascular outcomes (including ACS). Secondarily, we assessed the occurrence of a major event within 6 weeks of initial contact. We defined major events as a composite of all-cause mortality, and both cardiovascular and non-cardiovascular urgent conditions, that were linked to the initial complaint of chest pain, and required hospital admittance or urgent in-hospital treatment (*Supplement 1*).[25] Final diagnoses were verified using source documentation, including hospitalization and/or discharge letters related to the index consultation. We countered inter-observer variability between investigators by the use of standard operating procedures and by an internal audit of patients' baseline data.

Data analysis

Sex differences in patient- and symptom characteristics, triage results, and clinical outcomes were assessed using the Mann-Whitney-U test (continuous variables) and chi-square tests (categorical variables). P-values <0.05 were considered statistically significant. Within triage results, we focused on urgency code adjustments made by the triage assistants. We performed logistic regression modeling to identify factors associated with urgency code alterations. We included sex, age, variables indicating cardiovascular burden (i.e. prior cardiovascular disease (CVD) and cardiovascular risk factors), and symptom characteristics suggestive of an ACS (i.e. tightness, severe pain, presence of pain radiance, and associated symptoms). Furthermore, we conducted subgroup analyses comparing women and men diagnosed with ACS to identify possible sex differences among ACS patients. We assessed the diagnostic accuracy of U1 urgency allocation for women and men with ACS using sensitivity and specificity.

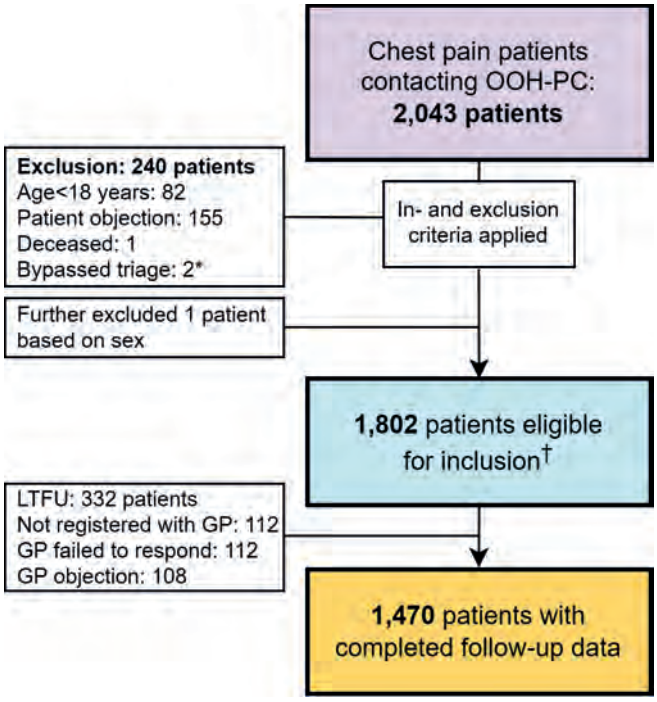
Categorical data were reported as frequencies. Non-normal distributed continuous variables were identified using histograms and expressed as medians (IQR). All analyses were carried out using IBM SPSS Statistics for Windows, version 28 (IBM Corp., Armonk, N.Y., USA).

RESULTS

Patient characteristics

Our study population consisted of 1,802 patients, of which 1,038 (57.6%) were female (*Figure 1*). The median age was 54 years in both sexes (*Table 1*). Female patients less frequently had a history of CVD or cardiovascular risk factors compared to male patients. Out of the total study population, immediate ambulance activation was followed in 23 patients with signs of hemodynamic instability, this number was comparable between women and men (*n*=17 vs *n*=6, p=0.14). In the remaining 1,779 patients (57.4% women), triage followed with detailed assessment of symptom characteristics. While we found no sex differences in most symptom characteristics, we did observe subtle differences, as men did more often report mild pain and left-sided localisation compared to women, while women more often reported retrosternal pain and radiance (both typical and atypical).

Figure 1. Flowchart showing in- and exclusion of patients.



A total of 2,043 patients contacted the OOH-PC facility regarding chest pain in 2017. During exclusions, one additional participant had to be excluded from the current analyses due to unclear information regarding their sex. *Two patients bypassed the triage system entirely and were excluded from the dataset. †Among the 1,802 included patients, 23 patients were deemed hemodynamically unstable, resulting in discontinuation of triage and immediate action. Symptom characteristics were therefore analyzed among the remaining 1,779 patients. Follow-up data including final diagnoses were gathered in 1,470 patients. Abbreviations: GP, general practitioner; LTFU, loss to follow-up; OOH-PC, out-of-hours primary care.

Table 1. Patient and symptom characteristics among the women and men in our study population.

	Women	Men	p
Patient characteristics	1,038 (57.6)	764 (42.4)	<0.001
Age	54 (36-70)	54 (37-70)	1.00
Prior CVD*	166 (16.0)	197 (25.8)	<0.001
Cardiovascular risk factors†	512 (49.3)	428 (56.0)	0.005
Symptom characteristics	1,021 (57.4)	758 (42.6)	<0.001
Type of pain			
Tightness/pressure	503 (49.3)	344 (45.4)	0.11
Stabbing/sharp	240 (23.5)	197 (26.0)	0.23
Fixed to respiration	113 (11.1)	88 (11.6)	0.72
Unknown/unclear	154 (15.1)	116 (15.3)	0.90
Duration of chest pain			
<12 hours	604 (59.2)	465 (61.3)	0.35
>12 hours	414 (40.5)	292 (38.5)	0.39
Chest pain severity (1-10 point scale)			
Mild (<4)	158 (15.5)	162 (21.4)	0.001
Moderate (5-7)	499 (48.9)	345 (45.5)	0.16
Severe (8-10)	155 (15.2)	107 (14.1)	0.53
Pain has subsided / no pain	190 (18.6)	129 (17.0)	0.39
Course of chest pain			
Gradual increase in intensity	504 (49.4)	361 (47.6)	0.47
Atypical and subsided	127 (12.4)	93 (12.3)	0.91
Typical and subsided	29 (2.8)	32 (4.2)	0.11
Rapidly progressive	58 (5.7)	44 (5.8)	0.91
Location on the chest			
Left chest	305 (29.9)	268 (35.4)	0.014
Right chest	149 (14.6)	101 (13.3)	0.45
Middle (retrosternal)	329 (32.2)	210 (27.7)	0.040
Pain radiation‡			
Typical cardiac radiation	307 (30.1)	189 (24.9)	0.017
Atypical radiation	147 (14.4)	84 (11.1)	0.040
Location not specified	72 (7.1)	59 (7.8)	0.56
No radiation	410 (40.2)	331 (43.7)	0.14

continues

continued			
Associated symptoms[§]			
Present	214 (21.0)	157 (20.7)	0.90
Subsided	50 (4.9)	46 (6.1)	0.28
No associated symptoms	647 (63.4)	471 (62.1)	0.60

Patient flow in the table: in total, 1,802 patients were included in the study, 1,038 women and 764 men. When assessing symptom characteristics, 1,779 patients (1,021 women and 758 men) could be analyzed. In the remaining 23 patients, triage was discontinued before symptoms could be discussed due to signs of hemodynamic instability (e.g. unconsciousness or severe dyspnea). In these patients, an ambulance was deployed immediately. *Cardiovascular disease (CVD) was defined as a history of myocardial infarction, transient ischemic attack, cerebrovascular accident, peripheral artery disease, previous percutaneous coronary intervention, and/or coronary artery bypass grafting. †Cardiovascular risk factors include prior CVD, a history of diabetes, hypertension, hypercholesterolemia, obesity, smoking, and/or a positive family history for cardiovascular disease. For women, a history of gestational hypertension or (pre)eclampsia were also considered cardiovascular risk factors. ‡Pain radiance was considered typical when the arm(s), shoulder(s), jaw(s) or throat were affected. All other locations of radiation were considered atypical. §Associated symptoms include the presence of sweating, nausea, vomiting, pallor, anxiety, fainting and/or near collapse. Continuous data are presented as a median and interquartile range due to a non-normal distribution. All categorical data are presented as number and percentage.

Triage: urgency code assignment and resulting action

In both women and men, triage often resulted in the allocation of urgency codes U1-U3, as is shown in *Table 2*. We found that in female patients, the initial urgency code was more frequently altered compared to men (16.4% vs 12.9%, p=0.045). After adjusting for possible confounders, female sex remained a factor associated with urgency code alteration (also see *Table 3*). Alterations can be divided in 'downscaling' (58.9% of revised urgencies, in 9.7% of women and 7.5% of men, p=0.11), 'upscaling' (32.1%, in 5.2% of women and 4.2% of men, p=0.34), and urgency codes that eventually remained equal to initial ones. Alterations of urgency codes by age strata can be found in *Supplemental Figure 2*.

The action following triage showed no significant differences between women and men. In both, telephone triage most frequently resulted in GP consultation, either at the OOH-PC facility or through a home-visit (women 56.0%, men 55.3%, p=0.75). Ambulance deployment followed in 31.3% of women and 33.5% of men (p=0.33).

Table 2. Urgency code allocation following triage.

	NTS urgency			Final urgency		
	Women (*n*=1,021)	**Men** (*n*=758)	**p**	**Women** (*n*=1,021)	**Men** (*n*=758)	**p**
U1	367 (35.9)	278 (36.7)	0.75	295 (28.9)	238 (31.4)	0.25
U2	237 (23.2)	156 (20.6)	0.19	322 (31.5)	194 (25.6)	0.006
U3	335 (32.8)	262 (34.6)	0.44	330 (32.3)	267 (35.2)	0.20
U4	3 (0.3)	2 (0.3)	1.00	3 (0.3)	5 (0.7)	0.30
U5	49 (4.8)	42 (5.5)	0.48	41 (4.0)	35 (4.6)	0.54
Not registered	30 (2.9)	18 (2.4)	0.47	30 (2.9)	19 (2.5)	0.58

The left side of the table illustrates the initial urgency codes calculated by the NTS algorithm based on the registered answers to the triage questions. On the right side of the table, the final urgency codes are displayed. These represent the urgency code allocation after correcting for revisions made by the triage assistants (i.e. up- and down-scaling).
Definition of urgency codes and their recommended 'time-until-care'.
U1: Life threatening (immediate: ambulance activation)
U2: Emergent (care <60 minutes)
U3: Urgent, circumstantial risk of harm (care within several hours)
U4: Non-urgent, low risk of harm (care within 24 hours)
U5: No risk of harm (advice)

Table 3. Results of multivariable logistic regression for urgency code alteration.

Variable	Coefficient	Significance	Exp (β)	95% Confidence interval
Age*	-0.090	0.023	0.914	0.846 - 0.988
Female sex	-0.274	0.049	0.760	0.578 - 0.999
Prior CVD†	-0.197	0.38	0.821	0.531 - 1.270
Cardiovascular risk factors‡	0.017	0.92	1.017	0.746 - 1.386
Tightness/pressure type pain	-0.297	0.046	0.743	0.554 - 0.995
Severe pain	-0.064	0.75	0.938	0.630 - 1.398
Typical radiation§	-0.036	0.83	0.965	0.690 - 1.349
Associated symptoms present	-0.061	0.75	0.941	0.651 - 1.360

* Age was stratified in age-categories (18-29 | 30-39 | 40-49 | 50-59 | 60-69 |70-79 | 80-89 | >90).
† Cardiovascular disease (CVD) was defined as a history of myocardial infarction, transient ischemic attack, cerebrovascular accident, peripheral artery disease, previous percutaneous coronary intervention, and/or coronary artery bypass grafting.
‡ Cardiovascular risk factors include prior CVD, a history of diabetes, hypertension, hypercholesterolemia, obesity, smoking, and/or a positive family history for cardiovascular disease. For women, a history of gestational hypertension or (pre)eclampsia were also considered cardiovascular risk factors.
§ Radiation was considered typical when the arm(s), shoulder(s), jaw(s) or throat were affected.

Clinical outcomes

Follow-up information, including clinical outcomes, was available for 1,470 (81.6%) patients, with comparable sex ratios to our total sample (57.8% women). A musculoskeletal cause of chest pain was found most commonly in both women and men (*Table 4*). Major events occurred more often in men compared to women (129 (20.8%) vs 109 (12.8%), p<0.001). The majority of major events were of cardiac origin, including ACS, atrial fibrillation or heart failure. *Supplemental Table 3* provides an overview of specific major event diagnoses for women and men. We found no difference in fatal outcomes, with fatal outcomes in 13 (1.5%) women and nine (1.4%) men during the first 6 weeks following index presentation (p=1.00).

Table 4. Distribution of final diagnoses.

	Women (*n*=849)	**Men** (*n*=621)	**p**
Cardiovascular diagnosis	179 (21.1)	184 (29.6)	<0.001
Acute coronary syndrome	46 (5.4)	53 (8.5)	0.019
Musculoskeletal	399 (47.0)	274 (44.1)	0.28
Respiratory	75 (8.8)	50 (8.1)	0.60
Abdominal	98 (11.5)	54 (8.7)	0.08
Psychological and mental health	62 (7.3)	41 (6.6)	0.60
Other	36 (4.2)	18 (2.9)	0.18

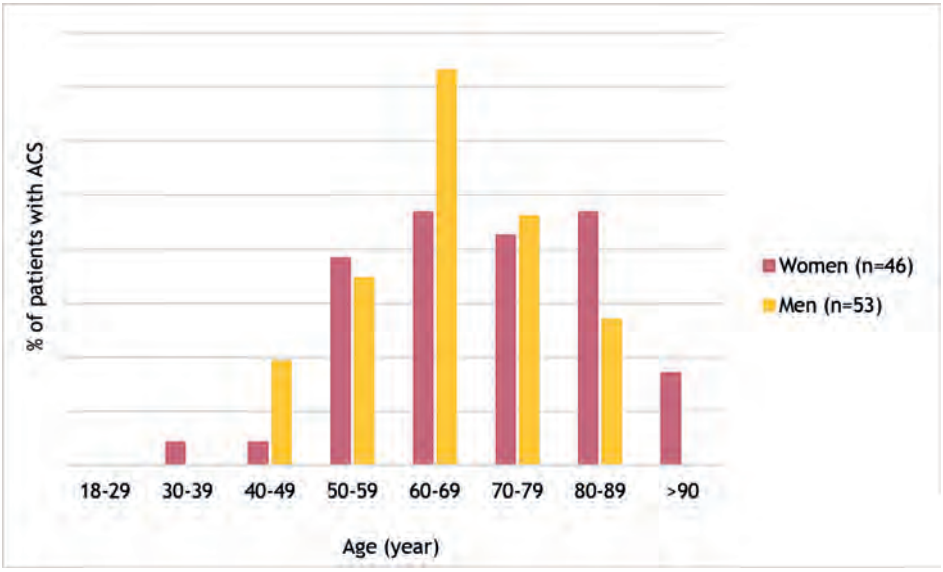
The table shows the distribution of final diagnoses among women and men with completed follow-up data. Abbreviations: acute coronary syndrome (ACS).

Triage of patients with ACS

In total, 99 patients were diagnosed with ACS, 53 (8.5%) men and 46 (5.4%) women (p=0.019). *Supplemental Table 4* provides a comparison of characteristics between women and men with ACS. Among these selected patients, there were no significant differences in patient- (i.e. age, CVD history and cardiovascular risk factors) and symptom characteristics. When patients with an ACS are stratified by age and sex (*Figure 2*), differences are noticeable among patients aged 60-69 years, however not statistically significant (p=0.20). The difference between women and men aged >90 is significant (p=0.043). Triage results were also similar among female and male ACS patients. In women, final U1 codes were allocated to 33/46 ACS patients, reflecting a sensitivity of 71.7% [95%-CI: 56.5-84.0] and specificity of 71.2% [68.0-74.3]. In men, final U1 codes were registered in 34/53 ACS patients, with a corresponding sensitivity and specificity of 64.2% [49.8-76.9] and 71.0% [67.0-

74.7], respectively. Furthermore, triage resulted in ambulance activation in 82.6% of women with an ACS and 66.0% of men with an ACS, p=0.06.

Figure 2. Patients diagnosed with ACS, stratified by age and sex.



The figure illustrates the difference between the 46 women and 53 men with an ACS, divided in decimal age groups.
P-values: 1.00 (30-39), 0.21 (40-49), 0.74 (50-59), 0.20 (60-69), 0.91 (70-79), 0.17 (80-89), 0.043 (>90).

DISCUSSION

In this study, we evaluated possible differences between women and men in patient- and symptom-characteristics, triage assessment, and clinical outcomes of acute chest pain in a regional, out-of-hours urgent primary care facility. We found that women more often contact OOH-PC with chest pain and that women who contacted the facility had an overall lower a priori cardiovascular risk, and similar symptom presentation when compared to men. While urgency code alterations were more common in women, resulting actions were comparable. Women were less likely to have an underlying major event, including cardiovascular diagnoses and ACS. The most commonly reported final diagnosis among both women and men was musculoskeletal pain.

Strengths and limitations

Our study involved a large consecutive sample of 1,802 patients who underwent structural and protocol-mandated symptom- and risk-assessment at a large-scale OOH-PC facility. Therefore, the results are likely to be generalizable to other OOH-PC facilities in the Netherlands. We optimised data quality by an internal audit of baseline data and by adjudication of registered final diagnoses.

The first and most important limitation is the presence of differential verification bias. Our study involved routine care data from a primary-care-based, retrospective, and observational study, in which we had no influence on the diagnostic work-up following primary care assessment. Therefore, although unlikely, the absence of urgent clinical outcomes (such as missed ACS cases) cannot be guaranteed in patients who were not referred to secondary care. Moreover, in a mentionable number of patients, data on clinical outcomes could not be obtained due to GPs failing to respond, or GPs who expressed liability concerns due to the recent implementation of European privacy regulations. The latter led them to refuse to provide follow-up data for their patients, despite the proven validity of the opt-out procedure.[26] However, this did not appear to differently affect female and male patients; hence, the consequences for our stratified analyses may be limited.

How our findings fit in with existing literature

Overall, the majority of our patients were female, and in both sexes, the majority of final diagnoses were of musculoskeletal origin. Both of these findings are consistent with previous research in acute primary care settings.[1,4,5] The higher incidence of ACS among men with chest pain compared to women is supported by earlier findings[9,27-29], as well as by two other Dutch studies conducted between 2013 and 2016 that illustrated ACS incidences of around 8% for women and 14% for men.[8,30] Furthermore, in these studies, triage resulted in equally high urgency codes in women and men (i.e. U1 or U2 code in 68.7% of women and 68.2% of men in Wouters *et al.*; 65.6% and 64.9% in van der Meer et al, respectively). In our study, 60.4% of women and 57.0% of men received either an U1 or U2 code (p=0.15), and ambulance activation rates were similar as well. Thus, despite a lower a-priori risk of ACS, triage assessment is comparable between women and men, leading to relatively more cautious triage in women (i.e. more unnecessary high urgencies).

This increased cautiousness in pre-hospital care may be related to the rising attention for unrecognized CVD in women. Although contradictory to our own results, others reported differences in the management of women and men with acute chest pain in prehospital settings. An Australian study by Dawson *et al.*[11] assessed sex differences in the care pathway from emergency

medical services (i.e. ambulance services) through to clinical outcomes following discharge. At the outset, women had a less pronounced risk profile compared to men, and throughout the care pathway, women (both total and ACS diagnosed) were less likely to receive guideline-directed care (e.g. more delays, less likely to be admitted or undergo coronary angiography). Eventually, mortality rates were higher among the women with a STEMI compared to men with STEMI. Albeit, many of these outcome measures concern management in secondary care and surpass the urgent primary care setting that we studied.

When we pursue the direction towards secondary care further, we see that research on sex differences among selected, hospital-based patients with cardiac ischemia shows conflicting results. Some studies illustrate that women with ACS are more likely to have an atypical symptom presentation, report chest pain less frequently, and tend to experience more additional symptoms, such as back pain, loss of appetite, and nausea.[9,17,31] In contrast, studies that employ systematic symptom reporting illustrate more similarities than differences, both in primary and secondary care settings.[32,33] While speculative, these differences might be the result of reporting and spectrum biases. At the very least, we can state that findings in urgent primary care are consistent in that sex differences are limited, and overall a more cautious triage route is opted in women, which in hindsight leads to more unnecessary ambulance deployments and emergency care evaluation in women than men.

Implications for further research

Adequate triage of undifferentiated chest pain remains a challenge in both women and men. Our study found that women and men are managed equally by the current triage system. Triage results in similar actions – despite differences in a priori risk of urgent clinical outcomes – resulting in relatively more cautious triage in women compared to men. Based on these results, future efforts to improve triage should investigate whether the addition of sex enhances risk stratification, independently from the cardiovascular risk burden.

Furthermore, a more extensive patient sample, also including patients with chest pain who contacted the national emergency number (i.e. ambulance services) would be beneficial to our understanding of urgent pre-hospital care. In addition, as prior research shows that ACS patients do not exclusively present themselves with chest pain, evaluation of other primary complaints, such as dyspnoea, would be valuable.

CONCLUSION

Our study illustrates more similarities than differences between women and men presenting with chest pain to urgent primary care. Women generally exhibit a lower cardiovascular risk profile and experience fewer adverse cardiovascular outcomes, including ACS. Despite this lower risk, current triage protocols do not account for these sex differences, resulting in a less efficient and relatively conservative triage approach for women. Future research should explore the potential benefits of incorporating sex as an additional risk factor in risk stratification tools.

REFERENCES

1. Bösner S, Becker A, Haasenritter J, et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. *Eur J Gen Pract*. 2009;15(3):141–6. doi:10.3109/13814780903329528
2. Frese T, Mahlmeister J, Heitzer M, Sandholzer H. Chest pain in general practice: Frequency, management, and results of encounter. *Journal of Family Medicine and Primary Care*. 2016;5(1)doi:10.4103/2249-4863.184625
3. Nilsson S, Scheike M, Engblom D, et al. Chest pain and ischaemic heart disease in primary care. *British Journal of General Practice*. 2003;53:378–382.
4. Svavarsdóttir AE, Jónasson MR, Gudmudsson GH, Fjeldsted K. Chest pain in family practice. *Canadian Family Physician*. 1996;42:1122–1128.
5. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340–347.
6. Jansen T, Ramerman L, Verheij R. Data of out-of-hours primary care - Triage: index complaints and urgency allocation. *Nivel Zorgregistraties Eerste Lijn* Geraadpleegd op 21–10–2020 2020;
7. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart*. Nov 2017;103(21):1727–1732. doi:10.1136/heartjnl-2016-310905
8. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA, Zwart DL. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open heart*. 2020;7(2):e001376.
9. Arora G, Bittner V. Chest pain characteristics and gender in the early diagnosis of acute myocardial infarction. *Curr Cardiol Rep*. Feb 2015;17(2):5. doi:10.1007/s11886-014-0557-5
10. Chiha J, Mitchell P, Gopinath B, Plant AJH, Kovoor P, Thiagalingam A. Gender differences in the severity and extent of coronary artery disease. *Int J Cardiol Heart Vasc*. 2015 July 30 2015;8:161–166. doi:10.1016/j.ijcha.2015.07.009
11. Dawson LP, Nehme E, Nehme Z, et al. Sex Differences in Epidemiology, Care, and Outcomes in Patients With Acute Chest Pain. *J Am Coll Cardiol*. Mar 14 2023;81(10):933–945. doi:10.1016/j.jacc.2022.12.025
12. Jones E, Eteiba W, Bairey Merz N. Cardiac Syndrome X and Microvascular Coronary Dysfunction. *Trends Cardiovasc Med*. 2012;22(6):161–168.
13. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. . *Heart*. 2020;106:487–492.
14. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women. A Scientific Statement From the American Heart Association. . *Circulation*. 2016;133:916–947.
15. Perdoncin E, Duvernoy C. Treatment of coronary artery disease in women. *Methodist DeBakey cardiovascular journal*. 2017;13(4):201.

16. Shaw JL, Merz CNB, Pepine CJ, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part I: gender differences in traditional and novel risk factors, symptom evaluation, and gender-optimized diagnostic strategies. *J Am Coll Cardiol*. 2006 Feb 7 2006;47:S4–S20. doi:10.1016/j.jacc.2005.01.072

17. Shin JY, Martin R, Suls J. Meta-analytic evaluation of gender differences and symptom measurement strategies in acute coronary syndromes. *Heart Lung*. Jul–Aug 2010;39(4):283–95. doi:10.1016/j.hrtlng.2009.10.010

18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *Ann Intern Med* 2007 Oct 16 2007;147(8):574–7. doi:10.7326/0003-4819-147-8-200710160-00010.

19. Register NT. Netherlands Trial Register - NL7581. https://www.trialregister.nl/trial/7581

20. Manten A, Cuijpers CJ, Rietveld R, et al. Rationale and design of a cohort study evaluating triage of acute chest pain in out-of-hours primary care in the Netherlands (TRACE). *Primary Health Care Research & Development*. 2020;21

21. Smits M, Rutten M, Keizer E, Wensing M, Westert G, Giesen P. The Development and Performance of After-Hours Primary Care in the Netherlands: A Narrative Review. *Ann Intern Med*. May 16 2017;166(10):737–742. doi:10.7326/M16-2776

22. Domus Medica - Netherlands Triage Standard. 2014.

23. Zeilstra R, Giesen P. Pijn op de borst: huisarts of ambulance? *Huisarts & Wetenschap*. 2017;60(10)

24. Castor Electronic Data Capture, Ciwit BV. 2016. http://castoredc.com

25. Manten A, De Clercq L, Rietveld R, Lucassen W, Moll van Charante E, Harskamp R. Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care. *Netherlands Heart Journal*. 2022:1–7.

26. Ploem C, Harskamp RE, van Dijk N, et al. Privacy legislation and scientific research. . *Huisarts & Wetenschap*. 8 januari 2020 2020;

27. Hillinger P, Twerenbold R, Wildi K, et al. Gender-specific uncertainties in the diagnosis of acute coronary syndrome. *Clin Res Cardiol*. Jan 2017;106(1):28–37. doi:10.1007/s00392-016-1020-y

28. Leite L, Baptista R, Leitao J, et al. Chest pain in the emergency department: risk stratification with Manchester triage system and HEART score. *BMC Cardiovasc Disord*. Jun 11 2015;15:48. doi:10.1186/s12872-015-0049-6

29. Rubini Gimenez M, Reiter M, Twerenbold R, et al. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. *JAMA Intern Med*. Feb 1 2014;174(2):241–9. doi:10.1001/jamainternmed.2013.12199

30. van der Meer MG, Appelman Y, Rutten KH, et al. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open*. 2019;9(11):e031613.

31. Arslanian-Engoren C, Engoren M. Physiological and anatomical bases for sex differences in pain and nausea as presenting symptoms of acute coronary syndromes. *Heart Lung*. Sep–Oct 2010;39(5):386–93. doi:10.1016/j.hrtlng.2009.10.013

32. DeVon HA, Rosenfeld A, Steffen AD, Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *Journal of the American Heart Association*. 2014;3(2):e000586.

33. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. *European heart journal*. 2011;32(24):3107–3114.

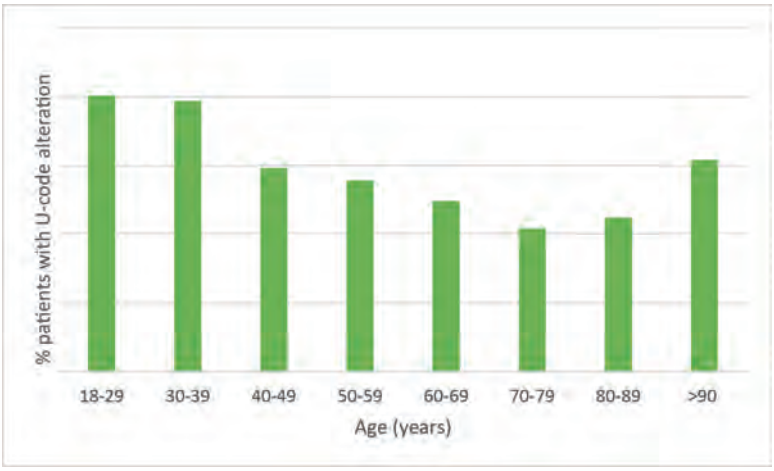
SUPPLEMENTARY MATERIAL

Supplement 1. Definition of major and non-major events.

	Final diagnosis	Condition
Major event	Death from any cause	
	Acute coronary syndrome	
	Urgent coronary revascularization	
	Pulmonary embolism	
	Thoracic aortic aneurysm (dissection or ruptured)	
	Severe/Acute congestive heart failure	Hospitalization
	Severe peri(myo)carditis	Hospitalization
	Symptomatic atrial fibrillation	Hospitalization (cardioversion or converted through medication)
	Aortic valve stenosis	Hospitalization
	(Tension) pneumothorax	Hospitalization
	Severe pneumonia	Hospitalization
	CVA/TIA	
	Inflammatory processes such as appendicitis, pancreatitis, cholecystitis	Hospitalization
	Other, such as: exacerbation COPD or hypertensive crisis	Hospitalization
	Traumatic event (with significant impact)	Hospitalization
Non-major event	Stable angina pectoris	Outpatient treatment
	Mild congestive heart failure	Outpatient treatment
	Mild peri(myo)carditis	Outpatient treatment
	Atrial fibrillation (recurrent/paroxysmal)	Outpatient treatment
	Hypertension	Outpatient treatment
	Mild pneumothorax	Outpatient treatment
	Mild pneumonia	Outpatient treatment
	Mild respiratory problems (such as viral infections)	
	Gastric/oesophagus problems	
	Muscoloskeletal	
	Traumatic (mild trauma)	Outpatient treatment
	Mental health/Panic attack/Anxiety disorder	

This table specifies the subdivision between major and non-major events, and states the additional condition for some of these diagnoses in the right column. Abbreviations: COPD, chronic pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Supplement 2. Patients with an urgency code alteration, stratified by age.



The total number of patients presented in graph: 265.

Supplement 3. Major events among women and men: specified final diagnoses.

	Women (*n*=849)	**Men** (*n*=621)	**p**
Major event *(total)*	**109 (12.8)**	**129 (20.8)**	**<0.001**
Cardiovascular	82 (9.7)	102 (16.4)	<0.001
Acute coronary syndrome	46 (5.4)	53 (8.5)	0.019
Chronic coronary syndrome *(e.g. stable angina, ischemic disease without angina)*	5 (0.6)	3 (0.5)	1.00
Atrial fibrillation	19 (2.2)	19 (3.1)	0.34
Congestive heart failure	6 (0.7)	7 (1.1)	0.40
Peri(myo)carditis	1 (0.1)	2 (0.3)	0.58
Aortic aneurysm or dissection	-	3 (0.5)	0.08
Pulmonary embolism	2 (0.2)	8 (1.3)	0.022
Cerebrovascular disease *(CVA and TIA)*	1 (0.1)	1 (0.2)	1.00
Hypertension	1 (0.1)	1 (0.2)	1.00
Other cardiovascular (*tachycardias, valvular disorders, unspecified complaints)*	3 (0.4)	3 (0.5)	0.70
Musculoskeletal	6 (0.7)	2 (0.3)	0.48
Respiratory	10 (1.2)	13 (2.1)	0.16
Pneumonia	5 (0.6)	10 (1.6)	0.05
Pneumothorax	1 (0.1)	1 (0.2)	1.00
Chronic pulmonary diseases *(e.g. asthma, COPD)*	2 (0.2)	1 (0.2)	1.00
Respiratory complaints other	2 (0.2)	1 (0.2)	100
Abdominal	8 (0.9)	9 (1.4)	0.37
Stomach and esophageal related complaints/ diseases *(e.g. heartburn, reflux disease, nausea, indigestion, epigastric pain)*	1 (0.1)	1 (0.2)	1.00
Inflammatory & biliary *(appendicitis, chronic enteritis, pancreatitis, cholecystitis w/o cholelithiasis)*	4 (0.5)	5 (0.8)	0.51
Urological infection or calculi	2 (0.2)	2 (0.3)	1.00
Other unspecified	1 (0.1)	1 (0.2)	1.00
Psychological and mental health (*intoxication*)	1 (0.1)	-	1.00
Other *(thyroid disease, diabetes related, fever, anaphylaxis)*	2 (0.2)	3 (0.5)	0.66

The table shows the total amount of major event for each sex and the subdivision of specific major event diagnoses. 'Major events' is a composite of all-cause mortality and urgent cardiovascular and non-cardiovascular conditions, occurring within 6 weeks of initial contact. Abbreviations: COPD, chronic pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Supplement 4. Patient and symptom characteristics among women and men with ACS.

	Women With ACS	Men With ACS	p
Patient characteristics	46 (5.4)	53 (8.5)	0.019
Age	70 (61-83)	67 (57-75)	0.07
Prior CVD*	19 (41.3)	21 (39.6)	0.87
Cardiovascular risk factors†	38 (82.6)	41 (77.4)	0.52
Symptom characteristics	45 (5.4)	53 (8.6)	0.015
Type of pain			
Tightness/pressure	38 (84.4)	34 (64.2)	0.023
Stabbing/sharp	3 (6.7)	3 (5.7)	1.00
Fixed to respiration	-	1 (1.9)	1.00
Unknown/unclear	4 (8.9)	13 (24.5)	0.042
Duration of chest pain			
<12 hours	38 (84.4)	41 (77.4)	0.38
>12 hours	7 (15.6)	12 (22.6)	0.38
Chest pain severity (1-10 point scale)			
Mild (<4)	9 (20.0)	9 (17.0)	0.70
Moderate (5-7)	15 (33.3)	23 (43.4)	0.31
Severe (8-10)	14 (31.1)	14 (26.4)	0.61
Pain has subsided / no pain	7 (15.6)	6 (11.3)	0.54
Course of chest pain			
Gradual increase in intensity	8 (17.8)	12 (22.6)	0.55
Atypical and subsided	4 (8.9)	3 (5.7)	0.70
Typical and subsided	-	4 (7.5)	0.12
Rapidly progressive	7 (15.6)	2 (3.8)	0.08
Location on the chest			
Left chest	5 (11.1)	7 (13.2)	0.75
Right chest	1 (2.2)	2 (3.8)	1.00
Middle (retrosternal)	21 (46.7)	18 (34.0)	0.20
Pain radiation‡			
Typical cardiac radiation	22 (48.9)	27 (50.9)	0.84
Atypical radiation	2 (4.4)	4 (7.5)	0.68
Location not specified	2 (4.4)	2 (3.8)	1.00
No radiation	9 (20.0)	12 (22.6)	0.75
Associated symptoms§			
Present	21 (46.7)	24 (45.3)	0.89

continues

continued

Subsided	3 (6.7)	7 (13.2)	0.34
No associated symptoms	11 (24.4)	16 (30.2)	0.53

Patient flow in the table: 46 women and 53 men were diagnosed with an ACS. Symptom characteristics could not be assessed in one of the female patients due to hemodynamic instability. *Cardiovascular disease (CVD) was defined as a history of myocardial infarction, transient ischemic attack, cerebrovascular accident, peripheral artery disease, previous percutaneous coronary intervention, and/or coronary artery bypass grafting. †Cardiovascular risk factors include prior CVD, a history of diabetes, hypertension, hypercholesterolemia, obesity, smoking, and/or a positive family history for cardiovascular disease. For women a history with gestational hypertension or (pre)eclampsia were also considered cardiovascular risk factors. ‡Pain radiance was considered typical when the arm(s), shoulder(s), jaw(s) or throat were affected. All other locations of radiation were considered atypical. §Associated symptoms include the presence of sweating, nausea, vomiting, pallor, anxiety, fainting and/or near collapse.
Continuous data are presented as a median and interquartile range due to a non-normal distribution. All categorical data are presented as number and percentage.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 6

Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care

Amy Manten, Lucas De Clercq, Remco P. Rietveld, Wim A.M. Lucassen, Eric P. Moll van Charante, Ralf E. Harskamp

Published in Netherlands Heart Journal, 2022

PMID: 36580267

DOI: 10.1007/s12471-022-01745-0

ABSTRACT

Introduction: Chest pain is a common and challenging symptom for telephone triage in urgent primary care. Existing chest-pain-specific risk scores originally developed for diagnostic purposes may outperform current telephone triage protocols.

Methods: This study involved a retrospective, observational cohort of consecutive patients evaluated for chest pain at a large-scale out-of-hours primary care facility in the Netherlands. We evaluated the performance of the Marburg Heart Score (MHS) and INTERCHEST score as stand-alone triage tools and compared them with the current decision support tool, the Netherlands Triage Standard (NTS). The outcomes of interest were: C-statistics, calibration and diagnostic accuracy for optimised thresholds with major events as the reference standard. Major events are a composite of all-cause mortality and both cardiovascular and non-cardiovascular urgent underlying conditions occurring within 6 weeks of initial contact.

Results: We included 1433 patients, 57.6% women, with a median age of 55.0 years. Major events occurred in 16.4% (*n*=235), of which acute coronary syndrome accounted for 6.8% (*n*=98). For predicting major events, C-statistics for the MHS and INTERCHEST score were 0.74 (95% confidence interval: 0.70-0.77) and 0.76 (0.73-0.80), respectively. In comparison, the NTS had a C-statistic of 0.66 (0.62-0.69). All had appropriate calibration. Both scores (at threshold ≥2) reduced the number of referrals (with lower false-positive rates) and maintained equal safety compared with the NTS.

Conclusion: Diagnostic risk stratification scores for chest pain may also improve telephone triage for major events in out-of-hours primary care, by reducing the number of unnecessary referrals without compromising triage safety. Further validation is warranted.

INTRODUCTION

Chest pain is a common symptom in out-of-hours primary care (OOH-PC). Only a minority of patients with chest pain suffer from an acute coronary syndrome (ACS) (1.5-3.6%)[1] or another life-threatening disease. Adequate triage is essential to maintain optimal patient flow in the care process and to avoid possible complications associated with life-threatening events. In Dutch primary care, triage is initially through telephone consultation using standardised Netherlands Triage Standard (NTS) protocols.[2,3] The NTS chest pain protocol was developed based on a consensus of expert opinion and not validated prior to its implementation.[4] A recent regional evaluation revealed that the NTS performs modestly, with a false-positive rate of 83%, and underestimated urgencies in 27% of patients with an ACS or another life-threatening event.[5] Moreover, it was shown that the current triage process leads to many unnecessary referrals, causing an increased workload, overburdening of ambulance services and overcrowding of emergency departments.[4,6]

We postulate that the use of validated clinical decision rules, such as the Marburg Heart Score (MHS) and INTERCHEST score, may also be of added value when employed as a telephone triage tool.[7-9] We therefore set out to evaluate the performance of the MHS and INTERCHEST score as stand-alone triage tools, and to compare their performance with the current NTS protocol on predicting the occurrence of a major event within 6 weeks of initial contact.

METHODS

Our study is reported in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 statement (Electronic Supplementary Material, Supplement 5).[10] The study protocol was approved by our institution's Medical Ethics Review Committee and registered in the Netherlands Trial Register (TRACE – Trial NL7581).[11]

Study design

This study was part of the TRiage of Acute Chest pain Evaluation in primary care (TRACE) project. A more elaborate description of the study methods was published previously.[12] In short, this study involved a retrospective, observational cohort of consecutive patients (≥18 years) with chest pain who contacted a large, regional primary care facility in Alkmaar, the Netherlands in 2017. This facility provides OOH-PC to approximately a quarter of a million inhabitants. Details on the organisation of Dutch OOH-PC can be found in the Supplementary Material (*Supplement 1*).

We gathered registered triage information, including patient and symptom characteristics, urgency levels and course of action following triage, using electronic health records at the OOH-PC facility. Final diagnoses were obtained from the patient file at the affiliated daytime primary care practices, with supporting hospitalisation and/or discharge letters related to the index consultation. Data were collected and processed using a secure, web-based electronic data capture platform (Castor EDC, Amsterdam, The Netherlands).[13]

NTS triage software

Trained triage assistants handle triage using NTS triage protocols.[2] These protocols are complaint-specific and start with an initial assessment of patients' vital signs using the ABCDE method.[14] The protocol for chest pain continues with seven questions regarding symptom characteristics (*Supplement 1*). The NTS algorithm uses the available answers to calculate an urgency level, linked to a recommended time until care. Triage assistants ultimately decide on the most fitting course of action.

Clinical decision rules

Supplement 2 gives an overview of the components of each clinical decision rule. The MHS is a point-based score with five elements, developed for ruling out coronary artery disease (CAD) among primary care patients presenting with chest pain.[8] Patients are assigned either 1 (when present) or 0 points (when absent) for each item and the MHS equals the sum, thus ranging from 0 to 5.

The INTERCHEST score is a similar point-based tool developed for the same purpose as the MHS.[7] It consists of six elements, of which five are assigned either 1 (when present) or 0 points (when absent), and one element ('pain reproducible by palpation') is given minus 1 point when present and 0 points when absent. Thus, the INTERCHEST score ranges from -1 to +5 points. In order to evaluate the INTERCHEST score as a triage tool, we replaced the physician's first impression with that of the triage assistant.

Clinical outcomes: major events

We defined 'major events' as a composite of all-cause mortality and urgent conditions, including ACS, linked to the initial complaint of chest pain which required hospital admission and/or urgent in-hospital treatment. *Supplement 3* specifies the diagnoses that constitute major and non-major events. The occurrence of an ACS was based on physician reporting.

Statistical analysis

We evaluated the performance of the NTS triage software, the MHS and the INTERCHEST score by assessing their discriminative ability (i.e. the ability to distinguish between patients with and without a major event) using C-statistics and visualised using an area under the receiver operating characteristics curve. We also generated calibration plots to illustrate the agreement between the predicted and observed major event rates. Perfect calibration implies that predictions have an intercept of 0 and a coefficient of 1 (i.e. a diagonal 45-degree slope).[15]

We divided NTS urgency into high (U1-U2; recommended care <1 h) and low (U3-U5; care >1 h) and determined the most optimal threshold for the MHS and INTERCHEST score for predicting a major event. When data elements of the MHS or INTERCHEST score were not reported, researchers blinded for clinical outcomes made maximum effort to retrieve the elements from available data. If the data elements were unavailable, they were presumed absent. Patients with an unknown NTS urgency level or without follow-up data were excluded. Hence we did not impute the dataset if triage or outcome data were missing. Furthermore, we performed more restricted analyses specifically for the occurrence of ACS.

RESULTS

During the study period, a total of 2043 patients reached out to the urgent primary care facility regarding chest pain. We excluded data from 240 patients who opted out of sharing data. We also excluded patients without follow-up information (*n*=333) or without an NTS software-derived urgency level (*n*=37), resulting in a final study population of 1433. The characteristics of this population are listed in *Table 1*. Overall, median age was 55.0 years (38.0-71.0), the majority were female (57.6%) and 22.5% had a history of cardiovascular disease.

Major events occurred in 16.4% (*n*=235). Cardiovascular conditions, such as ACS, comprised the majority of the major events (181/235, 77.0%), followed by respiratory and abdominal aetiologies (9.8% and 7.2%, respectively) (*Supplement 4*). Overall, patients with a major event were older, more often male and more likely to have pre-existing medical conditions.

Table 1. Patient characteristics.

	Total (*n*=1433)	**Major event** (*n*=235)	**Non-major** (*n*=1198)	***p***
Age (IQR)	55.0 (38.0-71.0)	71.0 (61.0-81.0)	51.0 (35.0-68.0)	<0.001
Sex				
Male	607 (42.4%)	128 (54.5%)	479 (40.0%)	<0.001
Female	826 (57.6%)	107 (45.5%)	719 (60.0%)	<0.001
Pre-existing medical condition (any)	1,061 (74.0%)	209 (88.9%)	852 (71.1%)	<0.001
History of cardiovascular disease	332 (22.5%)	98 (41.7%)	224 (18.7%)	<0.001
Prior CAD[a]	264 (18.4%)	82 (34.9%)	182 (15.2%)	<0.001
Prior stroke/TIA	100 (7.0%)	27 (11.5%)	73 (6.1%)	0.003
Prior peripheral arterial disease	36 (2.5%)	14 (6.0%)	22 (1.8%)	<0.001
Cardiovascular risk factors (any)	817 (57.0%)	183 (77.9%)	634 (52.9%)	<0.001
Smoking (current)	255 (17.8%)	37 (15.7%)	218 (18.2%)	0.37
Hypertension	446 (31.1%)	121 (51.5%)	325 (27.1%)	<0.001
Hypercholesterolaemia	238 (16.6%)	69 (29.4%)	169 (14.1%)	<0.001
Diabetes mellitus	176 (12.3%)	54 (23.0%)	122 (10.2%)	<0.001
Chronic use of medication (any)	917 (64.0%)	192 (81.7%)	725 (60.5%)	<0.001
Platelet aggregation inhibitor	91 (6.4%)	28 (11.9%)	63 (5.3%)	<0.001
Salicylates	207 (14.4%)	62 (26.4%)	145 (12.1%)	<0.001
Vitamin K antagonist	152 (10.6%)	47 (20.0%)	105 (8.8%)	<0.001
NOACs	49 (3.4%)	18 (7.7%)	31 (2.6%)	<0.001
Beta-blockers	353 (24.6%)	99 (42.1%)	254 (21.2%)	<0.001
ACE inhibitors/ARBs	340 (23.7%)	92 (39.1%)	248 (20.7%)	<0.001
Lipid-lowering drugs	350 (24.4%)	86 (36.6%)	264 (22.0%)	<0.001
Nitrates[b]	149 (10.4%)	52 (22.1%)	97 (8.1%)	<0.001

The table illustrates the patient characteristics for both the total group of patients (n=1433) and after division based on the occurrence of a major event. Continuous variables are presented as medians (IQR) due to a non-normal distribution.
Abbreviations: IQR, interquartile range; CAD, coronary artery disease; TIA, transient ischaemic attack; NOAC, novel oral anticoagulant; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a] Defined as a history of both acute and stable coronary syndromes.
[b] Both chronic and PRN (pro re nata) use of nitrates.

Performance of the NTS

Performance analyses of the NTS triage software were based on the urgency level allocation and the occurrence of a major event. *Figure 1* illustrates the discriminative properties with a C-statistic of 0.66 (95% confidence interval [CI]: 0.62-0.69). Calibration was adequate when comparing observed versus expected major events (*Figure 2*). Diagnostic properties were calculated after

dividing urgencies into high (U1-U2) and low (U3-U5) (*Table 2*), resulting in 886 (61.8%) recommended referrals (i.e. high urgency), of which 691 (48.2%) were unnecessary (i.e. false positive). In this case, 40 of 235 (17.0%) major events would have been missed (i.e. false negative). The sensitivity and specificity of the NTS were 83.0% and 42.3%, respectively.

Performance of the MHS

The MHS produced a C-statistic of 0.74 (95% CI: 0.70-0.77) (*Figure 1*) and calibration appeared adequate (*Figure 2*). Diagnostic properties were calculated at different thresholds. A threshold of 2 points showed optimal diagnostic accuracy with a sensitivity of 82.1% and a specificity of 58.8% (*Table 2*). Compared to the NTS software, MHS ≥2 resulted in 199 fewer referrals (-22.5%) and only two additional missed major events.

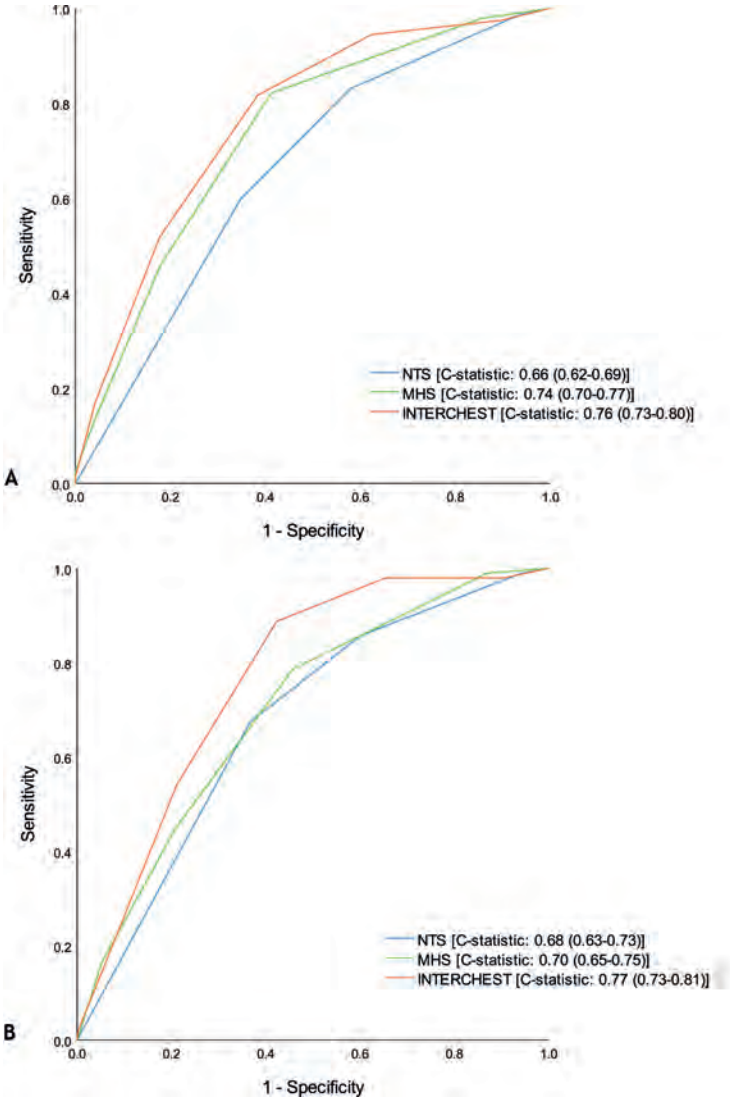
Performance of the INTERCHEST score

The INTERCHEST score resulted in a C-statistic of 0.76 (95% CI: 0.73-0.80) (*Figure 1*), and calibration appeared to be reasonably good (*Figure 2*). An INTERCHEST score with a threshold of ≥2 points showed optimal diagnostic accuracy with a sensitivity and specificity of 81.7% and 61.6%, respectively. Compared to the NTS, the INTERCHEST score improved efficiency by leading to fewer patient referrals (-234) with a similar number of missed cases (*n*=43 vs *n*=40).

Performance of NTS, MHS and INTERCHEST score regarding ACS

Overall, 98 (6.8%) patients suffered from an ACS. For the occurrence of an ACS, C-statistics were 0.68 (95% CI: 0.63-0.73), 0.70 (0.65-0.75) and 0.77 (0.73-0.81) for the NTS, MHS and INTERCHEST score, respectively (*Figure 1*). The NTS software showed a sensitivity of 85.7% and specificity of 39.9%, with 14 missed cases and an unnecessary referral rate of 56% (*n*=802) (*Table 3*). The MHS did not outperform the NTS, with more missed cases (*n*=7) and a sensitivity and specificity of 78.6 and 54.3%, respectively. The INTERCHEST score showed more favourable diagnostic capability, with a sensitivity and specificity of 88.8 and 57.6%, 234 fewer referrals and fewer missed ACS diagnoses (*n*=-3).

Figure 1. AUROC (area under the receiver operating characteristic) curves for major events (A) and acute coronary syndrome (ACS) (B).



The curves were based on the assigned urgency level (Netherlands Triage Standard, NTS) and calculated risk scores (Marburg Heart Score [MHS] and INTERCHEST score) regarding the occurrence of a major event or ACS.

Table 2. Diagnostic properties of Netherlands Triage Standard (NTS), Marburg Heart Score (MHS) and INTERCHEST score at different thresholds for predicting major events.

	Threshold (score)	**TP**	**FN**	**FP**	**TN**	**Sensitivity** (%)	**Specificity** (%)	**PPV** (%)	**NPV** (%)	**Accuracy** (%)
NTS	U1/U2	195	40	691	507	83.0 (77.6-87.6)	42.3 (39.5-45.2)	22.0 (20.7-23.3)	92.7 (90.5-94.4)	49.0 (46.4-51.6)
MHS	≥1	230	5	1026	172	97.9 (95.1-99.3)	14.4 (12.4-16.5)	18.3 (17.9-18.8)	97.2 (93.5-98.8)	28.1 (25.7-30.5)
	≥2	193	42	494	704	82.1 (76.6-86.8)	58.8 (55.9-61.6)	28.1 (26.3-30.0)	94.4 (92.7-95.7)	62.6 (60.0-65.1)
INTERCHEST	≥1	222	14	747	451	94.1 (90.3-96.7)	37.7 (34.9-40.5)	22.9 (22.0-23.9)	97.0 (95.1-98.2)	46.9 (44.3-49.6)
	≥2	192	43	460	738	81.7 (76.2-86.4)	61.6 (58.8-64.4)	29.5 (27.5-31.4)	94.5 (92.9-95.8)	64.9 (62.4-67.4]

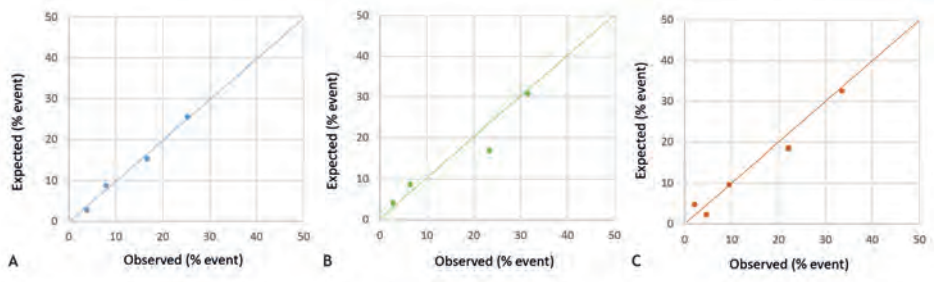
The table shows thresholds only for the MHS and INTERCHEST score with at least similar false-negative rates for major events. Test properties are displayed as percentages with the 95% confidence interval in parentheses. Abbreviations: TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value.

Table 3. Diagnostic properties of the Netherlands triage Standard (NTS), Marburg Heart Score (MHS) ≥2 and INTERCHEST score ≥2 for acute coronary syndrome.

	Threshold (score)	**TP**	**FN**	**FP**	**TN**	**Sensitivity** (%)	**Specificity** (%)	**PPV** (%)	**NPV** (%)	**Accuracy** (%)
NTS	U1/U2	84	14	802	533	85.7 (77.2-92.0)	39.9 (37.3-42.6)	9.5 (8.7-10.3)	97.4 (95.9-98.4)	43.1 (40.5-45.7)
MHS	≥2	77	21	610	725	78.6 (69.1-86.2)	54.3 (51.6-57.0)	11.2 (10.1-12.5)	97.2 (95.9-98.1)	56.0 (53.4-58.6)
INTERCHEST	≥2	87	11	565	770	88.8 (80.8-94.3)	57.7 (55.0-60.4)	13.3 (12.3-14.5)	98.6 (97.6-99.2)	59.8 (57.2-62.4)

Test properties are displayed as percentages with the 95% confidence interval in parentheses. Abbreviations: TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value.

Figure 2. Calibration plots of the NTS software, Marburg Heart Score and INTERCHEST score for major events.



A Calibration plot of NTS software, **B** Calibration plot of Marburg Heart Score, **C** Calibration plot of INTERCHEST score.

DISCUSSION

Adequate classification of patients with chest pain is paramount for any given triage system, certainly when an unselected patient population is involved. Balancing maximum efficiency while minimising the number of underestimated cases is a daunting challenge. Our study evaluated the use of existing chest-pain-specific clinical decision rules (MHS and INTERCHEST score) as stand-alone triage tools, and compared these to the current triage protocol (NTS). We found that the diagnostic capability of the NTS is modest at best for discriminating between patients with and without a major event or ACS. Both the MHS (≥2) and the INTERCHEST score (≥2) outperformed the NTS by improving efficiency without negatively impacting on false-negative rates.

Strengths and limitations

To our knowledge, this is the first study to evaluate and compare the test accuracy of an existing telephone triage tool with validated diagnostic prediction rules in OOH-PC for a broader set of chest-pain-related conditions. We assessed a relatively large study population, comprising all chest pain patients that contacted OOH-PC without further selection. While the organisational structures for European OOH-PC show several differences between and within countries, general practitioners (GPs) are generally positioned as gate-keepers to secondary care and often use integrated telephone triage systems.[3] Our findings may therefore be generalisable to similar settings across Europe.

The main limitation of our study is its retrospective nature. Verification bias may have been in play since only patients in whom there was a high suspicion

of a major event underwent further diagnostic work-up to confirm or rule out the occurrence of an event. However, we tried to minimise this bias by using a 6-week follow-up window for the outcome of interest, allowing us to capture initially missed events. Second, since the MHS and INTERCHEST score are not integrated into current practice, score elements were not registered structurally. We presumed the absence of a symptom or score element when it was not recorded by the triage assistant. Third, a mentionable amount of lost-to-follow-up was caused by GPs refusing to provide data on their patients (6.0% of baseline patients). These GPs expressed concerns due to the recent implementation of the European *General Data Protection Regulation*.

Prior research on the MHS and INTERCHEST score

The MHS was developed by Bösner *et al.*[8] for predicting CAD in daytime primary care among patients with chest pain. Overall, best results were obtained when applying a threshold of 3 points, and repeated validation showed a discriminative ability ranging from 0.84 to 0.90, with good sensitivity (87-91%) and specificity (61-81%).[8,9,16] Additional external validation of the MHS among patients in Southeast Asia resulted in a less favourable discriminative ability of 0.66 (95% CI: 0.62-0.70).[17] The MHS was also tested for its ability to rule out ACS among a selected patient population referred for immediate cardiac evaluation because an ACS was suspected.[18] Results of this study showed that the MHS alone had insufficient diagnostic accuracy (75.0% sensitivity and 44.0% specificity), and incorporation of the MHS in GP consultations produced a specificity of only 23.3% despite an increased sensitivity (94.4%). In the present study, the MHS was evaluated as a stand-alone triage tool for distinguishing between patients with and without major events. While the rule was not constructed for this purpose, it still outperformed the NTS with C-statistics of 0.74 versus 0.66 and increased specificity (+16.5%).

Similar to the MHS, the INTERCHEST score was designed for ruling out CAD in daytime primary care.[7] It was based on five cohort studies, including the MHS derivation study. Overall, studies found a sensitivity of 82-88% and specificity of 74-82% for ruling out CAD (threshold ≥2).[16] In urgent primary care, the INTERCHEST score demonstrated good discriminative ability (C-statistic >0.80) for predicting major adverse cardiovascular events.[19] The usability of the INTERCHEST score seems to be corroborated by the present study, which showed it to have the most favourable diagnostic capability for predicting both major events and ACS.

Implications for future research

Our results illustrate how existing clinical decision rules may improve triage risk-stratification in OOH-PC settings. However, in the light of the retrospective nature of our study, we should first conduct further prospective validation, preferably at multiple sites and settings, before recommending implementation in routine care. We believe that such studies should not focus on ACS alone, but rather focus on a broader set of chest-pain-related outcomes (or major events) that are relevant in unselected patient populations.

CONCLUSION

The Marburg Heart Score and INTERCHEST score have good discriminative ability for telephone triage purposes in primary care patients with chest pain. Both scores outperformed the current triage protocol in our study, but further prospective validation is warranted.

REFERENCES

1. Haasenritter J, Biroga T, Keunecke C, et al. Causes of chest pain in primary care--a systematic review and meta-analysis. *Croat Med J*. Oct 2015;56(5):422–30. doi:10.3325/cmj.2015.56.422
2. Domus Medica - Netherlands Triage Standard. 2014.
3. Steeman L, Uijen M, Plat E, Huibers L, Smits M, Giesen P. Out-of-hours primary care in 26 European countries: an overview of organizational models. *Family practice*. 2020;37(6):744–750.
4. Zeilstra R, Giesen P. Pijn op de borst: huisarts of ambulance? *Huisarts & Wetenschap*. 2017;60(10)
5. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA, Zwart DL. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open heart*. 2020;7(2):e001376.
6. Keizer E, Maassen I, Smits M, Wensing M, Giesen P. Reducing the use of out-of-hours primary care services: a survey among Dutch general practitioners. *European Journal of General Practice*. 2016;22(3):189–195.
7. International Working Group on Chest Pain in Primary Care (INTERCHEST), Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011
8. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212
9. Haasenritter J, Bösner S, Vaucher P, et al. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. *British Journal of General Practice*. 2012;62(599):e415–e421. doi:10.3399/bjgp12X649106
10. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Clinical chemistry*. 2015;61(12):1446–1452.
11. Netherlands Trial Register. https://www.trialregister.nl/trial/7581
12. Manten A, Cuijpers CJ, Rietveld R, et al. Rationale and design of a cohort study evaluating triage of acute chest pain in out-of-hours primary care in the Netherlands (TRACE). *Primary Health Care Research & Development*. 2020;21
13. Castor Electronic Data Capture, Ciwit BV. 2016. http://castoredc.com
14. Thim T, Krarup NHV, Grove EL, Rohde CV, Løfgren B. Initial assessment and treatment with the Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach. *International Journal of General Medicine*. 2012;5:117.
15. Steyerberg EW, Vickers AJ, Cook NR, et al. Assessing the performance of prediction models: a framework for some traditional and novel measures. *Epidemiology (Cambridge, Mass)*. 2010;21(1):128.

16. Harskamp RE, Laeven SC, Himmelreich JC, Lucassen WAM, van Weert H. Chest pain in general practice: a systematic review of prediction rules. *BMJ Open*. Feb 27 2019;9(2):e027081. doi:10.1136/bmjopen-2018-027081

17. Wang ZS, Yap J, Koh YLE, et al. Predicting Coronary Artery Disease in Primary Care: Development and Validation of a Diagnostic Risk Score for Major Ethnic Groups in Southeast Asia. *J Gen Intern Med*. 26 March 2021 2021;doi:10.1007/s11606-021-06701-z

18. Schols AM, Willemsen RT, Bonten TN, et al. A nationwide flash-mob study for suspected acute coronary syndrome. *The Annals of Family Medicine*. 2019;17(4):296–303.

19. Kleton M, Manten A, Smits I, Rietveld R, Lucassen WA, Harskamp RE. Performance of risk scores for coronary artery disease: a retrospective cohort study of patients with chest pain in urgent primary care. *BMJ open*. 2021;11(12):e045387.

SUPPLEMENTARY MATERIAL

Supplement 1. Text box explaining the organizational structure of Dutch out-of-hours primary care.

Organizational structure of out-of-hours primary care in the Netherlands

The dominant organizational structure for Dutch out-of-hours primary care is formed by general practitioner (GP) cooperatives. These large-scale, regional facilities provide care to the patients of the affiliated GPs during evenings, weekends and national holidays. Upon contact, patients are triaged in order to assess the urgency of their complaint. In most Dutch out-of-hours primary care facilities, trained triage assistants handle triage with the help of standardized protocols from the "Netherlands Triage Standard" (NTS). These protocols are complaint-specific and developed using 1) expert opinion, 2) a modified version of the Manchester Triage System, and 3) existing telephone guidelines used in primary care. However. The resulting protocols were never validated before their implementation in 2011 and the exact algorithm behind the NTS protocols remains unknown to the public.

All of the NTS protocols start with a check of vital signs using the ABCDE-method, followed by a number of hierarchically structured questions. The specific protocol for evaluating chest pain consists of seven questions encompassing the type, duration, severity, course of the pain, location on the chest, presence of radiation, and associated symptoms (i.e. diaphoresis, nausea, pallor, anxiety, fainting). The NTS algorithm continuously calculates a recommended urgency level based on the responses (minimum of 1). As shown in the table below, each urgency level is linked to a recommended time-until-care. Additional information from the triage conversation (e.g. additional symptoms or information from para-language) can be registered by the triage assistant in a free text box and is not included in the algorithm's calculations. However, triage assistants are able to overrule the NTS urgency if deemed necessary and ultimately decide on the most fitting course of action (i.e. ambulance activation, face-to-face GP consultation, referral to the own GP during office-hours or self-care advice).

continues

continued

Urgency level	Definition	Time-until-care
U0*	No vital signs	Immediate – resuscitation
U1	Life threatening	As soon as possible - ambulance
U2	Emergent	Care <60 minutes
U3	Urgent	Care within several hours
U4	Non-urgent	Care within 24 hours
U5	Advice	Next workday – self-care advice

Notes: *U0 urgency levels are reserved to patients in need of resuscitation, in such cases triage is not initiated and an ambulance is immediately activated.

Supplement 2. Components of the triage protocol and the two clinical decision rules.

Netherlands Triage Standard	**Marburg Heart Score**	**INTERCHEST Score**
Check of vital signs	Age/sex	Age/sex
Type of pain	(F ≥65 years, M ≥55 years)	(F ≥65 years, M ≥55 years)
Duration of the pain	Known CVD*	History of CAD†
Severity	Pain worse with exercise	Chest pain related to effort
Course of the pain	Pain not reproducible by palpation	Pain reproducible by palpation
Location on the chest	Patient assumes pain is of cardiac origin	Triage assistant suspects serious condition‡
Radiation		Chest pain feels like “pressure”
Associated symptoms		
Range: U1 – U5 level	*Range: 0 – 5 points*	*Range: -1 – 5 points*

Abbreviations: F, female; M, male; CVD, clinical vascular disease; CAD, coronary artery disease. Notes: *History of myocardial infarction, transient ischemic attack, cerebrovascular accident, peripheral artery disease, previous percutaneous coronary intervention or coronary artery bypass graft. †History of myocardial infarction, previous percutaneous coronary intervention or coronary artery bypass graft. ‡In order to evaluate the INTERCHEST score in a triage setting, we replaced the physician’s suspicion of a serious condition with that of the triage assistant. The component ‘suspicion’ was based on the triage assistants reaction based on their first impression or ‘gut feeling’. For instance, this item was considered present when patients received immediate ambulance activation, when triage assistants explicitly noted their concern or when assistants discussed the case with the attending GP due to doubt.

Supplement 3. Definition of major and non-major events.

	Final diagnosis	Conditional management
Major event	Death from any cause	
	Acute coronary syndrome	
	Urgent coronary revascularization	
	Pulmonary embolism	
	Thoracic aortic aneurysm (dissection or ruptured)	
	Severe/Acute congestive heart failure	Hospitalization
	Severe peri(myo)carditis	Hospitalization
	Symptomatic atrial fibrillation	Hospitalization (cardioversion or converted through medication)
	Aortic valve stenosis	Hospitalization
	(Tension) pneumothorax	Hospitalization
	Severe pneumonia	Hospitalization
	CVA/TIA	
	Inflammatory processes such as appendicitis, pancreatitis, cholecystitis	Hospitalization
	Other, such as: exacerbation COPD or hypertensive crisis	Hospitalization
	Traumatic event (with significant impact)	Hospitalization
Non-major event	Stable angina pectoris	Outpatient treatment
	Mild congestive heart failure	Outpatient treatment
	Mild peri(myo)carditis	Outpatient treatment
	Atrial fibrillation (recurrent/paroxysmal)	Outpatient treatment
	Hypertension	Outpatient treatment
	Mild pneumothorax	Outpatient treatment
	Mild pneumonia	Outpatient treatment
	Mild respiratory problems (such as viral infections)	
	Gastric/oesophagus problems	
	Muscoloskeletal	
	Traumatic (mild trauma)	Outpatient treatment
	Mental health/Panic attack/Anxiety disorder	

Major event was defined as a composite of all-cause mortality and urgent medical conditions linked to the initial complaint of chest pain which required hospital admittance, and/or urgent in-hospital treatment. Thus, major events includes both cardiovascular, as well as non-cardiovascular conditions. The table specifies the subdivision between major and non-major events, and states the conditional managements for some of these diagnoses in the right column. Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident (CVA); TIA, transient ischaemic attack.

Supplement 4. Subdivision of final diagnoses and their frequencies among the total group of patients and among the patients who suffered a major event.

	Total (*n*=1,433)	**Major events** (*n*=235)
Cardiovascular	**359 (25.1%)**	**181 (77.0%)**
Acute coronary syndrome	98 (6.8%)	98 (41.7%)
Chronic coronary syndrome *(e.g. stable angina, ischaemic disease without angina)*	68 (4.7%)	8 (3.4%)
Atrial fibrillation	61 (4.3%)	38 (16.2%)
Heart failure		
Congestive heart failure*	22 (1.5%)	13 (5.5%)
Other *(including cardiomyopathy)*	2 (0.1%)	-
Peri(myo)carditis	16 (1.1%)	3 (1.3%)
Aortic aneurysm or dissection	3 (0.2%)	3 (1.3%)
Pulmonary embolism	12 (0.8%)	9 (3.8%)
Cerebrovascular disease *(CVA and TIA)*	2 (0.1%)	2 (0.9%)
Abnormal blood pressure		
Hypertension	16 (1.1%)	1 (0.4%)
Postural hypotension	3 (0.2%)	-
Arrhythmias and conduction disorders		
Tachycardias *(paroxysmal, SVT, VT)*	6 (0.4%)	2 (0.9%)
Other *(extrasystole, atrioventricular block, presence of cardiac device)*	6 (0.4%)	-
Valvular disorders	4 (0.3%)	1 (0.4%)
Other cardiovascular *(e.g. palpitations NOS, heartdisease NOS)*	40 (2.8%)	3 (1.3%)
Musculoskeletal	**652 (45.5%)**	**8 (3.4%)**
Chest wall pain *(including herpes zoster, Tietze and breast pain)*†	578 (40.3%)	5 (2.1%)
Musculoskeletal other		
Neck and back pain/complaints	15 (1.0%)	-
Arm and shoulder pain/complaints	16 (1.1%)	-
Traumatic *(e.g. traumatic ruptured spleen, contusion or fractured ribs)*	32 (2.2%)	3 (1.3%)
Unspecified *(e.g. muscle pain, gout)*	11 (0.8%)	-
Respiratory	**122 (8.5%)**	**23 (9.8%)**
Pneumonia	38 (2.7%)	15 (6.4%)
Pneumothorax	3 (0.2%)	2 (0.9%)
Other respiratory		
Infectious other *(e.g. upper respiratory tract infections, viral pleurisy, bronchiolitis)*	27 (1.9%)	-
Chronic pulmonary diseases *(e.g. asthma, COPD)*	22 (1.5%)	3 (1.3%)
Respiratory complaints other *(including cough, dyspnoea, pain, known malignancy)*	32 (2.2%)	3 (1.3%)

continues

continued

Abdominal	**152 (10.6%)**	**17 (7.2%)**
Stomach and oesophageal related complaints/diseases *(e.g. heartburn, reflux disease, nausea, indigestion, epigastric pain)*	82 (5.7%)	2 (0.9%)
Biliary diseases *(cholelithiasis, cholecystitis)*	21 (1.5%)	5 (2.1%)
Pancreatitis	3 (0.2%)	2 (0.9%)
Abdominal other		
Undifferentiated abdominal pain	12 (0.8%)	-
Inflammatory *(appendicitis, chronic enteritis)*	3 (0.2%)	2 (0.9%)
Urological *(urinary infection, urinary calculus)*	14 (1.0%)	4 (1.7%)
Other unspecified *(including diverticular disease, constipation)*	17 (1.2%)	2 (0.9%)
Psychological and mental health	**95 (6.6%)**	**1 (0.4%)**
Anxiousness / fear of disease / panic disorders *(including hyperventilation)*	82 (5.7%)	-
Other psychological and mental health		
Substance abuse and intoxications‡	5 (0.3%)	1 (0.4%)
Other unspecified *(including dementia, delirium)*	8 (0.6%)	-
Other	**53 (3.7%)**	**5 (2.1%)**
General and unspecified diagnosis *(e.g. pain, fever, weakness, allergies and adverse drug reactions)*	22 (1.5%)	3 (1.3%)
Neurological *(including headache, dizziness, fainting and sensory complaints)*	21 (1.5%)	-
Skin/tissue problems	3 (0.2%)	-
Endocrine system *(including thyroid problems and diabetes)*	4 (0.3%)	2 (0.9%)
Haematological	3 (0.2%)	-

Abbreviations: CVA, cerebrovascular accident; TIA, transient ischemic attack; SVT, supraventricular tachycardia; VT, ventricular tachycardia; NOS, not otherwise specified; COPD, chronic obstructive pulmonary disease.
Notes: *Includes 1 patient witch cardiac asthma without ischemia. †Includes one patient with chest pain due to progressive Non-Hodgkin's lymphoma, the progression caused an impeding spinal cord injury. ‡Specifically no cases of cocaine induced ischemia.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 7

Marburg Heart Score and INTERCHEST score for telephone triage of acute chest pain: a prospective, diagnostic accuracy study in out-of-hours primary care

Amy Manten, Indra M.B. Melessen, Jelle C.L. Himmelreich, Eric P. Moll van Charante, Ralf E. Harskamp

Under review at BMJ Open

ABSTRACT

Objectives: To assess whether the Marburg Heart Score and INTERCHEST score may improve telephone triage of chest pain by providing better diagnostic discrimination compared to the triage protocol from the Netherlands Triage Standard (NTS).

Design: Prospective diagnostic accuracy study.

Setting: Large regional out-of-hours primary care (OOH-PC) facility in Alkmaar, the Netherlands.

Participants: A total of 1,254 eligible patients contacted the OOH-PC facility (median age 56.0 years, 57.9% female) between December 2022 and May 2023. The study was completed and verbal informed consent obtained in 280 (22.3%) patients.

Interventions: Triage assistants asked study questions in addition to the NTS protocol to complete the MHS and INTERCHEST score.

Primary and secondary outcome measures: Discrimination (C-statistics) and diagnostic test properties (e.g. sensitivity/specificity) were used; the reference standard was the occurrence of a major event (i.e. composite of all-cause mortality, and urgent cardiovascular and non-cardiovascular conditions) or acute coronary syndrome (ACS) within 6 weeks.

Results: A major event occurred in 36 patients (12.9%), including 13 (4.6%) ACS cases. For predicting major events, the MHS and INTERCHEST scores showed C-statistics of 0.67 (95%-CI: 0.57-0.77) and 0.64 (95%-CI: 0.54-0.74), respectively, compared to 0.62 (95%-CI: 0.53-0.71) for the NTS protocol. For ACS, C-statistics were 0.62 (95%-CI: 0.45-0.79), 0.59 (95%-CI: 0.43-0.75), and 0.62 (95%-CI: 0.49-0.75) for MHS, INTERCHEST and NTS, respectively. Regarding test characteristics, the MHS and INTERCHEST score showed higher point estimates for specificity (27.9% and 26.6%) versus the NTS (19.7%), but at the expense of lower sensitivity (88.9% and 86.1% versus 97.2%) for major events. For ACS, a similar pattern was observed (specificity 26.2% and 25.5% vs 18.4; sensitivity 84.6% and 84.6% vs 100.0%).

Conclusion: Simple clinical decision rules (MHS and INTERCHEST) have comparable, modest discriminative ability and diagnostic properties compared to the current protocol for telephone triage of acute chest pain in Dutch OOH-PC

Trial registration: Netherlands Trial Register (TRACE – NL-OMON20102).

INTRODUCTION

Acute chest pain presents a significant challenge in pre-hospital settings, with causes ranging from benign musculoskeletal complaints to urgent etiologies such as acute coronary syndrome (ACS), pulmonary embolism, or aortic dissection.[2-5] Rapid identification of patients requiring urgent care is crucial to enable timely treatment and prevent complications. However, pre-hospital settings lack the extensive diagnostic abilities offered by hospitals.

In the Netherlands, out-of-hours primary care (OOH-PC) facilities play a key role in pre-hospital care, managing approximately 11 chest pain-related contacts per 1,000 inhabitants each year.[6-8] The facilities function as an extension of general practitioners' position as gatekeepers, helping to coordinate and facilitate safe access to secondary care. Initial assessments are typically conducted over the telephone. In 2011, protocols from the Netherlands Triage Standard (NTS) were introduced to support timely identification of urgent cases and reduce unnecessary diagnostic testing or treatment.[10] The NTS protocol for chest pain consists of an assessment of the hemodynamic status and is followed by seven hierarchically structured questions to estimate the urgency. However, studies have reported disappointing diagnostic accuracies, with frequent over- and underestimations.[11,12]

The Marburg Heart Score (MHS) and INTERCHEST score are clinical decision rules developed to rule out coronary artery disease (CAD) in daytime primary care practices.[13,14] The MHS, developed in 2010, consists of five elements: age/sex criteria, known cardiovascular disease (CAD), exercise-related pain, reproducibility, and whether the patient assumes a cardiac cause.[14] The INTERCHEST score, developed in 2017, incorporates six items that are similar to those of the MHS plus physician suspicion and a pressure-type sensation.[13] Both scores have shown promise in primary care settings with C-statistics ranging from 0.64-0.85 for predicting ACS or major adverse cardiovascular events.[15] Retrospective evaluation of the scores as triage tools demonstrated potential advantages over the NTS protocol.[16]

In this prospective study, we evaluated the discriminatory and diagnostic test properties of the MHS and INTERCHEST score for ACS or other major events in patients with chest pain contacting an OOH-PC facility in the Netherlands, and compared their performance to the current Dutch triage protocol.

METHODS

We reported our study in accordance with the Standards for Reporting of Diagnostic Accuracy Studies (STARD) 2015 statement.[17] The study protocol

was reviewed by the Medical Ethical Review Committee of the Amsterdam University Medical Centers, location AMC, and was exempted from full evaluation, as it did not fall within the scope of the Dutch WMO.

Setting and study design

This study was conducted at a large regional OOH-PC facility in Alkmaar, the Netherlands, serving approximately 250,000 inhabitants with demographic characteristics representative of the overall Dutch population. This study represents the prospective phase of the TRACE project. A detailed description of earlier project phases and an overview of their results has been published previously.[11,18]

All consecutive patients (≥18 years) who contacted the facility with chest pain between December 1, 2022 and May 31, 2023 were eligible for inclusion. Upon contact, triage assistants used the chest pain-specific NTS protocol to assess urgency. For study purposes, they asked four additional chest pain-related questions along with two additional assessments to complete the MHS and INTERCHEST score elements (*Supplement 1*). These study items were not integrated into the digital triage system, and did not influence urgency codes. Researchers contacted participants at least 6 weeks later to collect follow-up data on patient reported clinical outcomes. Although the study did not require a formal patient consent, triage assistants and researchers were instructed to obtain verbal consent during both the initial and follow-up contact. For eligible patients that were not asked additional study questions, we only collected baseline information (i.e. age, sex, standardized NTS elements), unless they opted out. These patients were not contacted for follow-up, and no identifiable data were available to the research team. Patients who actively declined participation were excluded from all analyses.

Clinical decision rules

The individual components and scoring rules of the MHS and INTERCHEST scores are outlined in *Table 1*. The MHS consists of five elements; (1) female ≥65 years or male ≥55 years, (2) known coronary artery disease, cerebrovascular disease or peripheral vascular disease, (3) pain worsened by exercise, (4) pain reproducible with palpation, and (5) the patient assumes a cardiac cause. Each element is scored 0 or 1 points, resulting in a total score ranging from 0 to 5.[14]

The INTERCHEST score is a similar point based score containing six elements; (1) history of CAD, (2) female ≥65 years or male ≥65 years, (3) chest pain related to effort, (4) pain reproducible with palpation, (5) physician initially suspects a serious condition (adapted to the triage assistant's sense of alarm, scored

as ≥5.5 on 1-10 scale), and (6) chest discomfort described as “pressure”. Each element scores 0 or 1 points, except reproducibility, which scores -1 when present, resulting in a total score ranging from -1 to 5.[13]

We extracted all elements from the triage registry, including standardized NTS items and responses to additional study questions. During data coding, symptoms were classified as present when explicitly reported, and otherwise coded as absent. Scores were calculated by a researcher blinded to clinical outcomes.

Netherlands Triage Standard

During the study period, the OOH-PC facility employed version 9.50 of the NTS chest pain protocol.[10] The protocol initiates with a hemodynamic assessment, followed by seven hierarchical chest pain-specific questions that address pain characteristics, location, radiation and associated symptoms (*Table 1*). Based on the responses, the NTS generates urgency codes (U1-U5) that correspond to a recommended time-to-care. U1 and U2 are considered high urgencies requiring care within 60 minutes. Possible triage outcomes include ambulance dispatch, a general practitioner (GP) home visit or on-site consultation, or telephone advice. Triage assistants retain the ability to deviate from recommended urgency and/or action after consulting the attending GP.

Table 1. Elements of the current triage protocol for chest pain (NTS), the MHS and INTERCHEST score.

NTS protocol for chest pain	Marburg Heart Score	No	Yes	INTERCHEST score	No	Yes
Check of hemodynamic status	Female ≥65 years or male ≥55 years	0	+1	History of CAD	0	+1
Type of pain	Known CAD, cerebrovascular disease or peripheral vascular disease	0	+1	Female ≥65 years or male ≥55 years	0	+1
Severity (1-10 scale)				Chest pain related to effort	0	+1
Course of the pain						
Location on the chest	Pain worse with exercise	0	+1	Reproducible with palpation	0	-1
Radiation	Reproducible with palpation	+1	0	Triage assistant's sense of alarm (≥5.5 on 1-10 scale)	0	+1
Associated symptoms	Patient assumes cardiac cause	0	+1	Chest discomfort feels like 'pressure'	0	+1
Results in urgency code (U1-U5)	Results in score 0 – 5			Results in score -1 – 5		

The NTS protocol for chest pain version 9.50 was used during the conduct of our study. After a hemodynamic check, elements are hierarchically structured and result in a calculated urgency level ranging from U1 to U5. Urgency levels are linked to a recommended time-until-care (i.e. U1 life threatening, as soon as possible; U2 emergent, care <60 minutes; U3 urgent, care within several hours; U4 non-urgent, care within 24 hours; U5 advice, next workday). For the MHS and INTERCHEST score points are assigned to each element, resulting in a score of 0-5 and -1-5, respectively. The physician's suspicion of a serious condition was altered to the triage assistant's sense of alarm, positive if ≥5.5 on a 1-10 point scale. Abbreviations: NTS, Netherlands Triage Standard; CAD, coronary artery disease.

Clinical outcomes of interest

We assessed the occurrence of a major event or ACS within six weeks after the index contact. Major events were defined as a composite of all-cause mortality, and urgent cardiovascular and non-cardiovascular conditions, linked to the initial chest pain complaint and requiring hospital admission and/or urgent in-hospital treatment (*Supplement 2*). We verified all patient reported major events and gathered additional details through contact with the patient's GP, using supporting hospitalization and discharge letters related to the index consultation.

Analysis

We described patient characteristics (e.g. age, sex) and triage characteristics (e.g. time of contact, symptom features based on NTS elements, assigned

urgency and action following triage) for all eligible patients. Patients with available data on additional study questions and data on clinical outcomes were included in performance analyses of the MHS, INTERCHEST score and current triage protocol (NTS). Diagnostic accuracy measures (sensitivity, specificity, positive and negative predictive values (PPV and NPV)), were calculated using the presence or absence of a major event, and presence or absence of an ACS, respectively. We compared the performance of the MHS and INTERCHEST score to that of the NTS. The NTS was deemed positive when it allocated a high urgency code (U1 or U2). For the MHS and INTERCHEST, no established triage cut-offs exists. Therefore, we evaluated several thresholds to identify optimal diagnostic performance. Threshold selection was based on clinical interpretability, seeking the most favorable balance between sensitivity and specificity. We reported false positive rates (defined here as the number of false positives divided by the total number of patients in the analysis) to illustrate the percentage of patients that were unnecessarily identified as urgent by each test and respective cut-off.

We assessed the ability to discriminate between patients with and without a major event or ACS, using C-statistics. We visualized discrimination results using receiver operating characteristic (ROC) curves and corresponding areas under the curve (AUC). ROC curves were constructed, and 95% confidence intervals were estimated using the non-parametric approach. No model-based fitting was applied. When the lower bound of the C-statistic's 95%-CI was ≤0.50 we concluded that the model was unable to discriminate for the outcome of interest. For the ROC analyses, NTS urgency levels (U1-U5) were treated as an ordinal predictor, with U1 representing the highest urgency and U5 the lowest. We performed all statistical analyses using IBM SPSS Statistics (version 28).

After study enrollment was completed, the NTS protocol for chest pain was updated (October 2024). The protocol was revised to include elements of the Safety First model, a symptom-based prediction rule developed in 2022 to rule out ACS in patients with chest pain in OOH-PC.[1] To enable an up-to-date comparison between the clinical decision rules and the updated protocol, we performed an exploratory analysis of the revised NTS protocol. *Supplement 3* presents the decision tree underlying the update and provides further details on the Safety First model.[9]

Intended sample size

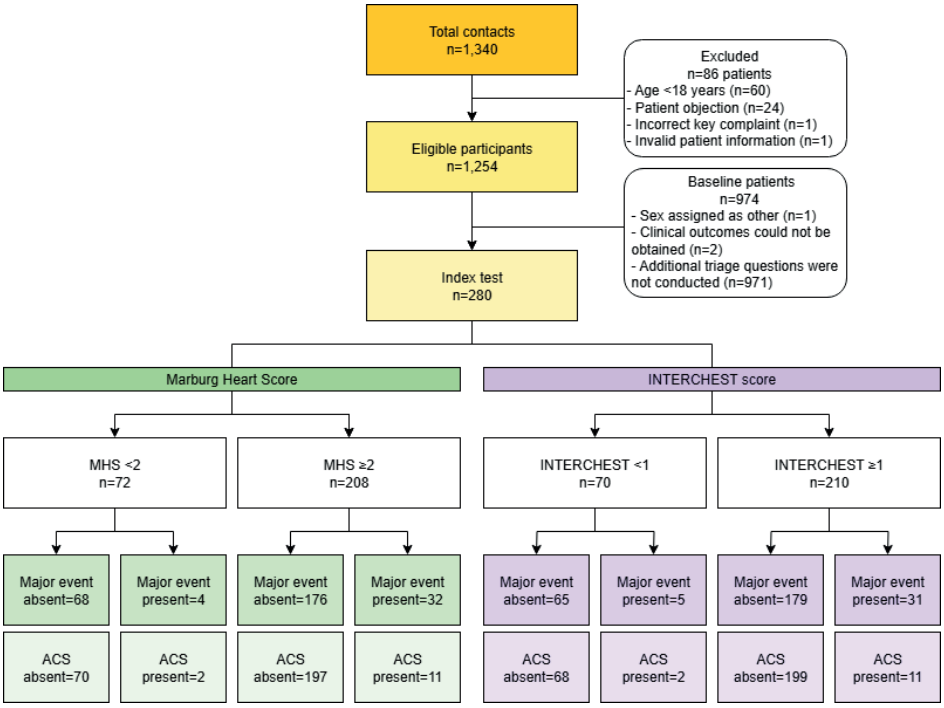
In a previous retrospective evaluation of the NTS protocol for chest pain by our research group, over 2,000 consecutive patients contacted the OOH-PC facility regarding chest pain in 2017. Of these, 88.3% were included, and 16.2% experienced a major event.[11] Extrapolating these proportions to a planned 6-month inclusion period yields an expected 165 major events if all eligible

patients are enrolled. The MHS and INTERCHEST score together introduce seven new predictors for analysis. Applying the conventional rule of 10 events per predictor requires at least 70 events. Therefore, an inclusion rate of ≥42.4% is needed to achieve the minimum number of events for reliable estimation.

Patient and public involvement statement

Patients or members of the public were not involved in the design, conduct, reporting, or dissemination plans of this research. This study focused on the diagnostic accuracy of existing clinical decision rules during routine telephone triage in out-of-hours primary care. Because the study evaluated protocols already in use, no direct patient involvement was sought in its development.

Figure 1. Flow of participants through the study.



The figure illustrates the in- and exclusion of patients. The MHS and INTERCHEST score are included as index tests. Performance results of the NTS protocol are not included in the flowchart.
Major events were defined as a composite of all-cause mortality and urgent conditions linked to the initial chest pain complaint and requiring hospital admission and/or urgent in-hospital treatment. Abbreviations: MHS, Marburg Heart Score; ACS, acute coronary syndrome.

RESULTS

Patient characteristics

During the inclusion period, 1,254 eligible patients contacted the facility with chest pain (median age 56.0 years, 57.9% female). *Figure 1* shows patient in- and exclusions. High urgency codes (U1 or U2) were assigned to 843 (67.2%) patients. Triage assistants completed the study questions in 280 (22.3%) patients (median age 58.0 years, 57.9% female). Compared to patients without registered study questions, those with available answers showed higher-risk profiles with more typical symptom characteristics and higher urgency. More details are provided in *Table 2*.

Clinical outcomes

Among the 280 patients with available data on study questions and clinical outcomes, 36 (12.9%) experienced a major event within 6 weeks, including 13 (4.6%) ACS cases (4 ST-elevated myocardial infarction (STEMI), 6 non-ST-segment elevation myocardial infarction (NSTEMI), 1 myocardial infarction with non-obstructive coronary arteries (MINOCA), 1 unstable angina, and 1 unspecified ACS). Most major events (79.5%) were diagnosed on the same day as the index contact. All-cause mortality (<6 weeks) occurred in 3 (1.1%) patients. Among those without a major event, musculoskeletal causes of chest pain were most common (in 39.6%).

Diagnostic performance

The MHS and INTERCHEST score resulted in C-statistics of 0.67 (95%-CI: 0.57-0.77) and 0.64 (95%-CI: 0.54-0.74) for major events. The NTS protocol demonstrated a C-statistic of 0.62 (95%-CI: 0.53-0.71) for major events. In the current sample, the MHS, INTERCHEST score and NTS were unable to discriminate for ACS with C-statistics of 0.62 (95%-CI: 0.45-0.79), 0.59 (95%-CI: 0.43-0.75) and 0.62 (95%-CI: 0.49-0.75), respectively (*Figure 2*).

Table 3 summarizes the diagnostic test characteristics of the clinical decision rules and the NTS protocol. For both the MHS and INTERCHEST score, only thresholds with at least similar false-negative rates for major events are shown.

The MHS showed optimal diagnostic accuracy at a threshold of ≥2 points. At this threshold, it classified 74.3% as high-risk, and failed to identify 4 major events. The false positive rate was lower than that of the NTS (62.9%), resulting in a sensitivity and specificity of 88.9% (95%-CI: 73.9-96.9) and 27.9% (95%-CI: 22.3-34.0), respectively. For ACS diagnosis, MHS (threshold ≥2) missed 2 cases and had a false positive rate of 70.4%, yielding a sensitivity and specificity of 84.6% (95%-CI: 54.6-98.1) and 26.2% (21.0-31.9), respectively.

Table 2. NTS protocol items and triage outcomes among eligible patients.

NTS item	Eligible participants (*n*=1,254)	Study questions not conducted (*n*=974)	Available data on study questions and clinical outcomes (*n*=280)	P-value
Hemodynamic check				
AVPU				
Alert	1,250 (99.7)	970 (99.6)	280 (100.0)	0.58
Verbal	1 (0.1)	1 (0.1)	-	1.00
Not registered	3 (0.2)	3 (0.3)	-	1.00
Color				
Normal	1005 (80.1)	778 (79.9)	227 (81.1)	0.66
Red/flushed	60 (4.8)	46 (4.7)	14 (5.0)	0.85
Pallor	164 (13.1)	133 (13.7)	31 (11.1)	0.26
Ashen	22 (1.8)	14 (1.4)	8 (2.9)	0.11
Not registered	3 (0.2)	3 (0.3)	-	1.00
External bleeding				
No	1,243 (99.1)	963 (98.9)	280 (100.0)	0.14
Moderately	3 (0.2)	3 (0.3)	-	1.00
Not registered	8 (0.6)	8 (0.8)	-	0.21
Stridor				
No	1,221 (97.4)	946 (97.1)	275 (98.2)	0.32
Non-obstructive	26 (2.1)	21 (2.2)	5 (1.8)	0.70
Yes	2 (0.2)	2 (0.2)	-	1.00
Not registered	5 (0.4)	5 (0.5)	-	0.59
Need for resuscitation				
No	1250 (99.7)	971 (99.7)	279 (99.6)	1.00
Not registered	4 (0.3)	3 (0.3)	1 (0.4)	1.00
Chest pain questions				
Severity[a]				
Mild (<4)	337 (26.9)	259 (26.6)	78 (27.9)	0.67
Moderate (5-7)	618 (49.3)	469 (48.2)	149 (53.2)	0.14
Severe (8-10)	113 (9.0)	82 (8.4)	31 (11.1)	0.17
No chest pain	169 (13.5)	151 (15.5)	18 (6.4)	<0.001
Not registered	17 (1.4)	13 (1.3)	4 (1.4)	1.00

continues

continued

Duration				
<12 hours	630 (50.2)	482 (49.5)	148 (52.9)	0.32
>12 hours and unchanged	240 (19.1)	189 (19.4)	51 (18.2)	0.66
>12 hours and changed/ worsened	197 (15.7)	147 (15.1)	50 (17.9)	0.26
Not registered	187 (14.9)	156 (16.0)	31 (11.1)	0.041
Location				
Left sided	340 (27.1)	275 (28.2)	65 (23.2)	0.10
Right sided	106 (8.5)	98 (10.1)	8 (2.9)	<0.001
Middle of chest	385 (30.7)	281 (28.9)	104 (37.1)	0.008
Band-like around chest	71 (5.7)	48 (4.9)	23 (8.2)	0.036
Not registered	352 (28.1)	272 (27.9)	80 (28.6)	0.83
Radiation				
None	469 (37.4)	404 (41.5)	65 (23.2)	<0.001
Typical radiation[b]	193 (15.4)	142 (14.6)	51 (18.2)	0.14
Atypical radiation[b]	202 (16.1)	168 (17.2)	34 (12.1)	0.041
Not registered	390 (31.1)	260 (26.7)	130 (46.4)	<0.001
Type of pain				
Pressure/heavy	227 (18.1)	162 (16.6)	65 (23.2)	0.012
Stabbing/sharp	294 (23.4)	258 (26.5)	36 (12.9)	<0.001
Related to respiration	142 (11.3)	119 (12.2)	23 (8.2)	0.06
Unclear	155 (12.4)	138 (14.2)	17 (6.1)	<0.001
Not registered	436 (34.8)	297 (30.5)	139 (49.6)	<0.001
Course				
Gradual increasing intensity	301 (24.0)	249 (25.6)	52 (18.6)	0.016
Typical and subsided	23 (1.8)	18 (1.8)	5 (1.8)	0.95
Atypical and subsided	62 (4.9)	54 (5.5)	8 (2.9)	0.07
Rapidly progressive	9 (0.7)	7 (0.7)	2 (0.7)	1.00
Not registered	859 (68.5)	646 (66.3)	213 (76.1)	0.002

continues

continued

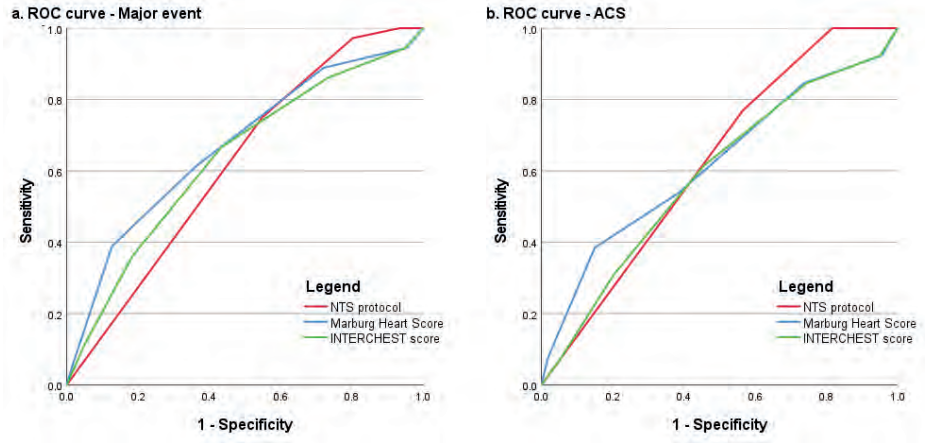
Accompanying symptoms[c]				
Yes	46 (3.7)	35 (3.6)	11 (3.9)	0.79
Subsided	27 (2.2)	23 (2.4)	4 (1.4)	0.34
No	670 (53.4)	565 (58.0)	105 (37.5)	<0.001
Not registered	511 (40.7)	351 (36.0)	160 (57.1)	<0.001
Triage outcomes				
High urgency (U1/U2)	830 (66.2)	604 (62.0)	226 (80.7)	<0.001
Activation of ambulance services	469 (37.4)	314 (32.2)	155 (55.4)	<0.001

The table illustrates the occurrence of symptom characteristics across the standardized NTS questions included in the chest pain protocol, and provides the main triage outcomes. Results are shown separately for all eligible patients and for patients with and without available data on additional study questions and clinical outcomes. P-value indicates difference between patients with and without available data.
Annotations: [a] Chest pain severity is scored on a 1-10 scale, 10 being most severe. [b] Triage assistants base whether radiation is typical or atypical by assessing the location and character of the radiation (e.g. pain, heaviness, tingling sensation). [c] Possible accompanying symptoms include sweating, nausea, pallor, fear/anxiety and (near) fainting.

The INTERCHEST score showed optimal diagnostic accuracy at a threshold of ≥1 point. At this threshold, the score classified 75.0% as high-risk, while failing to identify 5 major events. The false positive rate was lower than that of the NTS (63.9%), resulting in a sensitivity and specificity of 86.1% (95%-CI: 70.5-95.3) and 26.6% (95%-CI: 21.2-32.7), respectively. For ACS, the INTERCHEST score (≥1 threshold) missed 2 cases and had a false positive rate of 71.1%, yielding a sensitivity and specificity of 84.6% (95%-CI: 54.6-98.1) and 25.5% (95%-CI: 20.4-31.1), respectively.

The NTS protocol assigned high urgencies (U1 or U2) to 231/280 (82.5%) patients, correctly identifying 35/36 patients with a major event. However, 70% of patients were false positive, thus resulting in a sensitivity and specificity of 97.2% (95%-CI: 85.5-99.9) and 19.7% (95%-CI: 14.9-25.2), respectively. For ACS, all 13 cases were identified by the NTS (100% sensitivity), but two thirds of patients (77.9%) were false positive, resulting in a specificity of 18.4% (95%-CI: 13.9-23.5).

Figure 2. ROC curves illustrating the discriminative ability of the NTS protocol, MHS and INTERCHEST score for predicting (a) major events and (b) ACS.



The curve representing the NTS protocol was based on the allocation of a high urgency code (U1 or U2). The curves for the two clinical decision rules were based on the score results, ranging from 0-5 points (MHS) or -1-5 points (INTERCHEST). Abbreviations: ROC, receiver-operating characteristics; MHS, Marburg Heart Score; NTS, Netherlands Triage Standard; ACS, acute coronary syndrome.

Exploratory analysis: updated NTS protocol

The updated NTS protocol showed C-statistics of 0.59 (95%-CI: 0.50-0.67) for major event prediction and 0.64 (95%-CI: 0.51-0.77) for ACS. It assigned high urgency codes to only 94 (33.6%) patients, resulting in higher specificity (67.2% (95%-CI: 60.9-73.1) for major events, 67.4% (95%-CI: 61.4-73.0) for ACS). The updated protocol missed 22/36 (61.1%) major events and 6/13 (46.2%) ACS cases, causing a reduced sensitivity (38.9% (95%-CI: 23.1-56.5) for major events, 53.9% (95%-CI: 25.1-80.8) for ACS) (*Supplement 4*).

Table 3. Diagnostic accuracy of the NTS protocol, MHS and INTERCHEST score for predicting major events and ACS.

	Threshold	Positive test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Major event						
NTS protocol	U1/U2	82.5%	97.2 (85.5-99.9)	19.7 (14.9-25.2)	15.2 (14.1-16.3)	98.0 (87.2-99.7)
MHS	≥1	95.4%	94.4 (81.3-99.3)	4.5 (2.3-7.9)	12.7 (11.8-13.7)	84.6 (56.0-96.0)
	≥2	74.3%	88.9 (73.9-96.9)	27.9 (22.3-34.0)	15.4 (13.7-17.3)	94.4 (86.9-97.8)
INTERCHEST	≥0	95.0%	94.4 (81.3-99.3)	4.9 (2.6-8.4)	12.8 (11.9-13.8)	85.7 (58.3-96.3)
	≥1	75.0%	86.1 (70.5-95.3)	26.6 (21.2-32.7)	14.8 (13.0-16.8)	92.9 (84.9-96.8)
	≥2	46.4%.	66.7 (49.0-81.4)	56.6 (50.1-62.9)	18.5 (14.7-22.9)	92.0 (87.7-94.9)
ACS						
NTS protocol	U1/U2	82.5%	100.0 (75.3-100)	18.4 (13.9-23.5)	5.6 (5.3-5.9)	100.0 (92.8-100)
MHS	≥1	95.4%	92.3 (64.0-99.8)	4.5 (2.3-7.7)	4.5 (3.9-5.2)	92.3 (62.8-98.8)
	≥2	74.3%	84.6 (54.6-98.1)	26.2 (21.0-31.9)	5.3 (4.2-6.6)	97.2 (90.6-99.2)
INTERCHEST	≥0	95.0%	92.3 (64.0-99.8)	4.9 (2.6-8.2)	4.5 (3.9-5.3)	92.9 (64.8-98.9)
	≥1	75.0%	84.6 (54.6-98.1)	25.5 (20.4-31.1)	5.2 (4.2-6.6)	97.1 (90.3-99.2)
	≥2	46.4%	61.5 (31.6-86.1)	54.3 (48.1-60.4)	6.2 (4.0-9.3)	96.7 (93.5-98.3)

The table lists the diagnostic performance of the NTS protocol for chest pain and the two clinical decision rules. For both the MHS and INTERCHEST score, only thresholds with at least similar false-negative rates for major events are shown. Abbreviations: ACS, acute coronary syndrome; PPV, positive predictive value; NPV, negative predictive value; NTS, Netherlands Triage Standard; MHS, Marburg Heart Score.

DISCUSSION

In this prospective study, we found that the MHS and INTERCHEST scores had comparable discrimination, with higher specificity but lower sensitivity, compared to the current NTS protocol in patients contacting OOH-PC with acute chest pain. Given that optimal safety is the most important characteristic for triage purposes, this limits the clinical utility of these simple clinical decision rules for telephone triage.

Strengths and limitations

In this prospective study, we provide a head-to-head comparison between the performance of two clinical decision rules (i.e. MHS and INTERCHEST score) and the current standard for triage of acute chest pain in OOH-PC. We also included an exploratory analysis on the updated NTS protocol, implemented in October 2024. By using major events as a primary clinical outcome, we captured a broad range of serious underlying conditions of chest pain. Finally, although our study was conducted in the Netherlands, the findings may apply to other developed countries with similarly structured health care systems and integrated triage systems.

Our study also has limitations. First, triage assistants completed study questions in only 22.3% of eligible patients. These patients more often presented high-risk characteristics, suggesting selection bias due to diagnostic suspicion. Second, the number of events was low, a common finding due to low prevalences in primary care settings, resulting in wide confidence intervals. Third, symptoms not explicitly reported were assumed absent, which may have led to misclassification. Because this approach did not retain the distinction between 'not documented' and 'documented as absent', we were unable to quantify the amount of missing symptom information or perform sensitivity analyses based on missingness. This also affected the exploratory analyses of the updated NTS protocol, as several of its elements were not part of the original protocol or the additional study questions. Fourth, verification bias may have occurred as not all patients received diagnostic testing to confirm or exclude major events. However, our use of a delayed reference standard may have partly mitigated this. Lastly, the study was a single-center study, which may limit generalizability.

Comparison with literature

Safe and efficient triage of chest pain is pivotal to enable timely treatment and prevent complications of potential ACS. Prior research suggests an acceptable missed diagnosis rate of ≤1% and a maximum of 25-50 unnecessary referrals per ACS case, assuming a prevalence of 5%.[7,8,15] These benchmarks translate into a desired NPV ≥99% and specificity ≥50%. A previous retrospective assessment of the MHS and INTERCHEST showed a potential advantage of the scores compared to the NTS protocol, however both the scores and the NTS did not achieve the desired diagnostic accuracy.[16] Our current prospective study confirm these results: neither score reached optimal diagnostic accuracy, and both the MHS and INTERCHEST score failed to improve triage specificity without compromising safety.

For this study, we adapted the INTERCHEST score by replacing the original item 'physician's suspicion of a serious condition' with the triage assistant's sense of alarm, rated ≥5.5 on a 1-10 scale. Alternative thresholds did not significantly impact the score's diagnostic accuracy.

In October 2024, the NTS protocol was revised to incorporate elements of the Safety First model, a clinical prediction rule developed by Wouters *et al.* to predict ACS among patients with chest pain in OOH-PC.[1] In its original form, the model showed a C-statistic of 0.77-0.79 for ACS and a more favorable diagnostic accuracy compared to the NTS protocol.[1,19] For implementation, the model was converted to a decision tree, which had not been externally validated. In our exploratory analysis, the updated protocol achieved higher specificity, but markedly reduced sensitivity, resulting in a higher number of missed major events and ACS. These findings raise safety concerns and highlight the need for further validation. A key limitation of this analysis is potential misclassification due to missing data, as several elements of the updated protocol were not part of the NTS protocol that was in use during our study.

Clinical implications

Our findings show that neither the MHS nor the INTERCHEST score outperformed the NTS protocol, indicating that these tools may not be suitable for improving current telephone triage strategies. Although both scores include additional symptom information beyond what is used in the NTS, this added information did not translate into improved diagnostic accuracy. In addition, none of the strategies were able to significantly discriminate for ACS. Although, confidence intervals were wide, and the number of events was low.

The NTS protocol's high sensitivity (97.2% for major events; 100% for ACS) is a critical strength in telephone triage, where missing urgent cases has greater clinical consequences than generating false positives. The reduced sensitivity observed with both decision rules highlights the core challenge of telephone triage: safely assessing chest pain in a setting where clinical examination and diagnostic testing are unavailable. While improved specificity could theoretically reduce unnecessary resource utilization, the increased rate of missed urgent cases poses unacceptable safety risks.

Our study also revealed several logistical challenges. To improve feasibility, future prospective studies should aim to fully integrate study material (e.g. additional triage questions) into routine workflows. If this is not feasible, a retrospective design may reduce the risk of selection bias and improve generalizability. Finally, given that our study suggests limited safety of the

recently updated NTS protocol, sufficient evaluation of its performance in the near future is warranted.

Future directions

Our findings suggest that simple clinical decision rules may not meet the demands of telephone triage for chest pain. It is also important to note that other risk-stratification tools incorporate additional clinical factors, such as point-of-care troponin testing or ECG, which may improve the diagnostic accuracy but require in-person assessment or diagnostic resources not available during telephone triage. Future research should focus on developing triage-specific tools that account for the unique constraints of telephone assessment, while maintaining high sensitivity for urgent conditions.

CONCLUSION

The MHS and INTERCHEST score do not outperform current standards for telephone triage of chest pain in OOH-PC. Although both scores improved specificity, the concurrent reduction in sensitivity and increased amount of missed cases limits their clinical utility in the safety-critical context of telephone triage. The NTS protocol's high sensitivity for detecting major events and ACS, despite lower specificity, remains appropriate for telephone triage where missing urgent cases carries greater clinical risk than generating false positives.

REFERENCES

1. Wouters LT, Zwart DL, Erkelens DC, et al. Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study. *BMJ open*. 2022;12(10):e064402.
2. Frese T, Mahlmeister J, Heitzer M, Sandholzer H. Chest pain in general practice: Frequency, management, and results of encounter. *Journal of Family Medicine and Primary Care*. 2016;5(1)doi:10.4103/2249-4863.184625
3. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart*. Nov 2017;103(21):1727–1732. doi:10.1136/heartjnl-2016-310905
4. Svavarsdóttir AE, Jónasson MR, Gudmudsson GH, Fjeldsted K. Chest pain in family practice. *Canadian Family Physician*. 1996;42:1122–1128.
5. Verdon F, Herzig L, Burnand B, et al. Chest pain in daily practice: occurrence, causes and management. *Swiss Med Wkly*. 2008;138(23-24):340–347.
6. Ramerman L, Rijpkema C, Hek K, et al. Care through out-of-hours primary care. Nivel Care Registrations Primary Care: annual figures 2024 and trend figures 2020-2024. (Original Dutch title: "Zorg via de huisartsenspoedpost Nivel Zorgregistraties Eerste Lijn: jaarcijfers 2024 en trendcijfers 2020-2024") Utrecht: Nivel; 2025. p. 34.
7. Harskamp R, van Peet P, Bont J, Ligthart S, Lucassen W, van Weert H. The conundrum of acute chest pain in general practice: a nationwide survey in The Netherlands. *BJGP Open*. Dec 2018;2(4):bjgpopen18X101619. doi:10.3399/bjgpopen18X101619
8. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *International journal of cardiology*. 2013;166(3):752–754.
9. Julius Centrum Utrecht, Nederlandse Triage Standaard. Revision of the protocol for chest pain - supporting document and background information. (Original title: Aanpassing ingangsklacht "pijn/druk thorax" - Begeleidend document & inhoudelijke achtergrond), 2024.
10. Domus Medica - Netherlands Triage Standard. 2014.
11. Manten A, Rietveld RP, de Clercq L, et al. Evaluation of telephone triage among chest pain patients in out-of-hours primary care in the Netherlands (TRACE). *Fam Pract*. Jul 18 2022;doi:10.1093/fampra/cmac077
12. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA, Zwart DL. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open heart*. 2020;7(2):e001376.

13. International Working Group on Chest Pain in Primary Care (INTERCHEST), Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011

14. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212

15. van den Bulk S, Manten A, Bonten TN, Harskamp RE. Chest Pain in Primary Care: a systematic review of risk stratification tools to rule out Acute Coronary Syndrome. *The Annals of Family Medicine*. 2024;22(5):426–436.

16. Manten A, De Clercq L, Rietveld R, Lucassen W, Moll van Charante E, Harskamp R. Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care. *Netherlands Heart Journal*. 2022:1–7.

17. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *Radiology*. 2015;277(3):826–832.

18. Manten A, Cuijpers CJ, Rietveld R, et al. Rationale and design of a cohort study evaluating triage of acute chest pain in out-of-hours primary care in the Netherlands (TRACE). *Primary Health Care Research & Development*. 2020;21

19. Manten A, Harskamp RE, Busschers WB, Moll van Charante EP, Himmelreich JC. Telephone triage of chest pain in out-of-hours primary care: external validation of a symptom-based prediction rule to rule out acute coronary syndromes. *Family Practice*. 2024;41(5):832–840.

SUPPLEMENTARY MATERIAL

Supplement 1. Additional study items.

Upon contact with OOH-PC with key complaint of chest pain or when NTS protocol 'thoracic pain' is enabled:
Inform patient on study and request verbal consent
Additional triage questions: 1. Pain reproducible with palpation? 2. Pain related to or worsened by exertion? 3. Medical history of cardiovascular disease[a]? If yes, specify. 4. Patient believes pain is of cardiac origin?
Additional assessments: 1. Triage assistant's suspicion of a cardiac cause on a 1-10 scale? 2. Triage assistant agrees with urgency code generated by NTS protocol?

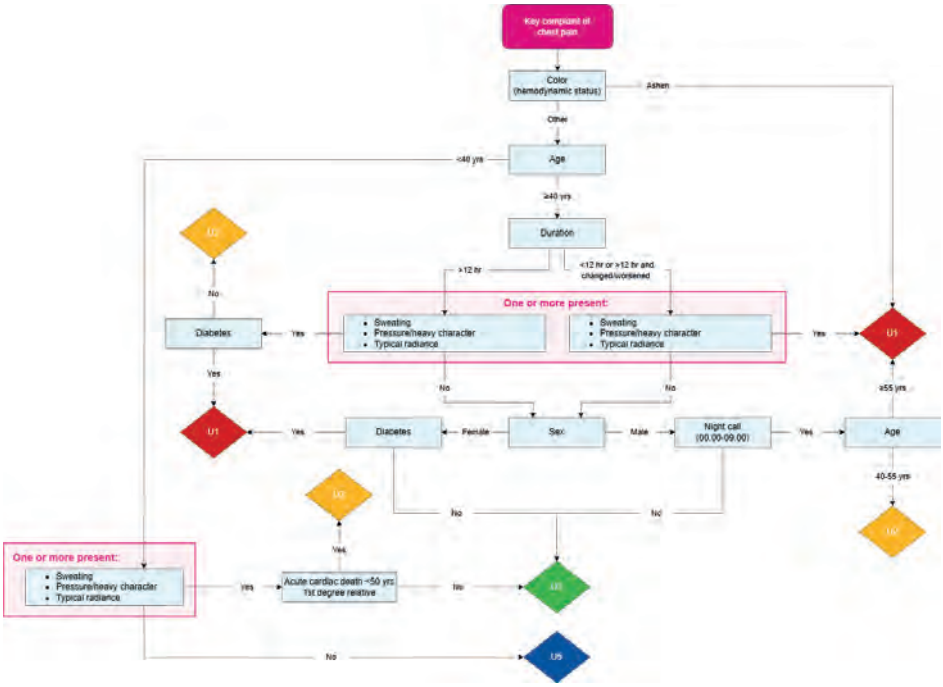
The table shows the composition of the study material used by the triage assistants to include eligible patients. After informing the patient about the study and requesting an initial verbal consent, triage assistants asked 4 additional questions and made 2 additional assessments. Annotations: [a] cardiovascular disease was defined as known coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Abbreviations: OOH-PC, out-of-hours primary care; NTS, Netherlands Triage Standard.

Supplement 2. Definition of major and non-major events.

	Final diagnosis	Precondition
Major events		
Cardiovascular conditions	Death from any cause	
	Acute coronary syndrome	
	Urgent coronary revascularization	
	Pulmonary embolism	
	Thoracic aortic aneurysm (dissection or ruptured)	
	Severe/Acute congestive heart failure	Hospitalization
	Severe peri(myo)carditis	Hospitalization
	Symptomatic atrial fibrillation	Hospitalization (cardioversion or converted through medication)
	Aortic valve stenosis	Hospitalization
	CVA/TIA	
Non-cardiovascular conditions	(Tension) pneumothorax	Hospitalization
	Severe pneumonia	Hospitalization
	Inflammatory processes such as appendicitis, pancreatitis, cholecystitis	Hospitalization
	Other, such as: exacerbation COPD or hypertensive crisis	Hospitalization
	Traumatic event (with significant impact)	Hospitalization
Non-major events		
	Stable angina pectoris	Outpatient treatment
	Mild congestive heart failure	Outpatient treatment
	Mild peri(myo)carditis	Outpatient treatment
	Atrial fibrillation (recurrent/ paroxysmal)	Outpatient treatment
	Hypertension	Outpatient treatment
	Mild pneumothorax	Outpatient treatment
	Mild pneumonia	Outpatient treatment
	Mild respiratory problems (such as viral infections)	
	Gastric/esophagus problems	
	Muscoloskeletal	
	Traumatic (mild trauma)	Outpatient treatment
	Mental health, panic attack, anxiety disorder	

The table specifies the distinction between major and non-major events as defined in the TRACE study. In some diagnoses the urgency is determined by preconditions. For example, severe congestive heart failure that requires hospitalization or immediate in-hospital treatment is considered a major event, whereas mild congestive heart failure that requires only outpatient treatment is not. Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Supplement 3. Decision tree of the updated NTS protocol (per October 2024).



In October 2024, the NTS protocol was updated based on the Safety First model[1]. Predictors from this model and elements from the prior NTS protocol were combined into a decision tree with corresponding urgency codes. Included Safety First predictors were: age, sex, sweating, and calling at night (between 00:00 and 09:00). Additionally, acute cardiac death <50 years in a first degree relative was included. Original NTS questions on pain severity, location and course were omitted. The urgency codes were based on the relative risk of an ACS or other life threatening event in the derivation cohort of the Safety First model (i.e. U1: ≥20%, U2: 15-20%, U3: 10-15%, U4; 5-10% and U5: <5%).

The decision tree displayed here was adopted and translated based on the original document: "Revision of the protocol for chest pain – supporting document and background information" released by the Julius Centrum UMC Utrecht and the Netherlands Triage Standard in September 2024 to support the alterations made to the protocol.[9]

Supplement 4. Diagnostic accuracy of the updated NTS protocol (per October 2024) for predicting major events and ACS.

	Threshold	Positive test	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Major event										
NTS protocol	U1/U2	33.6%	14	80	22	164	38.9 (23.1-56.5)	67.2 (60.9-73.1)	14.9 (10.1-21.5)	88.2 (85.0-90.8)
ACS										
NTS protocol	U1/U2	33.6%	7	87	6	180	53.9 (25.1-80.8)	67.4 (61.4-73.0)	7.5 (4.5-12.1)	96.8 (94.3-98.2)

The table lists the diagnostic performance of the updated NTS protocol for chest pain, installed in October 2024. Abbreviations: ACS, acute coronary syndrome; TP, true positive; FN, false negative; FP, false positive; TN, true negative; PPV, positive predictive value; NPV, negative predictive value; NTS, Netherlands Triage Standard.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 8

Telephone triage of chest pain in out-of-hours primary care: external validation of a symptom-based prediction rule to rule out acute coronary syndromes

Amy Manten, Ralf E. Harskamp, Wim B. Busschers, Eric P. Moll van Charante, Jelle C.L. Himmelreich

Published in Family Practice, 2024

PMID: 38801727

DOI: 10.1093/fampra/cmae028

ABSTRACT

Introduction: Telephone triage is pivotal for evaluating the urgency of patient care, and in the Netherlands, the Netherlands Triage Standard (NTS) demonstrates moderate discrimination for chest pain. To address this, the Safety First prediction rule (SFPR) was developed to improve the safety of ruling out acute coronary syndrome (ACS) during telephone triage.

Methods: We conducted an external validation of the SFPR using data from the TRACE study, a retrospective cohort study in out-of-hours primary care. We evaluated the diagnostic accuracy assessment for ACS, major adverse cardiovascular events (MACE), and major events within 6 weeks. Moreover, we compared its performance with that of the NTS algorithm.

Results: Among 1404 included patients (57.3% female, 6.8% ACS, 8.6% MACE), the SFPR demonstrated good discrimination for ACS (C-statistic: 0.79; 95%-CI:0.75-0.83) and MACE (C-statistic: 0.79; 95%-CI:0.0.76-0.82). Calibration was satisfactory, with overestimation observed in high-risk patients for ACS. The SFPR (risk threshold 2.5%) trended toward higher sensitivity (95.8% vs 86.3%) and negative predictive value (99.3% vs. 97.6%) with lower negative likelihood ratio (0.10 vs 0.34) than the NTS algorithm.

Conclusion: The SFPR proved robust for risk stratification in patients with acute chest pain seeking out-of-hours primary care in the Netherlands. Further prospective validation and implementation are warranted to refine and establish the rule's clinical utility.

INTRODUCTION

Telephone triage is often the first step in assessing whether a patient requires urgent care. To help primary care triage assistants in this process, triage protocols have been developed.[1] In the Netherlands, the leading triage protocol in primary care is the 'Netherlands Triage Standard' (NTS).[2] This protocol was derived from the Manchester triage protocol and adapted to a Dutch primary care setting. Prior evaluation of the NTS triage protocol shows that it has moderate discrimination for chest pain, a common symptom that may among others be the result from acute coronary syndrome (ACS).[3] Given the underperformance of this system, a new symptom-based prediction rule, the Safety First Prediction rule (SFPR), was developed for chest pain, with the primary goal of safely ruling out ACS.[4] This model consists of seven predictors, and internal-external cross validation showed good discriminative ability for ACS within 30 days after telephone triage (adjusted C-statistic 0.77 (95%CI: 0.74-0.79)). In the current study, we aimed to perform external validation of the SFPR for ACS and other relevant outcomes in a sample of patients who contacted an out-of-hours primary care (OOH-PC) facility for acute chest pain in a different region of the Netherlands.

METHODS

We reported our study in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement and used the checklist for Prediction Model Validation.[5] The Medical Ethics Committee of the Amsterdam University Medical Center, reviewed and approved our study protocol (National Trial Register NL7581).[6]

Study design and participants

We assessed the diagnostic accuracy of the SFPR using data from the 'TRiage of Acute Chest pain Evaluation in primary care (TRACE)' study.[3,7] TRACE is an observational, retrospective cohort study of patients with chest pain who contacted OOH-PC between 1 January 2017 and 31 December 2017. For this study, all consecutive patients ≥18 years with acute chest pain were considered eligible for inclusion at their first contact with the OOH-PC facility in Alkmaar, the Netherlands. At the outset of the TRACE study, all eligible patients received information by mail and were provided the opportunity to opt-out from sharing data. Patients who expressed objection to participation and those patients who bypassed the triage system were not eligible for inclusion. We further

excluded patients with missing data on any of the SFPR elements from the analyses.

In the Netherlands, OOH-PC facilities provide care to the patients of affiliated GPs when daytime practices are closed (i.e. evenings, nights, weekends and holidays). Given that referral by a GP is required for secondary care in the Netherlands, patients with chest pain will generally first present to OOH-PC facilities, with the exception of cases where immediate hospitalization is indicated. The facility in Alkmaar provides care to approximately a quarter million patients and covers both urban and rural areas. Upon telephone contact with the OOH-PC facility, trained triage assistants gather information on patient and symptom characteristics to assess the patient's urgency (using urgency codes U1-U5, in which U1 indicates the highest urgency) and determine the preferred course of action (e.g. ambulance activation, GP consultation, telephone advice). Here, triage assistants use standardized, symptom-based protocols from the NTS.

Safety First Prediction Rule

The SFPR consists of a multivariate model with seven predictors: (i) age, (ii) sex, (iii) acute onset of chest pain (<12 hours), (iv) a pressing/heavy character, (v) radiation of pain, (vi) sweating, and (vii) calling at night (i.e. between 00.00 and 09.00). The model was developed using a multivariate regression analysis with candidate predictors derived from the NTS protocol, existing chest pain risk scores, and prior analyses by the research group.[4] *Table 1* displays model variables, interaction terms, and applied coefficients verified by correspondence with the original authors.[4]

Table 1. Components of the SFPR.

Model variable	Original SFPR regression coefficients (SE)	Difference[a]	p-value
Intercept	-16.246 (3.527)	7.068	0.013
Age	0.293 (0.081)	-0.182	0.008
Age'	-0.391 (0.125)	0.316	0.011
Age"	1.063 (0.395)	-1.062	0.017
Female sex	2.504 (5.512)	-32.890	0.035
Acute onset of chest pain (<12 hours)	0.290 (0.198)	0.315	0.254
Sweating	0.457 (0.178)	0.282	0.236
Radiation of chest pain	0.609 (0.176)	0.086	0.708
Pressing or heavy pain	0.747 (0.200)	-0.142	0.576
Calling at night between 00.00 and 9.00 hours	0.504 (0.151)	-0.213	0.366
Age*female sex	-0.096 (0.126)	0.765	0.026
Age'*female sex	0.189 (0.195)	-1.173	0.014
Age"*female sex	-0.556 (0.605)	3.552	0.010

[a]Difference between the SFPR and TRACE coefficients when adding the SFPR linear predictor as an offset in the TRACE dataset for the primary outcome (acute coronary syndrome). Knots for cubic spline functions placed at 25, 51, 69 and 88. Abbreviations: SE, standard error; SFPR, Safety First prediction rule.

In the TRACE database, age, sex, and the time of contact are registered by default for each patient who contacts the OOH-PC facility. The other predictors consist of symptom characteristics that are part of the NTS protocol and are therefore readily available in our patient sample. Researchers coding the predictors from electronic health records were blinded for the outcome. Medical history items and symptom characteristics that were not explicitly mentioned in the triage registries were assumed absent and were coded as such.

Outcomes and reference standard

The primary outcome was ACS, defined as acute myocardial infarction (i.e. NSTEMI or STEMI) or unstable angina, as the underlying diagnosis for the index telephone contact. Secondary outcomes were major adverse cardiovascular events (MACE) and the occurrence of any major event up to 6 weeks after index contact. MACE is defined as the composite of all-cause mortality, acute myocardial infarction, and acute coronary interventions (i.e. percutaneous coronary intervention or coronary artery bypass graft surgery).[8] We defined

major events as all-cause mortality or the occurrence of any cardiovascular and noncardiovascular urgent condition that was linked to the initial complaint of chest pain if these required hospital admission or immediate in-hospital treatment (*Supplementary Table S1*).[3,7]

Reference diagnoses were established using a delayed-type reference standard. In the Netherlands, each inhabitant is registered with a GP practice that holds a patient record file, including correspondence from OOH-PC facilities, emergency departments, and hospital specialists. Follow-up data, including final diagnoses, were collected from these patient record files at least six weeks after initial contact with the OOH-PC facility, in order to assess MACE and major events and to allow for any delayed correspondence relating to ACS to have arrived back at the participating patient's GP. The researchers (A.M., R.E.H.) assessing the occurrence of ACS, MACE, or major events were not blinded to information from the triage report. An independent expert was available as a third assessor in case of disagreement.

Statistical analysis

We reported descriptives of categorical variables as number and percentage, and continuous and ordinal variables as median and interquartile range (IQR). We assessed differences using Pearson chi^2 test for categorical variables, and Student's *t*-test (normally distributed) or Mann–Whitney *U* test (non-normally distributed) for continuous data. We presented baseline characteristics for the complete cases as well as for the cases excluded for missing data for ≥1 of the SFPR variables and provided the percentage missing for each of the SFPR variables.

For the external validation of the SFPR, we performed a complete case analysis of TRACE patients who had available data on the rule's predictors and in whom a final diagnosis was established. We calculated risk as per the SFPR for each patient as 1/(1+exp(-LP)), with LP being the linear predictor calculated as the sum of coefficients as provided by the authors of the original derivation paper times the variable values of the model.[4] We modeled age similarly to the derivation paper, using a restricted cubic spline function with knots at 25, 51, 69, and 88 years of age. The intercept and variable coefficients used in the analyses are shown in *Table 1*.

We assessed discrimination of the SFPR for the outcomes ACS, MACE, and major event separately by the C-statistic and 95% confidence interval (CI) using DeLong's method.[9] In assessing calibration for each of the outcomes, we produced calibration plots and used the calibration slope of the linear predictor and its 95%-CI to assess the agreement between predicted and observed cases. In providing the calibration plot and slope, we corrected

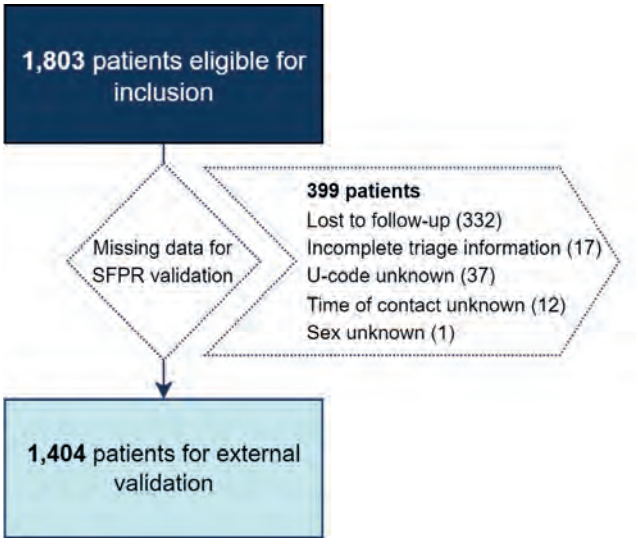
for optimism using 200 bootstrapping samples. We calculated the model's diagnostic accuracy for predicting each of the outcomes using sensitivity, specificity, positive and negative predictive values (PPV and NPV), and positive and negative likelihood ratios (LR+ and LR-). We applied a threshold of 2.5%, corresponding to previous validation of the NTS for ACS, where 61.8% of presentations were assessed as high risk. In addition, we used the risk threshold corresponding to a NPV of 99% for ACS, which is generally accepted for the exclusion of ACS.[10,11] In interpreting LR+ and LR-, an LR+>10 and LR-<0.1 are generally considered to indicate that a test can rule a diagnosis in or out, respectively.[12] We subsequently provided these same diagnostic accuracy parameters for high urgency as per original telephone triage (defined as NTS urgencies U1 or U2) for the outcomes of interest to facilitate a comparison between the SFPR and the current standard for telephone triage of chest pain.

To investigate possible differences in associations, we fitted the same model to our data, adding the Safety First linear predictor as an offset. We also provided the shrinkage factor for the overall model when validating for the primary outcome in our dataset to further assess the external validity of the original SFPR and its coefficients. We did not proceed to recalibrate the model due to the limited sample size and risk of overfitting. Finally, we plotted the probabilities of the outcomes as a function of age for the men and women separately to visualize the significant interaction between age and sex. This was analogous to the analysis reported in the SFPR derivation paper, which showed a significant interaction between sex and age with significant differences among patients between the ages of 40 and 70.

RESULTS

Between 1 January 2017 and 31 December 2017, 1803 eligible patients contacted the OOH-PC facility in Alkmaar regarding acute chest pain. A total of 399 (22.1%) patients with missing information on at least one of the model's predictors were excluded from the analysis (*Figure 1*). Patient characteristics and urgencies did not differ between these patients and those included in the final sample (*Table 2*). Among the 1404 included patients, the median age was 54 years (IQR: 37-71) and 57.3% were female. There were 95 ACS cases (5.5% among women and 8.5% among men, p=0.024), composed of unstable angina (*n*=19), NSTEMI (*n*=41), STEMI (*n*=24), and unspecified ACS (*n*=11). The majority of included patients (61.4%) received a high urgency code (i.e. U1 or U2) following triage at the OOH-PC facility, including 87.4% of patients with ACS. Overall, the median estimated SFPR risk in our sample was 0.050 (IQR: 0.005-0.121). The risk was 0.032 (IQR: 0.003-0.081) in women and 0.085 (IQR: 0.011-0.172) in men.

Figure 1. Flow of patients.



The TRACE cohort comprised 1803 patients eligible for inclusion. Due to missing data on SFPR predictors or outcome measures, 399 patients were excluded from the final analyses. Abbreviations: SFPR, Safety First Prediction Rule.

Safety First Prediction Rule validation for acute coronary syndrome

Assessment of the discriminatory ability showed a C-statistic of 0.79 (95%-CI: 0.75-0.83) for ACS. The calibration slope was 0.99 before and after bootstrap correction. The calibration plot indicated good overall calibration (*Figure 2*).

Safety First Prediction Rule validation for major adverse cardiovascular events and major events

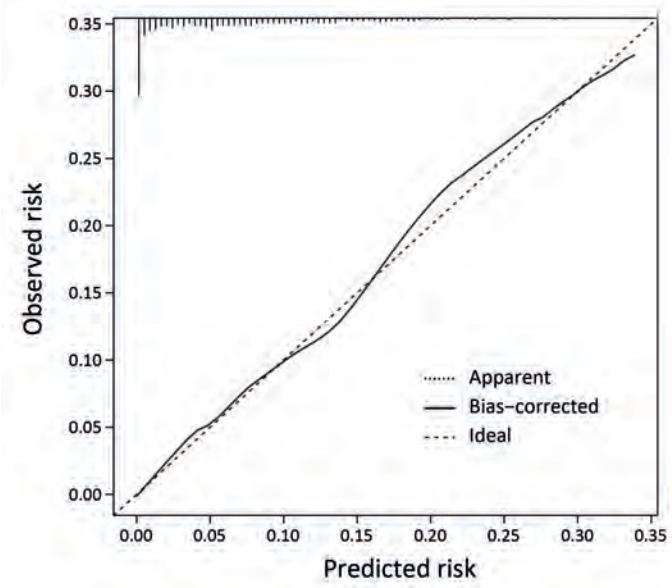
MACE occurred in 121 patients (7.1% among women and 10.7% among men, p=0.017). Major events were identified in 223 patients (12.2% among women and 20.9% among men, p<0.001), and were mostly of cardiovascular origin (76.7%), followed by respiratory (9.9%) and abdominal (7.2%) etiologies. The C-statistics (95%-CI) of the SFPR for MACE and major events were 0.79 (0.76-0.82) and 0.78 (0.75-0.81), respectively. Calibration of the SFPR for MACE showed good calibration for MACE in patients with low estimated risk but with a trend toward overestimation in the small group of patients with the highest predicted risks (*Figure 3, left*). Calibration for major events was good in the majority of patients, with slight underestimation of risk in those with the highest predicted risks (*Figure 3, right*). The calibration slope of the SFPR was 0.99 for both MACE and major events and was unchanged after correction for optimism.

Table 2. Characteristics of TRACE patients included in the SFPR analyses.

Patient characteristics	Included (*n*=1404)	Cases with missing SFPR data (*n*=399)	Overall (*n*=1803)
SFPR demographic variables			
Age	54 (37-71)	52 (33-70)	54 (37-70)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Female sex	805 (57.3)	233 (58.4)	1038 (57.6)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
SFPR symptoms			
Chest pain duration <12 hours	852 (60.7)	23 (5.8)	875 (48.5)
Missing	0 (0.0)	349 (87.5)	349 (19.4)
Pressing/heavy chest pain	679 (48.4)	22 (5.5%)	701 (38.9%)
Missing	0 (0.0)	349 (87.5)	349 (19.4)
Radiation of pain to any location	618 (44.0)	23 (5.8)	641 (35.6)
Missing	0 (0.0)	376 (94.2)	376 (20.8)
Sweating	267 (19.0)	6 (1.5)	273 (15.1)
Missing	0 (0.0)	332 (83.2)	332 (18.4)
Calling at night (00:00-09:00)	347 (24.7)	18 (4.5%)	365 (20.2%)
Missing	0 (0.0)	358 (89.7)	358 (19.9)
Medical history and risk factors			
History of coronary artery disease	256 (18.2)	40 (10.0)	296 (16.4)
Diabetes	172 (12.3)	27 (6.8)	199 (11.0)
Hypertension	432 (30.8)	58 (14.5)	490 (27.2)
Hypercholesterolaemia	235 (16.7)	16 (4.0)	251 (13.9)
Urgency			
High urgency (U1/U2)	862 (61.4)	199 (49.9)	1061 (58.8)
Urgency U1	532 (37.9)	136 (34.1)	668 (37.0)
Urgency U2	330 (23.5)	63 (15.8)	393 (21.8)
Outcomes			
ACS	95 (6.8)	4 (1.0)	99 (5.5)
Unstable angina	19 (1.4)	0 (0.0)	19 (1.1)
NSTEMI	41 (2.9)	3 (0.8)	44 (2.4)
STEMI	24 (1.7)	0 (0.0)	24 (1.3)
Not specified	11 (0.8)	1 (0.3)	12 (0.7)
MACE	121 (8.6)	7 (1.8)	128 (7.1)
Major event	223 (15.9)	15 (3.8)	238 (13.2)

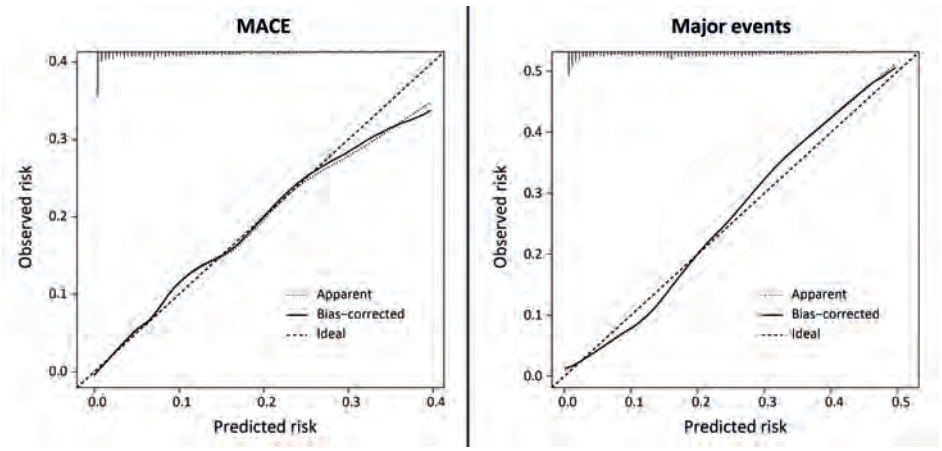
The table shows the characteristics of TRACE patients included in the analyses (n=1404). The middle column of the table illustrates the characteristics for the n=399 patients that were excluded from the analyses due to missing data for the SFPR variables. Percentage of missing data per group is provided for each of the SFPR variables. The right column summarizes the characteristics among the total group of TRACE patients (n=1803). Categorical variables are described using frequencies (%), age is described as median (IQR). Abbreviations: ACS, acute coronary syndrome; MACE, major adverse cardiovascular event; NSTEMI, non-ST-elevation myocardial infarction; SFPR, Safety First prediction rule; STEMI, ST-elevation myocardial infarction; U1, Netherlands Triage Standard urgency level U1; U2, Netherlands Triage Standard urgency level U2.

Figure 2. Calibration plot for the Safety First prediction rule for ACS.



Brackets on the top horizontal axis indicate the proportion of patients with respective predicted risk (x axis).

Figure 3. Calibration plots of the Safety First Prediction Rule for MACE and major events.



Brackets on the top horizontal axis indicate the proportion of patients with respective predicted risk (x axis). Abbreviations: MACE, major adverse cardiac events.

Diagnostic accuracy at different Safety First Prediction Rule risk thresholds and comparison with Netherlands Triage Standard

We calculated at which SFPR cutoff the NPV for ACS equaled 99%. This was established at a threshold of 3.3%, qualifying 57.3% of patients as high risk (*Table 3*). When applying the threshold for the other outcomes, the score performed sufficiently for ruling out MACE (NPV 99.0%), but not for major events (NPV 96.5%).

When stratifying for NTS urgencies U1 or U2, 61.5% of the included patients were assessed as high risk. When comparing diagnostic accuracy parameters of the SFPR at 2.5% predicted risk with NTS's U1/U2 urgency – each resulting in 61.5% of patients being assessed as having high risk – the SFPR trended toward higher sensitivity (95.8% vs 86.3%) and NPV (99.3% vs 97.6%) with lower LR- (0.10 vs 0.34) than the NTS triage urgencies (*Table 3*).

Supplementary tables S2 A-C illustrate the diagnostic accuracy of the SFPR and NTS for the outcomes of interest stratified by age, sex, and time of contact, respectively. Considerable differences were observed among patients stratified by age. Here, patients ≤54 years showed a sufficient NPV at a threshold of 3.3%, with only 22.3% of patients classified as high risk, whereas patients aged >54 years needed a SFPR threshold of 4.2% and 87.9% of patients were classified as high risk. When comparing women with men, optimal SFPR thresholds were set at 3.3% and 4.4%, respectively, classifying 49.2% of women and 66.6% of men as high risk. Stratifying for the time of contact did not result in considerable differences.

Additional analyses

Table 1 shows the results of adding the SFPR linear predictor as an offset in the TRACE dataset for the primary outcome (ACS). In TRACE, age and female sex, as well as their interaction variables, showed significantly different coefficients compared with the original SFPR coefficients. The shrinkage factor of the SFPR for ACS was 0.87 (95%-CI: 0.64-1.10), indicating that the overall deviations in model performance observed in the TRACE dataset were not statistically significant.

The interaction between age and sex for the probability of the outcomes of interest is illustrated in *Figure 4* . For all outcomes (ACS, MACE, major events), risk increased with age for both women and men. However, only the risk of major events showed significant differences between women and men in the ages 55-80 years.

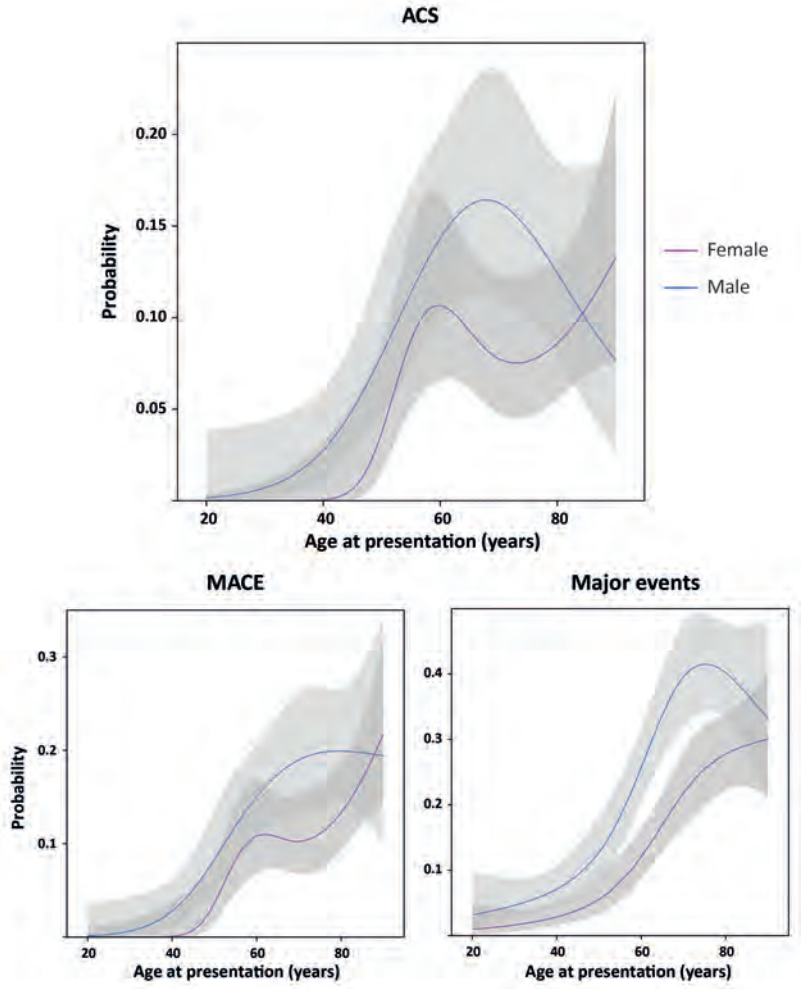
Table 3. Diagnostic accuracy of SFPR and NTS for the outcomes of interest in the TRACE cohort.

	Risk threshold	% 'high risk' at threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-
ACS	NTS U1/U2	61.5	86.3 (77.7-92.5)	40.4 (37.7-43.1)	9.5 (8.8-10.3)	97.6 (96.1-98.5)	1.45 (1.32-1.59)	0.34 (0.20-0.56)
	SFPR 0.025	61.5	95.8 (89.6-98.8)	41.3 (38.7-44.1)	10.6 (10.0-11.2)	99.3 (98.1-99.7)	1.63 (1.53-1.74)	0.10 (0.04-0.27)
	SFPR 0.033[a]	57.3	93.7 (86.8-97.7)	45.3 (42.6-48.0)	11.1 (10.4-11.8)	99.0 (97.9-99.5)	1.71 (1.59-1.84)	0.14 (0.06-0.30)
MACE	NTS U1/U2	61.5	85.1 (77.5-90.9)	40.8 (38.1-43.5)	12.0 (11.1-12.9)	96.7 (95.0-97.8)	1.44 (1.32-1.57)	0.36 (0.24-0.56)
	SFPR 0.025	61.5	96.7 (91.8-99.1)	42.2 (39.5-44.9)	13.6 (13.0-14.3)	99.3 (98.1-99.7)	1.67 (1.58-1.77)	0.08 (0.03-0.21)
	SFPR 0.033[a]	57.3	95.0 (89.5-98.2)	46.2 (43.5-49.0)	14.3 (13.5-15.1)	99.0 (97.8-99.5)	1.77 (1.66-1.89)	0.11 (0.05-0.23)
Major event	NTS U1/U2	61.5	82.5 (76.9-87.3)	42.6 (39.8-45.5)	21.4 (20.1-22.7)	92.8 (90.6-94.5)	1.44 (1.33-1.55)	0.41 (0.31-0.6)
	SFPR 0.025	61.5	93.3 (89.2-96.2)	44.9 (42.0-47.8)	24.2 (23.1-25.4)	97.3 (95.6-98.3)	1.69 (1.59-1.80)	0.15 (0.09-0.25)
	SFPR 0.033[a]	57.3	90.6 (86.0-94.1)	48.9 (46.1-51.8)	25.1 (23.8-26.4)	96.5 (94.8-97.7)	1.77 (1.65-1.90)	0.19 (0.13-0.29)

Sensitivity, specificity, PPV, and NPV are shown in percentages (%) with the 95%-CI between brackets. [a]Lowest cut-off where NPV for ACS best approached 99.0%.

Abbreviations: ACS, acute coronary syndrome; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MACE, major adverse cardiovascular event; NPV, negative predictive value; NTS U1/U2, Netherlands Triage Standard urgency level U1 or U2; PPV, positive predictive value; SFPR, Safety First prediction rule.

Figure 4. Association between seks and age for the probability of ACS, MACE and major events in the TRACE cohort.



Abbreviations: ACS, acute coronary syndrome; MACE, major adverse cardiovascular events.

DISCUSSION

In this study, we externally validated the SFPR for acute chest pain in OOH-PC. We found that the prediction rule had good discriminatory properties and was adequately calibrated. Moreover, it outperformed the current triage standard, with higher sensitivity and NPV, and lower LR-, indicating that the SFPR is better able to rule out chest pain using telephone triage in OOH-PC.

Strengths and limitations

External validation is pivotal prior to implementing a new risk score and/or decision support tool. In this study, we used a large, consecutive cohort of patients to conduct our analyses. Given the robust performance of the SFPR in an unrelated patient sample, we believe that the rule is generalizable to Dutch OOH-PC patients. While speculative, the rule might also be applicable in countries with similar health care systems, such as Scandinavian countries or the UK. We also extended our knowledge of the performance of the SFPR by evaluating the predictive value of the rule for other clinically relevant chest pain-related outcomes as well (i.e. MACE and major event).

The retrospective nature of our study constitutes its primary limitation. SFPR predictors were not systematically queried, leading to the exclusion of 22.1% of patients with missing data. Furthermore, our study used a delayed-type reference standard, which may introduce verification bias. However, we applied an extended follow-up period to accommodate any initially missed events, which is a common strategy in primary care-based studies. Another limitation is that our patient sample was too limited for recalibration and subsequent validation. Finally, triage in Dutch OOH-PC is based on key complaints (i.e. chest pain). This method is adopted in the SFPR, meaning that it assumes a key complaint of chest pain. Consequently, the rule is not tested in patients with atypical symptom presentations (e.g. without chest pain).

Comparison with existing literature

In the derivation paper of the SFPR, assessment of the final model and internal-external validation resulted in C-statistics of 0.79 (0.76-0.81) and 0.77 (0.74-0.79), respectively.[4] In our study, external validation confirmed the rule's discriminative abilities, with a C-statistic of 0.79 (0.75-0.83) for ACS. Calibration was satisfactory in the majority of patients, except for patients deemed at high risk (predicted probability >0.175), in whom absolute ACS risk was overestimated. This observation was found in both the original paper and our validation study. From a triage perspective, this may not be of clinical significance, as the risk threshold for high urgency and subsequent immediate

action lies well below 0.175. Furthermore, in the original paper, the diagnostic test accuracy was calculated across a range of model-based risk thresholds, following the example of Wynants *et al.*[13] We reproduced the threshold of 2.5% since this corresponds to previous validation of the NTS for ACS, where 61.8% of presentations were assessed as high risk.[3] In addition, we used the risk threshold corresponding of a NPV of 99% for ACS and applied this for all outcomes. An NPV of 99% is generally accepted for the exclusion of ACS in both recommendations from the European Society of Cardiology and prior research among Dutch GPs.[10,11]

With our study, we expanded the assessment of the SFPR to other relevant chest pain-related outcomes by including MACE and major events as outcome measures. The rule showed robust results for MACE and major events, with C-statistics of 0.79 (0.76-0.82) and 0.78 (0.75-0.81), respectively. Calibration was acceptable for both.

Although we used a comparable sample of adult patients presenting to a Dutch OOH-PC facility with chest pain, differences between the original sample of Wouters *et al.* and our patients do exist. The original patient sample involved overall higher-risk patients, illustrated by an ACS prevalence of 11.5% (8.3% among women and 15.3% among men), compared to 6.8% (5.5% among women and 8.5% among men) in our patients.[4] Furthermore, in the derivation study, the interaction between age and sex was more outspoken. Here, the ACS risk increased with age for both sexes, with a noticeable peak in men around the age of 60 years, whereas women showed a more gradual increase in ACS risk. Significant differences in ACS probabilities were seen between women and men in the ages 45-70 years.[4] Among our patients, ACS risks increased with age, without significant differences between sexes. Differences in the interaction between age and sex might be caused by the amount of knots used for the cubic splines, since too many knots might cause overfitting. However, reducing the amount of knots in the TRACE cohort (i.e. from four to three) did not affect our data.

For the derivation of the SFPR, the authors derived candidate predictors from current national triage guidelines (NTS) and previously developed decision rules, such as the Marburg Heart Score (MHS) and the INTERCHEST score.[14,15] To assess the benefit of their final model, they compared its performance with that of the NTS (based on urgency code allocation, with high urgencies (U1 and U2) indicating a positive test). In their results, the NTS generated a C-statistic of 0.58.[4] Comparison of the Safety First model with the MHS and/or INTERCHEST score is lacking. A prior study by our own research group did compare the performance of the NTS to that of the MHS and INTERCHEST scores, when the latter two were applied as stand-alone triage tools. Here,

the NTS resulted in a C-statistic of 0.68, which was outperformed by both the MHS and INTERCHEST scores, with C-statistics of 0.70 and 0.77, respectively.[16]

The 'calling at night' predictor in the SFPR is not part of the current NTS or existing clinical decision rules, but was derived from a previous study by Wouters *et al*.[17] In this study, an increased risk of ACS was observed among patients who initiated contact with the OOH-PC facility during the night. Within our data, the 'calling at night' predictor's coefficient was slightly lower (offset -0.213). Therefore, we explored the effect of adjusting the time interval from 00:00-09:00 to 22:00-05:00 and recalculated risk prediction. However, this did not change the discriminative ability of the model (data not shown).

Implications for further research

In this retrospective, external validation of the SFPR, results are promising, and certainly when compared with the current triage standard. However, further prospective validation of the rule is warranted, especially if implementation outside the Netherlands is considered. Furthermore, the rule lacks prespecified risk thresholds, which impedes further evaluation.

Some previously developed clinical decision rules, such as the INTERCHEST score, include the GPs suspicion or 'gut feeling' as a predictor for ACS.[14] In triage settings, triage assistants assess the patient's urgency, often without the influence of GPs. Therefore, we might consider taking the triage assistant's suspicion into account as an additional risk predictor in future research.

CONCLUSION

The Safety First prediction rule was found to be a robust prediction tool for risk stratification of patients with acute chest pain who reached out to an OOH-PC facility in The Netherlands. The rule holds promise for improving future telephone triage but warrants further prospective validation and implementation.

REFERENCES

1. Huibers L, Smits M, Renaud V, Giesen P, Wensing M. Safety of telephone triage in out-of-hours care: a systematic review. *Scand J Prim Health Care*. Dec 2011;29(4):198–209. doi:10.3109/02813432.2011.629150
2. Domus Medica - Netherlands Triage Standard. http://de-nts.nl/
3. Manten A, Rietveld RP, de Clercq L, et al. Evaluation of telephone triage among chest pain patients in out-of-hours primary care in the Netherlands (TRACE). *Fam Pract*. Jul 18 2022;doi:10.1093/fampra/cmac077
4. Wouters LT, Zwart DL, Erkelens DC, et al. Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study. *BMJ open*. 2022;12(10):e064402.
5. Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of internal medicine*. 2015;162(1):W1–W73.
6. Triage of Acute Chest Pain Evaluation in primary care [internet]. National Trial Register. 2019. Available from: https://onderzoekmetmensen.nl/en/trial/20102
7. Manten A, Cuijpers CJ, Rietveld R, et al. Rationale and design of a cohort study evaluating triage of acute chest pain in out-of-hours primary care in the Netherlands (TRACE). *Primary Health Care Research & Development*. 2020;21
8. Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *European Heart Journal: Acute Cardiovascular Care*. 2017;7(2):111–119. doi:10.1177/2048872617710788
9. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. Sep 1988;44(3):837–45.
10. Thygesen K, Alpert JS, Harvey D. Universal definition of myocardial infarction. *European heart journal*. 2007 28:2525–2538. doi:10.1093/eurheartj/ehm355
11. Harskamp R, van Peet P, Bont J, Ligthart S, Lucassen W, van Weert H. The conundrum of acute chest pain in general practice: a nationwide survey in The Netherlands. *BJGP Open*. Dec 2018;2(4):bjgpopen18X101619. doi:10.3399/bjgpopen18X101619
12. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. *BMJ*. Jul 17 2004;329(7458):168–9. doi:10.1136/bmj.329.7458.168
13. Wynants L, Van Smeden M, McLernon DJ, et al. Three myths about risk thresholds for prediction models. *BMC medicine*. 2019;17:1–7.

14. International Working Group on Chest Pain in Primary Care (INTERCHEST), Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011

15. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212

16. Manten A, De Clercq L, Rietveld R, Lucassen W, Moll van Charante E, Harskamp R. Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care. *Netherlands Heart Journal*. 2022:1–7.

17. Wouters LT, Zwart DL, Erkelens DC, et al. Chest discomfort at night and risk of acute coronary syndrome: cross-sectional study of telephone conversations. *Family practice*. 2020;37(4):473–478.

SUPPLEMENTARY MATERIAL

Supplementary Table S1. Definition of major and non-major events

	Final diagnosis	Precondition
Major events		
Cardiovascular conditions	Death from any cause	
	Acute coronary syndrome	
	Urgent coronary revascularization	
	Pulmonary embolism	
	Thoracic aortic aneurysm (dissection or ruptured)	
	Severe/Acute congestive heart failure	Hospitalization
	Severe peri(myo)carditis	Hospitalization
	Symptomatic atrial fibrillation	Hospitalization (cardioversion or converted through medication)
	Aortic valve stenosis	Hospitalization
	CVA/TIA	
Non-cardiovascular conditions	(Tension) pneumothorax	Hospitalization
	Severe pneumonia	Hospitalization
	Inflammatory processes such as appendicitis, pancreatitis, cholecystitis	Hospitalization
	Other, such as: exacerbation COPD or hypertensive crisis	Hospitalization
	Traumatic event (with significant impact)	Hospitalization
Non-major events		
	Stable angina pectoris	Outpatient treatment
	Mild congestive heart failure	Outpatient treatment
	Mild peri(myo)carditis	Outpatient treatment
	Atrial fibrillation (recurrent/ paroxysmal)	Outpatient treatment
	Hypertension	Outpatient treatment
	Mild pneumothorax	Outpatient treatment
	Mild pneumonia	Outpatient treatment
	Mild respiratory problems (such as viral infections)	
	Gastric/esophagus problems	
	Musculoskeletal	
	Traumatic (mild trauma)	Outpatient treatment
	Mental health, panic attack, anxiety disorder	

The table specifies the distinction between major and non-major events as defined in the TRACE study. In some diagnoses the urgency is determined by preconditions. For example, severe congestive heart failure that requires hospitalization or immediate in-hospital treatment is considered a major event, whereas mild congestive heart failure that requires only outpatient treatment is not. Abbreviations: COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; TIA, transient ischemic attack.

Supplementary Table S2 A. Diagnostic accuracy for SFPR and NTS for the outcomes of interest in the TRACE cohort, stratified by age.

	Risk threshold	Subgroup	% 'high risk' at threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-
ACS	NTS U1/U2	> 54 years (n = 700)	68.7	86.8 (77.1-93.5)	33.5 (29.8-37.4)	13.7 (12.5-15.0)	95.4 (92.1-97.4)	1.31 (1.18-1.45)	0.39 (0.22-0.71)
		≤ 54 years (n = 704)	54.1	84.2 (60.4-96.6)	46.7 (42.9-50.5)	4.2 (3.4-5.1)	99.1 (97.4-99.7)	1.58 (1.28-1.94)	0.34 (0.12-0.96)
	SFPR 0.025	> 54 years (n = 700)	96.0	98.7 (92.9-100.0)	4.3 (2.9-6.2)	11.2 (10.9-11.5)	96.4 (78.8-99.5)	1.03 (1.00-1.06)	0.30 (0.04-2.21)
		≤ 54 years (n = 704)	26.7	84.2 (60.4-96.6)	75.0 (71.6-78.2)	8.6 (6.9-10.6)	99.4 (98.4-99.8)	3.37 (2.67-4.26)	0.21 (0.07-0.59)
	SFPR 0.042[a]	> 54 years (n = 700)	87.9	98.7 (92.9-100.0)	13.5 (10.9-16.4)	12.2 (11.8-12.6)	98.8 (92.2-99.8)	1.14 (1.10-1.19)	0.10 (0.01-0.69)
	SFPR 0.033[a]	≤ 54 years (n = 704)	22.3	73.7 (48.8-90.9)	79.1 (75.9-82.1)	8.9 (6.7-11.7)	99.1 (98.1-99.6)	3.53 (2.60-4.79)	0.33 (0.16-0.71)
MACE	NTS U1/U2	> 54 years (n = 700)	68.7	85.3 (76.9-91.5)	34.1 (30.3-38.1)	18.1 (16.7-19.6)	93.2 (89.4-95.7)	1.29 (1.17-1.43)	0.43 (0.27-0.70)
		≤ 54 years (n = 704)	54.1	84.2 (60.4-96.6)	46.7 (42.9-50.5)	4.2 (3.4-5.1)	99.1 (97.4-99.7)	1.58 (1.28-1.94)	0.34 (0.12-0.96)
	SFPR 0.025	> 54 years (n = 700)	96.0	99.0 (94.7-100.0)	4.5 (3.0-6.5)	15.0 (14.7-15.4)	96.4 (78.8-99.5)	1.04 (1.01-1.06)	0.22 (0.03-1.58)
		≤ 54 years (n = 704)	26.7	84.2 (60.4-96.6)	75.0 (71.6-78.2)	8.6 (6.9-10.6)	99.4 (98.4-99.8)	3.37 (2.67-4.26)	0.21 (0.07-0.59)
	SFPR 0.042[a]	> 54 years (n = 700)	87.9	99.0 (94.7-100.0)	14.1 (11.4-17.1)	16.4 (15.9-17.0)	98.8 (92.2-99.8)	1.15 (1.11-1.20)	0.07 (0.01-0.50)
	SFPR 0.033[a]	≤ 54 years (n = 704)	22.3	73.7 (48.8-90.9)	79.1 (75.9-82.1)	8.9 (6.7-11.7)	99.1 (98.1-99.6)	3.53 (2.60-4.79)	0.33 (0.16-0.71)

continues

continued

Major event	**NTS U1/U2**	> 54 years (n = 700)	68.7	83.4 (77.3-88.5)	36.7 (32.5-41.0)	32.4 (30.5-34.5)	85.8 (81.2-89.5	1.32 (1.20-1.44)	0.45 (0.32-0.64)
		≤ 54 years (n = 704)	54.1	77.8 (60.9-89.9)	47.2 (43.3-51.0)	7.4 (6.2-8.7)	97.5 (95.5-98.7)	1.47 (1.22-1.78)	0.47 (0.25-0.87)
	SFPR 0.025	> 54 years (n = 700)	96.0	98.9 (96.2-99.9)	5.1 (3.3-7.3)	27.5 (27.0-28.0)	92.9 (75.7-98.2)	1.04 (1.02-1.07)	0.21 (0.05-0.88)
		≤ 54 years (n = 704)	26.7	63.9 (46.2-79.2)	75.5 (72.0-78.7)	12.3 (9.6-15.6)	97.5 (96.2-98.4)	2.60 (1.97-3.44)	0.48 (0.31-0.74)
	SFPR 0.042[a]	> 54 years (n = 700)	87.9	97.3 (93.9-99.1)	15.6 (12.6-19.0)	29.6 (28.7-30.5)	94.1 (86.8-97.5)	1.15 (1.10-1.21)	0.17 (0.07-0.42)
	SFPR 0.033[a]	≤ 54 years (n = 704)	22.3	52.8 (35.5-69.6)	82.3 (79.2-85.2)	13.9 (10.2-18.6)	97.0 (95.8-97.9)	2.99 (2.11-4.24)	0.57 (0.41-0.81)

Sensitivity, specificity, PPV, and NPV are shown in percentages (%) with the 95%-CI between brackets.
Abbreviations: ACS, acute coronary syndrome; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MACE, major adverse cardiovascular event; NPV, negative predictive value; NTS U1/U2, Netherlands Triage Standard urgency level U1 or U2; PPV, positive predictive value; SFPR, Safety First prediction rule.
[a] Lowest cut-off where NPV for ACS best approached 99.0% for this subgroup.

Supplementary Table S2 B. Diagnostic accuracy for SFPR and NTS for the outcomes of interest in the TRACE cohort, stratified by sex.

	Risk threshold	Subgroup	% 'high risk' at threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-
ACS	NTS U1/U2	Women (n = 805)	62.9	88.6 (75.4-96.2)	38.6 (35.2-42.2)	7.7 (6.9-8.6)	98.3 (96.3-99.3)	1.44 (1.28-1.63)	0.29 (0.13-0.67)
		Men (n = 599)	59.4	84.3 (71.4-93.0)	42.9 (38.7-47.2)	12.1 (10.7-13.6)	96.7 (93.9-98.2)	1.48 (1.28-1.70)	0.37 (0.19-0.70)
	SFPR 0.025	Women (n = 805)	54.4	95.5 (84.5-99.4)	48.0 (44.4-51.6)	9.6 (8.8-10.4)	99.5 (97.9-99.9)	1.83 (1.67-2.01)	0.09 (0.02-0.37
		Men (n = 599)	70.3	96.1 (86.5-99.5)	32.1 (28.2-36.2)	11.6 (10.8-12.5)	98.9 (95.7-99.7)	1.42 (1.31-1.53)	0.12 (0.03-0.48)
	SFPR 0.033[a]	Women (n = 805)	49.2	90.9 78.3-97.5)	53.2 (49.6-56.8)	10.1 (9.1-11.3)	99.0 (97.5-99.6)	1.94 (1.72-2.19)	0.17 (0.07-0.44)
	SFPR 0.044[a]	Men (n = 599)	66.6	96.1 (86.5-99.5)	36.1 (32.1-40.3)	12.3 (11.4-13.2)	99.0 (96.2-99.74)	1.50 (1.38-1.64)	0.11 (0.03-0.42)
MACE	NTS U1/U2	Women (n = 805)	62.9	84.2 (72.1-92.5)	38.8 (35.3-42.4)	9.5 (8.5-10.6)	97.0 (94.6-98.3)	1.38 (1.21-1.56)	0.41 (0.22-0.75)
		Men (n = 599)	59.4	85.9 (75.0-93.4)	43.7 (39.5-48.1)	15.5 (13.9-17.1)	96.3 (93.4-98.0)	1.53 (1.35-1.73)	0.32 (0.17-0.59)
	SFPR 0.025	Women (n = 805)	54.4	96.5 (87.9-99.6)	48.8 (45.2-52.4)	12.6 (11.7-13.5)	99.5 (97.9-99.9)	1.88 (1.73-2.05)	0.07 (0.02-0.28)
		Men (n = 599)	70.3	96.9 (89.2-99.6)	32.9 (28.9-37.1)	14.7 (13.8-15.7)	98.9 (95.7-99.7)	1.44 (1.34-1.55)	0.09 (0.02-0.37)
	SFPR 0.033[a]	Women (n = 805)	49.2	93.0 (83.0-98.1)	54.1 (50.5-57.8)	13.4 (12.2-14.7)	99.0 (97.5-99.6)	2.03 (1.82-2.25)	0.13 (0.05-0.33)
	SFPR 0.044[a]	Men (n = 599)	66.6	96.9 (89.2-99.6)	37.0 (32.9-41.3)	15.5 (14.5-16.6)	99.0 (96.2-99.7)	1.54 (1.42-1.66)	0.08 (0.02-0.33)

continues

continued

Major event	**NTS U1/U2**	Women (n = 805)	62.9	82.7 (73.7-89.6)	39.9 (36.3-43.6)	16.0 (14.6-17.5)	94.3 (91.4-96.3)	1.37 (1.23-1.53)	0.43 (0.28-0.68)
		Men (n = 599)	59.4	82.4 (74.6-88.6)	46.6 (42.1-51.2)	28.9 (26.6-31.4)	91.0 (87.2-93.7)	1.54 (1.37-1.74)	0.38 (0.26-0.56)
	SFPR 0.025	Women (n = 805)	54.4	90.8 (83.3-95.7)	50.6 (46.9-54.4)	20.3 (18.8-22.0)	97.6 (95.5-98.7)	1.84 (1.67-2.03)	0.18 (0.10-0.34)
		Men (n = 599)	70.3	95.2 (89.9-98.2)	36.3 (32.0-40.8)	28.3 (26.7-29.9)	96.6 (92.9-98.4)	1.49 (1.38-1.62)	0.13 (0.06-0.29)
	SFPR 0.033[a]	Women (n = 805)	49.2	86.7 (78.4-92.7)	56.0 (52.3-59.7)	21.5 (19.6-23.4)	96.8 (94.8-98.1)	1.97 (1.76-2.21)	0.24 (0.14-0.39)
	SFPR 0.044[a]	Men (n = 599)	66.6	93.6 (87.8-97.2)	40.5 (36.1-45.1)	29.3 (27.6-31.2)	96.0 (92.4-97.9)	1.57 (1.44-1.72)	0.16 (0.08-0.31)

Sensitivity, specificity, PPV, and NPV are shown in percentages (%) with the 95%-CI between brackets.
Abbreviations: ACS, acute coronary syndrome; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MACE, major adverse cardiovascular event; NPV, negative predictive value; NTS U1/U2, Netherlands Triage Standard urgency level U1 or U2; PPV, positive predictive value; SFPR, Safety First prediction rule.
[a] Lowest cut-off where NPV for ACS best approached 99.0% for this subgroup.

Supplementary Table S2 C. Diagnostic accuracy for SFPR and NTS for the outcomes of interest in the TRACE cohort, stratified by time of contact.

	Risk threshold	Subgroup	% 'high risk' at threshold	Sensitivity	Specificity	PPV	NPV	LR+	LR-
ACS	NTS U1/U2	Night call[b] (n = 347)	64.8	80.0 (63.1-91.6)	36.9 (31.5-42.5)	12.4 (10.6-14.6)	94.3 (89.3-97.0)	1.27 (1.05-1.53)	0.54 (0.28-1.07)
		Day call[c] (n = 1057)	60.3	90.0 (79.5-96.2)	41.5 (38.4-44.7)	8.5 (7.7-9.3)	98.6 (97.0-99.3)	1.54 (1.39-1.70)	0.24 (0.11-0.52)
	SFPR 0.025	Night call[b] (n = 347)	74.1	97.1 (85.1-99.9)	28.5 (23.6-33.9)	13.2 (12.2-14.3)	98.9 (92.8-99.8)	1.36 (1.24-1.49)	0.10 (0.01-0.70)
		Day call[c] (n = 1057)	57.0	95.0 (86.1-99.0)	45.3 (42.2-48.5)	9.5 (8.8-10.2)	99.3 (98.0-99.8)	1.74 (1.60-1.88)	0.11 (0.04-0.33)
	SFPR 0.0315[a]	Night call[b] (n = 347)	71.2	97.1 (85.1-99.9)	31.7 (26.6-37.2)	13.8 (12.7-14.9)	99.0 (93.4-99.9)	1.42 (1.29-1.56)	0.09 (0.01-0.63)
	SFPR 0.0335[a]	Day call[c] (n = 1057)	52.5	91.7 (81.6-97.2)	49.9 (46.7-53.0)	9.9 (9.1-10.8)	99.0 (97.7-99.6)	1.83 (1.66-2.02)	0.17 (0.07-0.39)
MACE	NTS U1/U2	Night call[b] (n = 347)	64.8	82.5 (67.2-92.7)	37.5 (32.0-43.1)	14.7 (12.7-16.9)	94.3 (89.2-97.0)	1.32 (1.12-1.56)	0.46 (0.23-0.93)
		Day call[c] (n = 1057)	60.3	86.4 (77.0-93.0)	41.9 (38.8-45.1)	11.0 (10.0-12.0)	97.4 (95.5-98.5)	1.49 (1.34-1.65)	0.32 (0.19-0.56)
	SFPR 0.025	Night call[b] (n = 347)	74.1	97.5 (86.8-99.9)	29.0 (24.0-34.4)	15.2 (14.1-16.3)	98.9 (92.7-99.8)	1.37 (1.26-1.50)	0.09 (0.01-0.60)
		Day call[c] (n = 1057)	57.0	96.3 (89.6-99.2)	46.3 (43.2-49.5)	13.0 (12.2-13.8)	99.3 (98.0-99.8)	1.79 (1.67-1.93)	0.08 (0.03-0.24)
	SFPR 0.0315[a]	Night call[b] (n = 347)	71.2	97.5 (86.8-99.9)	32.3 (27.1-37.8)	15.8 (14.6-17.1)	99.0 (93.4-99.9)	1.44 (1.31-1.58)	0.08 (0.01-0.54)
	SFPR 0.0335[a]	Day call[c] (n = 1057)	52.5	93.8 (86.2-98.0)	50.9 (47.7-54.1)	13.7 (12.7-14.7)	99.0 (97.7-99.6)	1.91 (1.76-2.08)	0.12 (0.05-0.28)

continues

continued

Major event	**NTS U1/U2**	Night call[b] (n = 347)	64.8	81.1 (70.3-89.3)	39.6 (33.7-45.6)	26.7 (23.9-29.6)	88.5 (82.5-92.7)	1.34 (1.16-1.55)	0.48 (0.29-0.78)
		Day call[c] (n = 1057)	60.3	83.2 (76.2-88.8)	43.5 (40.3-46.8)	19.5 (18.1-21.0)	94.1 (91.6-95.8)	1.47 (1.34-1.61)	0.39 (0.27-0.56)
	SFPR 0.025	Night call[b] (n = 347)	74.1	96.0 (88.6-99.2)	31.9 (26.4-37.8)	27.6 (25.8-29.5)	96.7 (90.4-98.9)	1.41 (1.28-1.55)	0.13 (0.04-0.39)
		Day call[c] (n = 1057)	57.0	92.0 (86.4-95.8)	48.8 (45.5-52.1)	22.8 (21.4-24.2)	97.4 (95.5-98.5)	1.80 (1.66-1.94)	0.17 (0.10-0.29)
	SFPR 0.0315[a]	Night call[b] (n = 347)	71.2	93.2 (84.9-97.8)	34.8 (29.2-40.8)	27.9 (25.9-30.1)	95.0 (88.9-97.8)	1.43 (1.29-1.59)	0.19 (0.08-0.46)
	SFPR 0.0335[a]	Day call[c] (n = 1057)	52.5	89.3 (83.2-93.7)	53.5 (50.2-56.8)	24.0 (22.4-25.6)	96.8 (95.0-98.0)	1.92 (1.76-2.10)	0.20 (0.13-0.32)

Sensitivity, specificity, PPV, and NPV are shown in percentages (%) with the 95%-CI between brackets.
Abbreviations: ACS, acute coronary syndrome; LR+, positive likelihood ratio; LR-, negative likelihood ratio; MACE, major adverse cardiovascular event; NPV, negative predictive value; NTS U1/U2, Netherlands Triage Standard urgency level U1 or U2; PPV, positive predictive value; SFPR, Safety First prediction rule.
[a] Lowest cut-off where NPV for ACS best approached 99.0% for this subgroup. [b] Call between 00.00h and 09.00h. [c] Call between 09.00h and 24.00h.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 9

Chest pain in primary care: a systematic review of risk stratification tools to rule out acute coronary syndrome

Simone van den Bulk*, Amy Manten*, Tobias N. Bonten, Ralf E. Harskamp

*Contributed equally

Published in Annals of Family Medicine, 2024

PMID: 39313342

DOI: 10.1370/afm.3141

ABSTRACT

Purpose: Chest pain frequently poses a diagnostic challenge for general practitioners (GP). Utilizing risk stratification tools might help GPs to rule out acute coronary syndrome (ACS) and make appropriate referral decisions. We conducted a systematic review of studies evaluating risk stratification tools for chest pain in primary care settings, both with and without troponin assays. Our aims were to assess the performance of tools for ruling out ACS and to provide a comprehensive review of the current evidence.

Methods: We searched PubMed and Embase for articles up to October 9, 2023 concerning adult patients with acute chest pain in primary care settings, for whom risk stratification tools (clinical decision rules [CDRs] and/or single biomarker tests) were used. To identify eligible studies, a combination of active learning and backward snowballing was applied. Screening, data extraction, and quality assessment (following Quality Assessment of Diagnostic Accuracy Studies-2 tool) were performed independently by 2 researchers.

Results: Of the 1,204 studies screened, 14 were included in the final review. Nine studies validated 7 different CDRs without troponin. Sensitivities ranged from 75.0% to 97.0%, and negative predictive values (NPV) ranged from 82.4% to 99.7%. None of the CDRs outperformed the unaided judgement of GP's. Five studies reported on strategies using troponin measurements. Studies using high-sensitivity troponin showed highest diagnostic accuracy with sensitivity 83.3% to 100% and NPV 98.8% to 100%.

Conclusion: Clinical decision rules without troponin and the use of conventional troponin showed insufficient sensitivity to rule out ACS in primary care and are not recommended as standalone tools. High-sensitivity troponin strategies are promising, but studies are limited. Further prospective validation in primary care is needed before implementation.

INTRODUCTION

Chest pain often poses a diagnostic challenge for general practitioners (GPs). While chest pain is the hallmark symptom of acute coronary syndrome (ACS), it is often caused by less urgent conditions. It is difficult for GPs to differentiate possible ACS from other causes based on symptoms and physical examination alone. This, unfortunately, results in a low threshold for referral, leading to additional burden and cost on the healthcare system.[1-3]

Only 1.5% to 3.6% of patients with chest pain in primary care are diagnosed with ACS.[3,4] More often, chest pain is caused by non-cardiac conditions, such as musculoskeletal complaints or gastro-intestinal disease.[2] It is thought that risk stratification tools, such as clinical decision rules (CDRs) or troponin point-of-care tests (POCT), could help GPs to make more informed referral decisions when evaluating patients with acute chest pain.

Due to different ACS risks in primary and secondary care, the use of risk stratification tools may differ in these settings and results from studies in secondary care cannot be assumed to apply to primary care.[5] A systematic review from 2019 that assessed CDRs for coronary artery disease and ACS in primary care, concluded that no CDR demonstrated sufficient sensitivity to rule out ACS.[6] Since then new studies have emerged, and high-sensitivity troponin POCTs became available to pre-hospital settings. In this systematic review, our aim was to assess the performance of risk stratification tools for ruling out ACS in patients with chest pain in primary care and to provide a comprehensive review of the current evidence.

METHODS

This study is reported in accordance with the 2018 Preferred Reporting Items for a Systematic review and Meta-Analysis of diagnostic test accuracy studies statement.[7] The protocol is available upon request.

Search Strategy and Eligibility Criteria

We searched the electronic databases PubMed and Embase for original articles published in English, up to October 9, 2023. A complete overview of the search is presented in *Supplemental Appendix 1*. Two authors (S.B. and A.M.) identified articles for potential inclusion. A third author (R.E.H.) was available to resolve any disagreements. Eligibility criteria were: (1) adults (aged 18 years or more); (2) acute chest pain; (3) enrollment in primary care; (4) available outcome data ACS, acute myocardial infarction (AMI), or the composite endpoint of major

adverse cardiac events (MACE); and (5) use of diagnostic tools. Diagnostic tools were defined as risk stratification tools constructed by a set of condition-specific findings that are applicable in a primary care setting. Exclusion criteria were: studies conducted in ambulance care or emergency department settings or requiring advanced diagnostic testing (eg, coronary angiography, serial biomarker testing); or cardiac monitoring.

Outcomes of Interest

Outcomes of interest were the diagnostic test characteristics of the risk stratification tool: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall discriminative properties (C-statistic). Reference diagnoses of interest were ACS, AMI, and MACE. Major adverse cardiac events are typically defined as a composite of death from any cause, ACS, and urgent coronary interventions. When applicable, we reported the performance of risk stratification tools compared with unaided clinical judgement.

Selection Process

For the selection process, we used an open-source machine learning-aided software (ASReview, Utrecht University) for the initial screening of the titles and abstracts. We followed the principles of the SYstematic review Methodology Blending Active Learning and Snowballing (SYMBALS).[8,9] A more complete description of ASReview's methods and evidence, including clarification of our stopping criteria can be found in S*upplemental Appendix 2*. Selected articles were imported into the Covidence systematic review software (Veritas Health Innovation), for full text screening, quality assessment and data extraction. After reaching the final subset of articles, those reference lists were then screened for possible additional inclusions.

Quality Assessment and Data Extraction

Two researchers (S.B. and A.M.) separately extracted data elements from each study. The quality of the included articles was assessed by S.B. and A.M. using the 4 domains of the Quality Assessment of Diagnostic Accuracy Studies-2 tool: patient selection, index test, reference standard, and flow and timing.[10] Risk of bias and applicability concerns were assessed separately. A third author (R.E.H.) independently reviewed the extracted data and quality assessment for accuracy.

Data Synthesis and Analysis

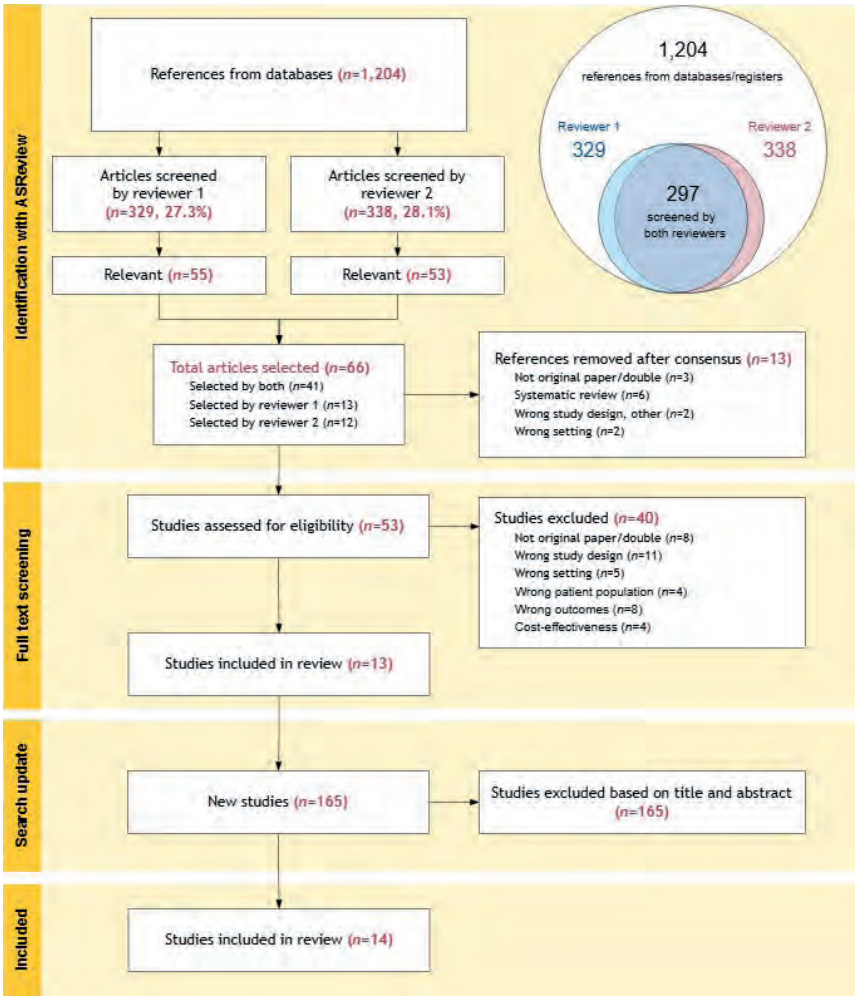
Extracted data on study and patient characteristics, outcome measures, and follow-up information are presented in *Table 1*. Diagnostic test characteristics and discriminative properties are shown in *Table 2*.

Table 1. Study and patient characteristics of included studies (n=14).

Source, year	Risk stratification strategy	Type of evaluation	Study design	Follow up	Country	Patients, No.	Mean age, y	Female, %	Endpoint	Endpoint prevalence, %
A. Risk stratification tools without troponin										
Grijseels et al, 1995 (16)	Grijseels	Derivation	Prospective study	30 days	The Netherlands	906	67.0	46.0	Acute cardiac pathology	46.2
Grijseels et al, 1996 (15)	Grijseels	Validation	Prospective study	30 days	The Netherlands	977	65.6	47.0	Acute cardiac pathology	47.8
Bruins Slot et al, 2011 (1)	Bruins Slot (updated Grijseels rule)	Derivation Internal validation	Diagnostic accuracy study	30 days	The Netherlands	298	66.0	52.0	ACS	22.0
Willemsen et al, 2019 (18)	H-FABP CDR	Valiation Derivation Internal validation	Prospective non-randomized diagnostic study	30 days	The Netherlands	303	58.3	51.2	ACS	10.6
Schols et al, 2019 (17)	MHS	Validation	Prospective, observational flash-mob study	6 weeks	The Netherlands	243	64.0	47.7	ACS	18.5
Kleton et al, 2020 (12)	Bruins Slot MHS INTERCHEST Gencer rule	Validation	Retrospective, observational cohort study	6 months	The Netherlands	664	48.0	56.9	MACE	4.8
Manten et al, 2022 (13)	MHS INTERCHEST	Validation	Retrospective, observational cohort study	6 months	The Netherlands	1,433	55.0	57.6	ACS	6.8
Wouters et al, 2022 (22)	Safety First	Derivation Internal validation	Cross-sectional study	30 days	The Netherlands	2,192	59.1	55.3	ACS	11.5
Harskamp et al, 2021 (11)	Simplified HEART HEART-GP	Validation	Retrospective, observational cohort study	6 months	The Netherlands	664	48.0	56.9	MACE	4.8
B. Troponin based risk stratification tools										
Planer et al, 2006 (24)	POCT cTnT	Validation	Prospective study	2 months	Israel	349	58.6	41.8	ACS	6.9
Tomonaga et al, 2011 (14)	3-in-1 POCT	Validation	Clustered, randomized controlled trial	3 weeks	Switzerland	369	65.0	42.0	ACS	8.9
Nilsson et al, 2013 (25)	POCT cTnT	Validation	Prospective observational study	30 days	Sweden	196	66.0	42.0	ACS	6.6
Andersson et al, 2015 (26)	hs-cTnT	Validation	Prospective observational study	30 days	Sweden	115	65.0	34.0	ACS	5.2
Johannessen et al, 2021 (27)	Single troponin HEART-score Modified HEART	Validation	Prospective observational study	90 days	Norway	1,711	56.0	48.0	AMI	3.6

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; CDR, clinical decision rule; cTnT, cardiac troponin T; HEART, History, ECG, Age, Risk factors and Troponin; H-FABP, heart-type fatty acid-binding protein; hs, high-sensitivity; INTERCHEST, international chest pain prediction; MACE, major adverse cardiovascular events; MHS, Marburg Heart Score; POCT, point of care test.

Figure 1. Flowchart of systematic review of the literature.



Abbreviations: ASReview, Active learning for Systematic Reviews.

RESULTS

Search Results

After deduplication, the initial search yielded 1,204 titles and abstracts eligible for inclusion. Following further screening, 53 articles remained, of which 40 were excluded after full text screening. An update of the search resulted in 1 additional article (*Figure 1*). Backward snowballing yielded no additional inclusions.

Study and Patient Characteristics

Table 1 displays the characteristics of the 14 included studies. Nine studies derived or validated a CDR and 5 studies validated various troponin assays. Study populations ranged from 115 to 2,192 patients, with follow-up periods from 3 weeks to 6 months. An overview of the components of the included CDRs can be found in *Supplementary Table 1*. *Supplementary Table 2* shows troponin assay characteristics and threshold values.

Quality Assessment

Five of the 14 (35.7%) studies showed a high risk of bias in at least 1 of the quality domains. High risks of bias was most common in the index test and reference standard domains.[11-14] Applicability concerns were most frequent in patient selection and index test.[15-17] A detailed overview of the risk of bias and applicability assessment can be found in *Supplemental Appendix 3*.

Risk Stratification Tools

A complete overview of diagnostic test characteristics can be found in *Table 2*.

Grijseels / Bruins Slot Rule

Grijseels et al developed an algorithm in 1995 which consists of a combination of patient and symptom characteristics, and electrocardiogram (ECG) findings.[15,16] Discriminative properties showed C-statistics ranging from 0.70 to 0.72. In 2011, Bruins Slot et al updated the algorithm to a point-based rule with 3 risk categories for ACS.[1] Validation of the updated rule resulted in C-statistics of 0.66-0.72, sensitivity of 84.4% to 97.0%, and NPV of 91.7% to 98.2%. When comparing the CDR to unaided clinical judgment, GPs categorized patients with and without ACS better.[1,12]

Willemsen CDR

In 2019, Willemsen et al evaluated a heart-type fatty acid-binding protein (H-FABP) POCT.[18] The diagnostic accuracy of H-FABP as standalone test to rule out ACS had a sensitivity of 25.8% and NPV of 91.6%. Using H-FABP with a CDR increased the sensitivity to 87.5% and NPV to 97.2%. Compared with unaided clinical judgment, fewer ACS cases were missed (1.3% vs 2.6%), but there were 13.9% more referrals.

Marburg Heart Score

The Marburg Heart Score (MHS) was developed in 2010 to rule out coronary artery disease.[19] Later, it was evaluated to rule out ACS or MACE in 1 prospective and 2 retrospective studies, with different rule-out thresholds (*Table 1*).[12,13,17] C-statistics ranged from 0.64 to 0.77, with sensitivity of 75.0% to 81.3% and NPV of 88.0% to 98.6%. The MHS did not outperform unaided clinical judgement.[17]

INTERCHEST

Like the MHS, the 2017 International Chest pain prediction (INTERCHEST) score was developed to rule out coronary artery disease, and later tested to rule out ACS or MACE. The rule was derived from pooled individual patient data of 5 studies (3,099 patients total).[20] Twofold retrospective validation resulted in C-statistics of 0.77 to 0.85, sensitivity of 87.5% to 88.8%, and NPV of 98.6% to 99.1%.[12,13] Discriminative power was similar to unaided clinical judgement.

Gencer Rule

The Gencer rule was developed in 2010 to rule out coronary artery disease and consists of 7 components.[21] It was validated to rule out MACE in 1 study with a C-statistic of 0.72, sensitivity of 84.4% and NPV of 98.0%.[12] The performance of the rule was equivalent to unaided clinical judgement.

Safety First

Wouters et al in 2022 developed a computerized risk stratification tool for the triage of acute chest pain patients in out-of-hours primary care settings.[22] The tool includes 7 predictors of ACS. After derivation, an internal-external validation technique was used, resulting in a C-statistic of 0.77 to 0.79. The authors did not recommend a cut-off point, however diagnostic accuracy for various risk thresholds (0.1% to 20%), showed a sensitivity of 46% to 98% and NPV of 93% to 99%.

HEART-Score Variants

The original HEART-score tool (History, ECG, Age, Risk factors, and Troponin), was developed to identify patients at low risk for short-term MACE among patients with acute chest pain in the emergency department.[23] For use in primary care, the original HEART-score was modified.[11] The first variation (simplified HEART-score) simply omits troponin. The second variation, HEART-GP, replaces troponin with the GP's sense of alarm. The modified scores had a C-statistic of 0.86 and 0.90, respectively, sensitivity of 96.9%, and NPV of 99.7% for both versions. Compared with unaided clinical judgment, both scores

improved safety, at the cost of additional referrals (simplified HEART had 26% more, and HEART-GP had 4% more).

Conventional Troponin

In a study by Planer et al in 2006, a qualitative cardiac troponin T (cTnT) test was combined with the GP's clinical assessment.[24] The combined strategy resulted in a sensitivity of 95.8% and NPV of 99.6%. The cTnT test as a standalone test showed poor sensitivity (20.8%) and did not outperform unaided clinical judgment.

Tomonaga et al in 2011 compared the use of a 3-in-1 POCT for cTnT, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and D-dimer to usual care in patients with chest pain, dyspnea, or symptoms suggestive for thromboembolic events.[14] The use of this combined POCT test led to more accurate working diagnoses (76% vs 60%) and fewer referrals (30% vs 55% false positives). For ACS, however, the sensitivity was 89.5% compared with 100% in the usual care group, with a NPV of 98.9%, compared with 100%. Sensitivity for troponin as standalone test to rule out ACS was 58.8%, missing 7 out of 17 (41.2%) patients with ACS.

A Swedish study by Nilsson *et al* in 2013 compared 3 primary care practices that already incorporated the use of cTnT-POCT to 4 practices that did not use cTnT-POCT.[25] Use of cTnT-POCT by GPs reduced hospital referrals (25% vs 43%), but at the expense of sensitivity (71.4% in the practices using cTnT-POCT vs 100% in the control group). Troponin as standalone test showed a sensitivity of 28.6% and NPV of 95.9%, missing 5 out of 7 (71%) patients with ACS.

High-Sensitivity Troponin

In 2015, Andersson et al used the original (stored) samples from the study by Nilsson et al in 2013 to measure high-sensitivity (hs) cTnT and compare the diagnostic outcomes with the outcomes for conventional troponin.[26] They found a sensitivity of 83.3% compared to 33.3%, missing 1 out of 6 (17%) patients with ACS. This came at the expense of specificity (76.2% vs 97.5%) and thus led to additional referrals (23% vs 2% false positives).

Lastly, in 2021, Johannessen et al validated 3 strategies to rule out AMI using hs-cTnT in a primary care emergency outpatient clinic in Norway.[27] The first was a single hs-cTnT rule out strategy. High sensitivity cTnT was measured at presentation and AMI was ruled out if hs-cTnT was below the limit of detection (ie, very low). No AMI were missed and sensitivity and NPV were 100% with a C-statistic of 0.85. The second and third strategies were the original HEART-score and a modified HEART-score with lower hs-cTnT thresholds. The modified HEART-score outperformed the original HEART-score (sensitivity 98.4% vs 91.8% and NPV 99.8% vs 99.4%), but not the single hs-cTnT rule out strategy.

Table 2. Diagnostic accuracy of risk stratification tools for ACS/MACE.

Tool	Source, year	RS strategy	Subtype	AUC (95% CI)	Sensitivity	95% CI	Specificity	95% CI	PPV, %	95% CI	NPV, %	95% CI
A. Risk stratification tools without troponin												
Grijseels/Bruins Slot rule	Grijseels et al, 1995 (16)	Grijseels rule	Derivation	0.72	–	–	–	–	–	–	–	–
	Grijseels et al, 1996 (15)	Grijseels rule	Validation	0.70	91.4	(88.5-93.8)	36.7	(32.5-41.0)	56.9	(55.2-58.7)	82.4	(77.3-86.5)
		Aided clinical judgement	GP + Grijseels rule	–	98.3	(96.7-99.3)	17.8	(14.6-21.5)	52.3	(51.2-53.3)	91.9	(84.8-95.9)
	Bruins Slot et al, 2011 (1)	Bruins Slot (updated Grijseels rule)[a]	Update of rule	0.66 (0.58-0.73)	97.0	(89.5-99.6)	9.5	(6.0-14.0)	23.4	(22.3-24.4)	91.7	(72.6-97.9)
		GP unaided	GP risk estimate	0.75 (0.68-0.82)	93.4	(85.2-98.3)	19.4	(14.5-25.1)	24.9	(23.3-26.6)	91.8	(80.8-96.8)
	Kleton et al**, 2021 (12)	Bruins Slot (<5)	External validation for MACE	0.72 (0.63-0.81)	84.4	(67.2-94.7)	43.8	(39.9-47.8)	7.1	(6.1-8.2)	98.2	(96.1-99.2)
		GP unaided	GP risk estimate	–	81.3	(63.6-92.8)	79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
Willemsen CDR	Willemsen et al, 2019 (18)	POCT H-FABP	H-FABP	–	25.8	(12.5-44.9)	96.9	(93.8-98.6)	50.0	(25.5-74.5)	91.6	(87.6-94.5)
			H-FABP embedded in CDR	0.78	87.5	(70.1-95.9)	51.0	(45.9-58.1)	17.7	(12.3-24.8)	97.2	(92.6-99.1)
			GP risk estimate	–	75.0	(56.2-87.9)	67.5	(61.6-73.0)	21.4	(14.5-30.4)	95.8	(91.6-98.0)
Marburg Heart Score	Schols et al, 2019 (17)	MHS (<3)	External validation for ACS	0.64 (0.54-0.74)	75.0	(57.5-87.3)	44.0	(36.0-52.3)	24.3	(16.9-33.6)	88.0	(78.0-94.0)
		GP unaided	GP risk estimate	0.71 (0.61-0.80)	86.7	(72.5-94.5)	41.4	(34.5-48.6)	25.2	(18.7-32.9)	93.2	(85.2-97.2)
		Aided clinical judgement	GP + MHS	–	100	(88.0-100.0)	23.3	(17.0-31.1)	23.8	(17.5-31.6)	100	(87.7-100)
	Kleton et al**, 2021 (12)	MHS (<2)	External validation for MACE	0.77 (0.69-0.84)	81.3	(63.6-92.8)	67.1	(63.3-70.7)	11.1	(9.3-12.3)	98.6	(97.2-99.3)
		GP unaided	GP risk estimate	–	81.3	(63.6-92.8)	79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
	Manten et al, 2022 (13)	MHS (<2)	MHS as triage tool for ACS	0.70 (0.65-0.75)	78.6	(69.1-86.2)	54.3	(51.6-57.0)	11.2	(10.1-12.5)	97.2	(95.9-98.1)
INTERCHEST	Kleton et al**, 2021 (12)	INTERCHEST (<2)	External validation for MACE	0.85 (0.78-0.92)	87.5	(71.0-96.5)	78.8	(75.4-81.9)	17.3	(14.6-20.3)	99.1	(97.4-99.7)
		GP unaided	GP risk estimate	–	81.3	(63.6-92.8)	79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)
	Manten et al, 2022 (13)	INTERCHEST (<2)	INTERCHEST as triage tool for ACS	0.77 (0.73-0.81)	88.8	(80.8-94.3)	57.7	(55.0-60.4)	13.3	(12.3-14.5)	98.6	(97.6-99.2)
Gencer rule	Kleton et al**, 2021 (12)	Gencer rule (<2)	External validation for MACE	0.72 (0.63-0.81)	84.4	(67.2-94.7)	37.8	(34.0-41.7)	6.4	(5.5-7.5)	98.0	(95.5-99.1)
		GP unaided	GP risk estimate	–	81.3	(63.6-92.8)	79.3	(75.9-82.9)	16.6	(13.7-19.9)	98.8	(97.6-99.4)

continues

Tool	Source, year	RS strategy	Subtype	AUC (95% CI)	Sensitivity	95% CI	Specificity	95% CI	PPV, %	95% CI	NPV, %	95% CI
A. Risk stratification tools without troponin												
continued												
HEART-score variants	Harskamp et al, 2021 (11)	Modified HEART	Simplified HEART-score (COV<2)	0.86 (0.80-0.91)	96.9	(83.8-99.9)	52.4	(48.4-56.3)	9.3	(8.5-10.2)	99.7	(98.0-100)
			HEART-GP (COV<3)	0.90 (0.85-0.95)	96.9	(83.8-99.9)	58.5	(54.6-64.2)	10.6	(9.6-11.7)	99.7	(98.2-100)
		GP unaided	GP risk estimate	_	81.3	(63.3-92.8)	79.3	(75.9-82.4)	16.6	(13.6-19.9)	98.8	(97.6-99.4)
Safety First	Wouters et al;, 2022 (22)	Safety First	Derivation	0.79 (0.76-0.81)	N/A		_	_	_	_	_	_
			Internal-external validation	0.77 (0.74-0.79)	46-98¥		21-93¥		14-46¥		93-99¥	
B. Troponin based risk stratification tools												
Conventional troponin	Planer et al, 2006 (24)	POCT cTnT	Single POCT cTnT	_	20.8	(7.1-42.2)	100	(98.9-100)	100	(47.8-100)	94.5	(93.3-95.5)
		GP unaided	GP risk estimate	_	91.7	(73.0-99.0)	72.6	(67.4-77.4)	19.8	(16.6-23.4)	99.2	(96.9-99.8)
		Aided clinical judgement	GP + POCT cTnT	_	95.8	(78.9-99.9)	72.6	(67.4-77.4)	20.5	(17.5-23.9)	99.6	(97.2-99.9)
	Tomonaga et al, 2011 (14)	POCT 3-in-1	POCT 3-in-1	_	89.5	(66.7-98.7)	92.0	(87.3-95.3)	51.5	(39.3-63.5)	98.9	(96.1-99.7)
		POCT cTnT	Single POCT cTnT	0.82 (0.69-0.95)	58.8	(32.9-81.6)	93.1	(87.3-96.8)	52.6	(34.5-70.1)	94.5	(90.7-96.8)
		GP unaided	GP risk estimate	_	100	(76.8-100)	78.7	(70.2-84.7)	31.8	(25.4-39.0)	100	(96.6-100)
	Nilsson et al, 2013 (25)	POCT cTnT	Single POCT cTnT	_	28.6	(3.7-71.0)	97.5	(92.3-99.5)	40.0	(11.7-77.1)	95.9	(93.7-97.4)
		GP unaided	GP risk estimate	_	100	(54.1-100)	62.9	(49.7-74.8)	20.7	(15.9-26.5)	100	(91.0-100)
		Aided clinical judgement	GP + POCT cTnT	_	71.4	(29.0-96.3)	77.7	(69.2-84.8)	15.6	(9.4-24.8)	97.9	(93.6-99.4)
hs-troponin	Andersson et al, 2015 (26)	hs-cTnT	Single hs-cTnT	_	83.3	(35.9-99.6)	76.2	(67.0-83.8)	16.1	(10.5-23.9)	98.8	(93.3-99.8)
	Johannessen et al, 2021 (27)	hs-cTnT	Single hs-cTnT	0.85 (0.81-0.89)	100	(94.1-100.0)	34.5	(32.2-36.8)	5.3	(5.2-5.5)	100	(99.4-100)
			HEART-score	0.77 (0.73-0.82)	91.8	(81.9-97.3)	52.5	(50.0-54.9)	6.7	(6.1-7.3)	99.4	(98.7-99.8)
			Modified HEART-score	0.74 (0.70-0.78)	98.4	(91.2-100.0)	38.7	(36.3-41.1)	5.6	(5.3-5.9)	99.8	(98.9-100)

Abbreviations: ACS, acute coronary syndrome; AMI, acute myocardial infarction; AUC, area under the curve; CDR, clinical decision rule; COV, cut-off value; cTnT, cardiac troponin T; GP, general practitioner; H-FABP, heart-type fatty acid-binding protein; hs, high-sensitivity; INTERCHEST, international chest pain prediction; MACE, major adverse cardiovascular events; MHS, Marburg Heart Score; NPV, negative predictive value; POCT, point of care test; PPV, positive predictive value; RS, risk stratification.

Note: We calculated the sensitivity, specificity, PPV, and NPV using 2x2 contingency tables. Note: Some CI values missing in original articles, therefore not shown here.

* Risk < 10% for ACS was considered low-risk. ** Kleton et al assessed the diagnostic accuracty of the Bruins Slot rule, Marburg Heart Score, INTERCHEST score and Gencer rule. Therefore, the study is mentioned four times in the table. † Study did not provide 2x2 tabels to calculate diagnostic test characteristics. ¥ Risk threshold range: 0.1-20%.

DISCUSSION

This systematic review provides an overview of the evidence on risk stratification tools for acute chest pain in primary care. Seven CDRs with variable diagnostic properties have been evaluated. Some, may improve safety (ie, modifications of the HEART-score), but at the expense of more referrals. None of the CDRs demonstrated superiority over unaided GP assessment. In studies evaluating strategies using troponin we found promising results among those that used high sensitivity troponin assays, either as a standalone tool, or incorporated into a CDR, however further study is needed.

Strengths and Limitations

This systematic review is an extensive and up-to-date overview of risk stratification tools for acute chest pain in primary care. It will aid GPs in their decision for referral and additional testing. A strength of this review is the inclusion of relatively new strategies using hs-troponin. A limitation is the considerable heterogeneity of the included studies, particularly in patient selection, (a delayed-type) reference standard, and follow-up intervals. Furthermore, several of the included studies were limited by small sample sizes (7 had fewer than 500 patients) and low ACS prevalence. This automatically generates high NPVs and might cause overestimation of the tool's performance if the sensitivity is not taken into consideration. Finally, we only included English articles in the review, which might introduce language bias.

Interpretation of Results

Prior international research indicates that a 1% miss rate is considered acceptable for ACS and MACE.[28,29] Additionally, a risk stratification tool also needs to be efficient. Other research found that Dutch GPs would accept 25-50 unnecessary referrals for every patient with ACS.[28] Assuming an ACS prevalence of 5%, a specificity of at least 50% is needed. Among the studied CDRs, none met the desired sensitivity and specificity. Only the modified HEART-scores may approach these requirements, but they need further validation. Hence, we cannot recommend currently available CDRs as standalone tools to rule out ACS.

Conventional troponin as a standalone test did not meet the desired diagnostic accuracy, and its use seems to be outdated since the introduction of hs-troponin assays. The studies using hs-troponin measurement show the most promising results with sensitivities up to 100%. Although the study by Andersson reported a lower sensitivity (83%) for their single measurement

rule-out strategy, this might be caused due to using a hs-cTnT threshold below the 99th percentile.[26] In contrast, the study by Johannessen used a much lower threshold below the limit of detection with 100% sensitivity.[27] The European Society of Cardiology guidelines underline the necessity of a very low threshold to rule out ACS by a single hs-troponin measurement and report assay specific thresholds.[30]

The One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome (OUT-ACS) study (published in 2020), prospectively validated the European Society of Cardiology 0/1-hr algorithm, including hs-troponin, to rule out AMI in primary care.[30,31] Although this strategy approaches both desired sensitivity and specificity (98.4% and 79.4%), the algorithm requires serial troponin tests and observation of patients, which is often not possible in primary care settings.

Finding a tool that exceeds the GP's accuracy might be challenging, since unaided clinical judgment is already reasonably good with a sensitivity 75% to 100% and specificity 18% to 79%.[1,12,14,17,18,24] Best diagnostic accuracy might therefore be achieved by combining the GP's risk assessment with a stratification tool instead of risk stratification tools as standalone tests.

Future Research

Results for risk stratification strategies using hs-troponin are promising, but require further prospective validation, since studies in primary care are limited.[26,27] Although hs-troponin strategies are extensively researched and found to be safe in emergency department settings, results cannot be automatically transferred to primary care due to the lower pre-test probability for ACS.[5] While the CDRs did not meet the desired test accuracy to rule out ACS, a combination of a CDR with hs-troponin measurement might offer optimal results. Such strategies are currently under research in primary care practices (Pijn op de borst-HELP)[32] and out-of-hours primary care (HEART-GP)[33].

Variations in health care systems across countries may influence the applicability of risk stratification tools. All but 1 of the included studies were conducted in Europe, where GPs often function as gatekeepers to secondary care. These rule-out strategies, however, could also benefit countries with other primary care structures, such as the United States or countries with large rural regions, where specialized care is scarce and diagnostic options are limited, especially since cardiac monitoring is not required. Such changes, however, require cultural and organizational changes.

Finally, pre-hospital care comprises both primary care and ambulance services and we advocate standardized care across the entire continuum.

Future research should focus on risk stratification tools that are applicable in the entire pre-hospital care chain, and preferably in line with hospital care. The latter is especially important for strategies using troponin since different assays and thresholds hamper communication between health care providers.

CONCLUSION

Clinical decision rules without troponin or with conventional troponin do not show sufficient sensitivity to rule out ACS in primary care and are not recommended as standalone tools. The first hs-troponin studies in primary care show promising results, but further prospective validation in primary care is needed before recommending its implementation.

REFERENCES

1. Bruins Slot M, Rutten F, van der Heijden GJ, Geersing G, Glatz J, Hoes AW. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Family Practice*. 2011;28(3):323–328.
2. Hoorweg BB, Willemsen RT, Cleef LE, et al. Frequency of chest pain in primary care, diagnostic tests performed and final diagnoses. *Heart*. Nov 2017;103(21):1727–1732. doi:10.1136/heartjnl-2016-310905
3. van Dongen DN, Fokkert MJ, Tolsma RT, et al. Accuracy of pre-hospital HEART score risk classification using point of care versus high sensitive troponin in suspected NSTE-ACS. *The American Journal of Emergency Medicine*. 2020;38(8):1616–1620.
4. Haasenritter J, Biroga T, Keunecke C, et al. Causes of chest pain in primary care--a systematic review and meta-analysis. *Croat Med J*. Oct 2015;56(5):422–30. doi:10.3325/cmj.2015.56.422
5. Usher-Smith JA, Sharp SJ, Griffin SJ. The spectrum effect in tests for risk prediction, screening, and diagnosis. *bmj*. 2016;353
6. Harskamp RE, Laeven SC, Himmelreich JC, Lucassen WAM, van Weert H. Chest pain in general practice: a systematic review of prediction rules. *BMJ Open*. Feb 27 2019;9(2):e027081. doi:10.1136/bmjopen-2018-027081
7. McInnes MD, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *Jama*. 2018;319(4):388–396.
8. Van De Schoot R, De Bruin J, Schram R, et al. An open source machine learning framework for efficient and transparent systematic reviews. *Nature machine intelligence*. 2021;3(2):125–133.
9. van Haastrecht M, Sarhan I, Yigit Ozkan B, Brinkhuis M, Spruit M. SYMBALS: A systematic review methodology blending active learning and snowballing. *Frontiers in research metrics and analytics*. 2021;6:685591.
10. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of internal medicine*. 2011;155(8):529–536.
11. Harskamp RE, Kleton M, Smits IH, et al. Performance of a simplified HEART score and HEART-GP score for evaluating chest pain in urgent primary care. *Neth Heart J*. 2021;doi:10.1007/s12471-020-01529-4
12. Kleton M, Manten A, Smits I, Rietveld R, Lucassen WA, Harskamp RE. Performance of risk scores for coronary artery disease: a retrospective cohort study of patients with chest pain in urgent primary care. *BMJ open*. 2021;11(12):e045387.
13. Manten A, De Clercq L, Rietveld R, Lucassen W, Moll van Charante E, Harskamp R. Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care. *Netherlands Heart Journal*. 2022:1–7.

14. Tomonaga Y, Gutzwiller F, Lüscher TF, et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. *BMC family practice*. 2011;12(1):12.

15. Grijseels E, Deckers eJ, Hoes A, et al. Implementation of a pre-hospital decision rule in general practice: Triage of patients with suspected myocardial infarction. *European heart journal*. 1996;17(1):89–95.

16. Grijseels E, Deckers J, Hoes A, et al. Pre-hospital triage of patients with suspected myocardial infarction. Evaluation of previously developed algorithms and new proposals. *European heart journal*. 1995;16(3):325–332.

17. Schols AM, Willemsen RT, Bonten TN, et al. A nationwide flash-mob study for suspected acute coronary syndrome. *The Annals of Family Medicine*. 2019;17(4):296–303.

18. Willemsen RT, Winkens B, Kietselaer BL, et al. Evaluating possible acute coronary syndrome in primary care: the value of signs, symptoms, and plasma heart-type fatty acid-binding protein (H-FABP). A diagnostic study. *BJGP open*. 2019;3(3)

19. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212

20. International Working Group on Chest Pain in Primary Care (INTERCHEST), Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011

21. Gencer B, Vaucher P, Herzig L, et al. Ruling out coronary heart disease in primary care patients with chest pain: a clinical prediction score. *BMC Medicine*. Jan 21 2010 2010;8(9) doi:10.1186/1741-7015-8-9

22. Wouters LT, Zwart DL, Erkelens DC, et al. Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study. *BMJ open*. 2022;12(10):e064402.

23. Six A, Backus B, Kelder J. Chest pain in the emergency room: value of the HEART score. *Netherlands Heart Journal*. 2008;16(6):191–196.

24. Planer D, Leibowitz D, Paltiel O, Boukhobza R, Lotan C, Weiss TA. The diagnostic value of troponin T testing in the community setting. *International journal of cardiology*. 2006;107(3):369–375.

25. Nilsson S, Andersson PO, Borgquist L, et al. Point-of-care troponin T testing in the management of patients with chest pain in the Swedish primary care. *International journal of family medicine*. 2013;2013(1):532093.

26. Andersson PO, Karlsson J-E, Landberg E, Festin K, Nilsson S. Consequences of high-sensitivity troponin T testing applied in a primary care population with chest pain compared with a commercially available point-of-care troponin T analysis: an observational prospective study. *BMC research notes*. 2015;8(1):210.

27. Johannessen TR, Atar D, Vallersnes OM, Larstorp ACK, Mdala I, Halvorsen S. Comparison of a single high-sensitivity cardiac troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study. *BMJ open*. 2021;11(2):e046024.

28. Harskamp R, van Peet P, Bont J, Ligthart S, Lucassen W, van Weert H. The conundrum of acute chest pain in general practice: a nationwide survey in The Netherlands. *BJGP Open*. Dec 2018;2(4):bjgpopen18X101619. doi:10.3399/bjgpopen18X101619

29. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *International journal of cardiology*. 2013;166(3):752–754.

30. Byrne RA, Rossello X, Coughlan J, et al. 2023 ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal: Acute Cardiovascular Care*. 2024;13(1):55–161.

31. Johannessen TR, Vallersnes OM, Halvorsen S, Larstorp ACK, Mdala I, Atar D. Pre-hospital One-Hour Troponin in a Low-Prevalence Population of Acute Coronary Syndrome: OUT-ACS study. *Open Heart*. 26 May 2020 2020;7(e001296) doi:10.1136/openhrt-2020-001296

32. Van Den Bulk S, Petrus AH, Willemsen RT, et al. Ruling out acute coronary syndrome in primary care with a clinical decision rule and a capillary, high-sensitive troponin I point of care test: study protocol of a diagnostic RCT in the Netherlands (POB HELP). *BMJ open*. 2023;13(6):e071822.

33. Harskamp RE. HEART-GP: developing a quick way to check for heart issues in primary care ISRCTN registry.

SUPPLEMENTARY MATERIAL

Supplemental Appendix 1. Search components in PubMed and Embase.

PUBMED

("Primary Health Care"[Mesh] OR "Physicians, Family"[Mesh] OR "primary care"[all fields] OR "Physicians, Family"[Mesh] OR general pract*[all fields] OR "family"[ad] OR family pract*[all fields] OR family physician*[tw])

AND

("Chest Pain"[Mesh] OR "Angina Pectoris"[Mesh] OR "Myocardial Ischemia"[Mesh] OR chest pain*[tiab] OR angina pectoris[tiab] OR stable angina*[tiab] OR unstable angina*[tiab] OR preinfarction angina*[tiab] OR angina at rest[tiab] OR variant angina*[tiab] OR prinzmetal*[tiab] OR myocardial ischemi*[tiab] OR myocardial ischaemi*[tiab] OR acute coronary syndrome*[tiab] OR angina pectoris[tiab] OR coronary disease*[tiab] OR coronary heart disease*[tiab] OR coronary artery disease*[tiab] OR coronary arteriosclerosis[tiab] OR coronary atherosclerosis[tiab] OR myocardial infarct*[tiab] OR heart attack*[tiab])

AND

("Decision Support Techniques"[Mesh] OR decision rule*[tiab] OR decision aid*[tiab] OR prediction rule*[tiab] OR decision model*[tiab] OR decision tool*[tiab] OR risk classification*[tiab] OR "Troponin"[Mesh] OR troponin*[tiab] OR cardiac enzyme*[tiab])

EMBASE (OVID)

Database(s): Embase Classic+Embase 1947 to 2022 December 02

Search Strategy:

#	Searches	Results
1	exp primary health care/	199421
2	general practitioner/	118066
3	primary care.af.	268351
4	general pract$.af.	267273
5	family pract$.af.	27286
6	family.in.	231204
7	family physician$.mp.	21161

continues

continued

8	1 or 2 or 3 or 4 or 5 or 6 or 7	737318
9	thorax pain/	112065
10	exp angina pectoris/	115463
11	exp heart muscle ischemia/	100749
12	(chest pain* or angina pectoris or stable angina* or unstable angina* or preinfarction angina* or angina at rest or variant angina* or prinzmetal* or myocardial ischemi* or myocardial ischaemi* or acute coronary syndrome* or angina pectoris or coronary disease* or coronary heart disease* or coronary artery disease* or coronary arteriosclerosis or coronary atherosclerosis or myocardial infarct* or heart attack*).ti,ab,kf.	681062
13	9 or 10 or 11 or 12	812212
14	exp decision support system/	32187
15	exp troponin/	79218
16	(decision rule* or decision aid* or prediction rule* or decision model* or decision tool* or risk classification* or troponin* or cardiac enzyme*).ti,ab,kf.	85222
17	14 or 15 or 16	142557
18	8 and 13 and 17	857

UPDATE

The search was updated up to October 9th 2023 with an additional search-term: decision support*[tiab].

Supplemental Appendix 2. ASReview

ASReview is an open-source machine learning-aided software application, in accordance with the validated SYMBALS methodology for efficient screening of available literature.[1,2] The active learning technique of ASReview accelerates the screening process and makes it more efficient, while exceeding the performance of manual-screening.[3] In ASReview, researchers are presented with the most relevant article first. The relevance is calculated in repeating learning cycles in which the algorithm continuously retrains based on the researcher's input. The tool offers several classifiers and query strategies, of which we applied Naïve Bayes and certainty based sampling. Two researchers (SB and AM) independently initiated the screening process in ASReview by selecting five unique relevant and five unique irrelevant articles (i.e. training phase), and proceeded to independently screen titles and abstracts until predefined stopping criteria were met. Stopping criteria were based on prior research using technology assisted reviewing and were twofold.[4,5] First, an estimate of the total number of relevant papers was calculated using a random sample of 10%. In our sample this lead to an estimate of 40 relevant records. Second, when the estimate was reached, we elected to stop screening after marking 50 consecutive papers irrelevant. The two researchers reached the stopping criteria after screening 329 (27.3%) and 338 (28.1%) records with 55 and 53 relevant titels and abstracts, respectively. Conflicts between researchers were discussed and resolved (*n*=25/370 (6.7%) screened).

REFERENCES

1. Van De Schoot R, De Bruin J, Schram R, et al. An open source machine learning framework for efficient and transparent systematic reviews. *Nature machine intelligence*. 2021;3(2):125–133.
2. van Haastrecht M, Sarhan I, Yigit Ozkan B, Brinkhuis M, Spruit M. SYMBALS: A systematic review methodology blending active learning and snowballing. *Frontiers in research metrics and analytics*. 2021;6:685591.
3. Ferdinands G, Schram R, de Bruin J, et al. Active learning for screening prioritization in systematic reviews-A simulation study. 2020;
4. Cormack GV, Grossman MR. Engineering quality and reliability in technology-assisted review. 2016:75–84.
5. Ros R, Bjarnason E, Runeson P. A machine learning approach for semi-automated search and selection in literature studies. 2017:118–127.

Supplementary Table 1. Components of risk stratification tools.

Grijseels rule				
Variables: 1 History of CAD 2 Male sex 3 Presence of radiation of pain 4 Presence of nausea/sweating	# variables present	Normal ECG	Possible/ minor MI on ECG	Major MI on ECG
	0	Home	Possible referral	Always referral and start treating as ACS
	1	Home	Referral	
	2	Possible referral	Referral	
	≥3	Referral	Referral	
Bruins Slot rule				
History of CAD	2	Score ranges from 0 to 20 points Cut-off values for low-risk, intermediate-risk and high-risk groups were not reported		
Male sex	5			
Presence of radiation of pain	8			
Presence of nausea/sweating	5			
Willemsen rule				
ECG ST-depression	1	Score ranges from 0 to 6 points 0-1 points: negative result 2-6 points: positive result		
ECG ST-elevations	1			
Dyspnea	1			
Feeling of pressure on chest	1			
Absent lateral chest pain left	1			
POCT H-FABP result positive	1			
Marburg Heart Score				
Known clinical vascular disease*	1	Score ranges from 0 to 5 points 0–2 points: negative result 3–5 points: positive result		
Age/sex (F ≥65 years or M ≥55 years)	1			
Increased pain with exercise	1			
Pain not reproducible by palpation	1			
Patient assumes pain is of cardiac origin	1			
INTERCHEST				
History of CAD	1	Score ranges from –1 to +5 points ≤1 points: negative result 2-5 points: positive result		
Age/sex (F ≥65 years or M ≥55 years)	1			
Increased pain with exercise	1			
Pain reproducible by palpation	-1			
Physician assumes cardiac origin	1			
Pain feels like ‘pressure’	1			
Gencer rule				
History of CVD	2	Score ranges from 0 to 11 points 0–4 points: low risk 5–7 points: moderate risk 8–11 points: high risk		
Age/sex (F ≥65 years or M ≥55 years)	2			
Increased pain with exercise	1			
Pain not reproducible by palpation	1			
CVD risk factor**	2			
Duration of pain 1–60min	1			
Substernal location of pain	2			

continues

continued

Safety First			
Sex		-	The authors did not put forth a specific scoring system
Age		-	
Acute onset of chest pain < 12 hours		-	
Pressing/ heavy character of the pain		-	
Radiation of pain		-	
Presence of sweating		-	
Calling at night		-	
Original HEART-score			
History	Highly suspicious for ACS	2	Score ranges from 0 to 10 points 0–3 points: low risk 4–6 points: moderate risk 7–10 points: high risk
	Moderately suspicious	1	
	Slightly or not suspicious	0	
ECG	Significant ST-depression	2	
	Non-specific changes‡	1	
	Normal	0	
Age	≥65 years	2	
	46–64 years	1	
	≤45 years	0	
Risk factors§	≥3 risk factors or previous CAD	2	
	One or two risk factors	1	
	No risk factors	0	
Troponin	≥3 × URL	2	
	>1 to <3 × URL	1	
	≤URL	0	

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; POCT, point of care test; URL, upper reference limit

* CAD, occlusive vascular disease or cerebrovascular disease.

** Family history of CVD, diabetes mellitus, (treated) hypertension, (treated) hyperlipidemia, smoking or obesity (body mass index ≥30)

‡ Left bundle branch block, left ventricular hypertrophy, repolarization changes, pacemaker.

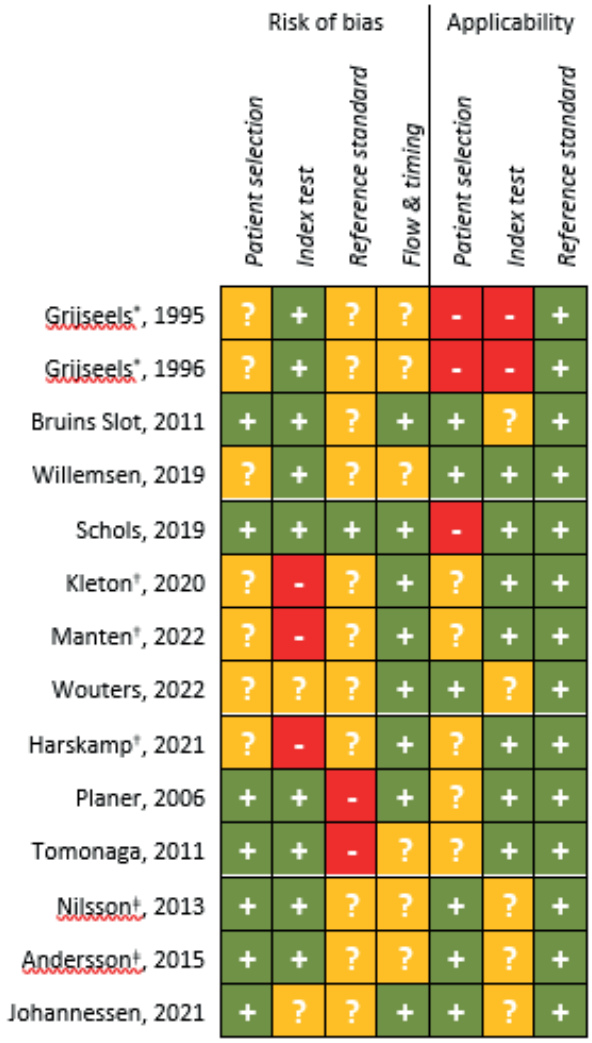
§ Family history of CVD, diabetes mellitus, (treated) hypertension, (treated) hyperlipidemia, smoking or obesity (body mass index ≥30)

Supplementary Table 2. Cardiac troponin assays and threshold values.

First author, year	Analyzer/assay	Threshold, ng/L	URL*, ng/L	LoD, ng/L	POCT
Planer, 2006	TROPT *Sensitive* (cTnT)	≥80 ng/L	80 ng/L**	50 ng/L	Yes
Tomonaga, 2011	Cardiac Reader Roche diagnostics (cTnT)	≥0.1 ng/L	Not mentioned	Not mentioned	Yes
Nilsson, 2023	Cobas h232 Roche diagnostics (cTnT)	≥30 ng/L	100 ng/L	30 ng/L	Yes
Andersson, 2015	Cobas e602 Roche diagnostics (high-sensitive-cTnT)	≥15 ng/L	14 ng/L	1 ng/L	No
Johannessen, 2021	Cobas 8000 e602 Cobas 8000 e801 Roche diagnostics (high sensitive-cTnT)	Single rule out: <5 ng/L HEART-score: ≤14 ng/L 0 points 15-41 ng/L 1 point ≥42 ng/L 2 points Modified HEART-score: ≤5 ng/L 0 points 5-14 ng/L 1 point ≥14 ng/L 2 points	14 ng/L	5 ng/L	No

Abbreviations: URL, upper reference limit; LoD, limit of detection; POCT, point of care test. *99th percentile unless stated otherwise, ** 90th percentile.

Supplemental Appendix 3. Risk of bias and applicability assessment.



Studies marked by the same symbol (*, †, ‡, respectively) refer to multiple studies with one overarching design.

For the quality assessment of included studies we used the four domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool.

Patient selection

Regarding patient selection we assessed the inclusion criteria and methods of selection. No risk of bias was assigned to studies including a consecutive,

or random sample of adult patients with acute chest pain in whom an acute coronary syndrome was considered possible. Patients had to be enrolled in a primary care setting (defined as either daytime or out-of-hours general practice). Retrospective designs were considered to be a potential risk of bias.

Patient selection was considered less applicable when patient samples did not fully match a primary care setting (e.g. only high-risk patients that would receive ambulance transport regardless of primary care assessment (i.e. emergency department population), inclusion of patients with chest pain with obvious, non-cardiac causes, like trauma, or inclusion of patients with other complaints than chest pain).

Index test

We assessed whether the index test had pre-specified thresholds and whether the interpreter of the index test was blinded for the results of the reference standard. Furthermore, we evaluated the presence of missing data and how these were handled.

Index tests were deemed applicable when the test could be reproduced, executed and interpreted in primary care settings. For example, tools that require advanced computer algorithms or advanced diagnostic testing were not deemed applicable.

Reference standard

For the reference standard, we used the ESC guideline recommendations for ruling-out ACS as a golden standard: repeated measurements of troponin, preferably using high-sensitivity or ultra-sensitivity assays. In the assessment of the reference standard, we presumed that diagnostic testing in the hospital following primary care assessment adhered to these recommendations. Therefore, delayed reference standards in which not all patients received further diagnostic testing in hospital may introduce verification bias. We assessed whether interpretation of the reference standard results (including assigning final diagnoses) were blinded for the results of the index test. Furthermore, we evaluated the source of final diagnoses. Here, data based solely on registries without further consideration of patient records, were considered a risk of bias.

For applicability of the reference standard we assessed whether the target condition included a form of ACS or MACE.

Flow and timing

For the interval between index test and reference standard we did not apply a specific threshold but rather evaluated the interval in relation to the reference

standard applied. For delayed type reference standards we agreed on a minimum of 4-6 weeks follow-up to accommodate cases that were initially missed. Although this window remains arbitrary, we expect missed events to be uncovered within that period. Moreover, we assessed whether all included patients received the same reference standard and whether all patients were included in the final analysis.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Chapter 10

General discussion

GENERAL DISCUSSION

This thesis evaluated triage of acute chest pain in Dutch out-of-hours primary care (OOH-PC) and explored opportunities for its optimization using clinical decision support tools.

We started from the premise that the current protocol for triage of chest pain is overly defensive, resulting in many potentially unnecessary referrals to secondary care. Furthermore, we anticipated that triage performance might differ between women and men. Finally, we hypothesized that incorporating elements of validated clinical decision rules could improve triage accuracy without compromising patient safety.

To test these assumptions, we explored patient flow in a Dutch pre-hospital setting, assessing the relative burden on OOH-PC and emergency medical services (EMS). Furthermore, we established the TRiage of Acute Chest pain Evaluation in primary care (TRACE) project, which focused on evaluating the performance of the current telephone triage protocol for chest pain, as issued by the Netherlands Triage Standard (NTS). Performance was measured in terms of triage safety and efficiency regarding a broad range of relevant clinical outcomes in patients contacting OOH-PC in the Netherlands.

The TRACE project comprised two phases. In the retrospective phase of the project, we established a large cohort to gain insights into triage performance and potential sex differences in management and outcomes. Using this cohort, we performed an initial evaluation of two validated clinical decision rules: the Marburg Heart Score (MHS) and INTERCHEST score. Additionally, we externally validated the Safety First Prediction Rule, a multivariate model specifically developed to rule out acute coronary syndrome (ACS) in OOH-PC. In the prospective phase, we further validated the MHS and INTERCHEST score, and re-evaluated NTS performance.

Finally, through a systematic review, we examined the body of evidence for a variety of risk stratification tools available for acute chest pain assessment across primary care, including those using troponin measurements.

In this chapter, we summarize the main findings, reflect on their clinical implications in the light of existing literature, and consider methodological aspects. We conclude with directions for future research and suggestions to further improve telephone triage of chest pain.

INTERPRETATION OF MAIN FINDINGS

Chest pain-related demand on pre-hospital care

In the Netherlands, chest pain-related contacts contribute substantially to the high workloads across the entire acute care chain. A significant share of this workload involves non-urgent cases. For OOH-PC, this was demonstrated in **Chapters 4** and **7** as only 13-16% of patients with chest pain were found to have a major event.

The exact distribution of patient flow across Dutch pre-hospital care is unknown. Therefore, in **Chapter 2**, we explored the relative burden of chest pain-related contacts between emergency medical services (EMS) and OOH-PC. In 2023 and 2024, we found that OOH-PC facilities managed more contacts than EMS dispatched ambulances for acute chest pain. However, available data differed, and EMS data did not include telephone contacts that were handled without an ambulance dispatch.

We also explored time trends in pre-hospital demand between 2019 and 2024. Over time, the demand increased for both OOH-PC and EMS. Furthermore, OOH-PC contacts increasingly resulted in the request for an ambulance, while EMS showed a growing share of potentially unnecessary ambulance rides. These trends may indicate suboptimal use of resources, although firm conclusions are restricted by the absence of outcome data.

Together, these findings highlight the importance of further research on relative patient volumes in a pre-hospital setting to better understand how chest pain patients navigate the system. Such knowledge is necessary to help identify opportunities to improve coordination, align workflows, and use pre-hospital resources more efficiently.

NTS performance in OOH-PC

This thesis evaluated the performance of the current NTS protocol for telephone triage of acute chest pain in two separate patient cohorts in Dutch OOH-PC. **Chapter 3** describes the rationale and design of the retrospective phase of the TRACE project, which included 2,043 patients (57.6% female) who contacted a regional OOH-PC facility for chest pain in 2017. In this consecutive cohort, more than half of the patients were assigned an urgency level that was higher than clinically warranted (i.e. no major event or ACS). Furthermore, urgency levels were underestimated in 17% of major events and 14% of ACS cases, resulting in a sensitivity of 83.0-85.7% and a specificity of 40.0-42.4% (*Table 1*). Even after incorporating the subsequent clinical judgement of the triage assistant and general practitioner (GP) (i.e. beyond NTS urgency classification), the overall safety and accuracy remained moderate at best (**Chapter 4**).

In the prospective phase of the TRACE project (**Chapter 7**), 1,254 patients (57.9% female) were eligible for inclusion, but data were collected in only 280 (22.3%) patients between December 2022 and May 2023. In this cohort, inappropriate urgency levels were even more frequent (in 70%), though underestimation was rare (1/36 major events and none of the ACS cases). The resulting sensitivity ranged from 97.2-100.0% and specificity from 18.4-19.7% (*Table 1*).

Table 1. Diagnostic accuracy parameters of the NTS for major events and ACS.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Major events				
NTS				
Retrospective cohort	83.0 (77.6-87.6)	42.4 (39.6-45.2)	22.0 (20.7-23.3)	92.7 (90.5-94.4)
Prospective cohort	97.2 (85.5-99.9)	19.7 (14.9-25.2)	15.2 (14.1-16.3)	98.0 (87.2-99.7)
ACS				
NTS				
Retrospective cohort	85.7 (77.2-92.0)	40.0 37.3-42.7)	9.5 (8.7-10.3)	97.5 (95.9-98.4)
Prospective cohort	100.0 (75.3-100)	18.4 (13.9-23.5)	5.6 (5.3-5.9)	100.0 (92.8-100)

The table shows performance parameters for both the retrospective and prospective evaluation of the NTS protocol for chest pain. Results are shown for the prediction of major events (i.e. a composite of all-cause mortality and urgent conditions, including ACS, requiring hospital admittance or urgent in-hospital treatment), and ACS alone. Test properties are displayed as percentages with the 95% confidence interval in parentheses. Abbreviations: ACS, acute coronary syndrome; PPV, positive predictive value; NPV, negative predictive value; NTS, Netherlands Triage Standard.

To further weigh these results, it is important to define what level of diagnostic accuracy would be considered acceptable for ruling out urgent underlying conditions. Both safety and efficiency considerations are relevant. With regard to safety, international studies have suggested that a miss rate of up to 1% is acceptable for ACS.[1,2] In terms of efficiency, prior research among Dutch GPs indicated that 25-50 unnecessary referrals would be acceptable for each patient correctly identified with ACS.[1] Assuming a disease prevalence of 5%, this corresponds to a negative predictive value (NPV) of at least 99% and a specificity of at least 50%. Since *major events* were defined specifically for the use in our studies, comparable reference criteria for this composite outcome are not available.

Considering these benchmarks, the NTS protocol for chest pain does not meet the desired balance between safety and efficiency. Its high proportion of overtriage suggests a defensive approach aimed at minimizing missed diagnoses, yet miss rates exceed the accepted 1% threshold.

From a safety perspective, the higher NPV and sensitivity observed in the prospective cohort may appear favorable. However, this apparent improvement likely reflects selection bias, as the 280 patients in whom triage assistants collected data showed more high-risk characteristics than those eligible but not enrolled. In contrast, the retrospective study included consecutive patients, providing a better representation of everyday practice. Moreover, the NTS performance observed in **Chapter 4** was consistent with another recent Dutch study on telephone triage of chest pain in an OOH-PC setting, which reported a sensitivity of 73% and specificity of 43%.[3]

Nevertheless, these conclusions should be interpreted with caution, as the number of ACS cases in our cohorts was limited, resulting in wide confidence intervals around the sensitivity estimates. With a larger sample, the observed differences between cohorts might have been smaller, and the confidence intervals may have overlapped more substantially.

Assessing the validity of triage systems such as the NTS is inherently difficult. Ideally, validation studies should test whether triage accurately classifies urgency levels and ultimately reduces morbidity and mortality. However, no single outcome measure can fully capture the underlying clinical urgency.[4,5] Researchers therefore rely on proxy markers. In this thesis, we used the occurrence of a major event or ACS as proxies and assessed whether these outcomes corresponded with the allocated urgency levels (i.e. criterion validity).

A systematic review by Nishi *et al.* assessed the validity of the Manchester Triage System, from which the NTS protocols originate, in a similar fashion.[6,7] They evaluated MTS performance in patients with suspected ACS in the emergency department using the occurrence of an ACS as proxy marker for the underlying clinical urgency, and reported a sensitivity of 0.70-0.80 and specificity of 0.59-0.97. A Dutch study applied a different method and used patient vignettes to test the reliability and validity of the MTS. Their results showed moderate to substantial inter-rater reliability and a tendency toward undertriage rather than overtriage.[8]

Together, these findings underline that while structured triage systems such as the NTS and MTS offer a standardized approach, efforts to validate them remain highly heterogeneous. As shown in our work, such heterogeneity translates into substantial variation in diagnostic accuracy, with frequent misclassification of urgency levels limiting the systems' clinical reliability.

Improving telephone triage

Marburg Heart Score and INTERCHEST score

In **Chapter 6** and **Chapter 7** of this thesis, we assessed two clinical decision rules for their ability to predict major events (including ACS) and ACS alone among patients with chest pain in an OOH-PC setting. The Marburg Heart Score (MHS) and INTERCHEST score were both originally developed for ruling out coronary artery disease (CAD) in daytime primary care.[9,10] Prior internal and external validation of the MHS and INTERCHEST score for CAD resulted in a good discriminative ability.[10-12] Since both scores rely on patient and symptom characteristics that are also applicable in a telephone triage setting, we hypothesized that the scores might aid the assessment of acute chest pain in OOH-PC.

In our retrospective cohort (**Chapter 6**), both the MHS and INTERCHEST score slightly outperformed the NTS protocol by reducing the amount of overestimated urgencies (i.e. an urgency level that was higher than clinically warranted), while maintaining similar safety. Nevertheless, the resulting sensitivity and specificity remained insufficient to safely and accurately assess patients with chest pain (*Table 2).*

In our prospective cohort (**Chapter 7**), the MHS and INTERCHEST score showed even poorer diagnostic accuracies. Although sensitivities were slightly higher, specificities were remarkably lower compared to the retrospective evaluation. Compared to the NTS, both scores resulted in additional underestimated cases (i.e. low urgency assigned to a patient with a major event or ACS), thereby reducing triage safety (*Table 2*).

Table 2. Diagnostic accuracy parameters of the NTS, MHS and INTERCHEST score for major events and ACS.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Major events				
NTS				
Retrospective cohort	83.0 (77.6-87.6)	42.3 (39.5-45.2)	22.0 (20.7-23.3)	92.7 (90.5-94.4)
Prospective cohort	97.2 (85.5-99.9)	19.7 (14.9-25.2)	15.2 (14.1-16.3)	98.0 (87.2-99.7)
MHS				
Retrospective cohort	82.1 (76.6-86.8)	58.8 (55.9-61.6)	28.1 (26.3-30.0)	94.4 (92.7-95.7)
				continues
continued				
Prospective cohort	88.9 (73.9-96.9)	27.9 (22.3-34.0)	15.4 (13.7-17.3)	94.4 (86.9-97.8)
INTERCHEST				

Retrospective cohort	81.7 (76.2-86.4)	61.6 (58.8-64.4)	29.5 (27.5-31.4)	94.5 (92.9-95.8)
Prospective cohort	86.1 (70.5-95.3)	26.6 (21.2-32.7)	14.8 (13.0-16.8)	92.9 (84.9-96.8)
ACS				
NTS				
Retrospective cohort	85.7 (77.2-92.0)	39.9 (37.3-42.6)	9.5 (8.7-10.3)	97.4 (95.9-98.4)
Prospective cohort	100.0 (75.3-100)	18.4 (13.9-23.5)	5.6 (5.3-5.9)	100.0 (92.8-100)
MHS				
Retrospective cohort	78.6 (69.1-86.2)	54.3 (51.6-57.0)	11.2 (10.1-12.5)	97.2 (95.9-98.1)
Prospective cohort	84.6 (54.6-98.1)	26.2 (21.0-31.9)	5.3 (4.2-6.6)	97.2 (90.6-99.2)
INTERCHEST				
Retrospective cohort	88.8 (80.8-94.3)	57.7 (55.0-60.4)	13.3 (12.3-14.5)	98.6 (97.6-99.2)
Prospective cohort	84.6 (54.6-98.1)	25.5 (20.4-31.1)	5.2 (4.2-6.6)	97.1 (90.3-99.2)

The table shows performance parameters for both the retrospective and prospective evaluation of the NTS protocol for chest pain, the MHS and INTERCHEST score. Results are shown for the prediction of major events (i.e. a composite of all-cause mortality and urgent conditions, including ACS, requiring hospital admittance or urgent in-hospital treatment), and ACS alone. Test properties are displayed as percentages with the 95% confidence interval in parentheses.
Abbreviations: ACS, acute coronary syndrome; MHS, Marburg Heart Score; PPV, positive predictive value; NPV, negative predictive value; NTS, Netherlands Triage Standard.

Taken together, our results indicate that although the MHS and INTERCHEST score perform well for identifying CAD, they are less suitable for telephone triage of acute chest pain complaints and are both unable to reach the benchmarks for safety and efficiency. Compared with the NTS protocol, both scores may improve efficiency, but at the cost of sensitivity, which limits their clinical utility in this setting.

Recent changes to the NTS protocol for telephone triage of chest pain

In October 2024, the NTS protocol for telephone triage of chest pain was updated with the aim of improving both safety and efficiency. These alterations were based on the newly developed Safety First Prediction Rule, a multivariate regression model developed to rule out ACS and other life-threatening events in an OOH-PC setting in the Netherlands.[13] Candidate predictors were derived from the existing NTS protocol and from clinical decision rules, including the MHS and INTERCHEST score. The final model consists of seven predictors: (i) age, (ii) sex, (iii) acute onset of chest pain (<12 hours), (iv) a pressing/heavy

character, (v) radiation of pain, (vi) sweating, and (vii) calling at night (i.e. between 00:00 and 09:00). Internal validation resulted in good discriminative properties with C-statistics of 0.79 and 0.77, respectively.[13]

In **Chapter 8**, we externally validated the Safety First Prediction Rule using the retrospective TRACE data. This showed similar discriminative properties with a C-statistic of 0.78 (95%-CI: 0.75-0.81) for major events and 0.79 (95%-CI: 0.75-0.83) for ACS. Compared to the NTS protocol, MHS and INTERCHEST score, the Safety First Prediction Rule (using a risk threshold of 2.5%) achieved a higher sensitivity and NPV, indicating improved safety for ruling out major events and ACS. However, the rule was not able to optimize triage efficiency (*Table 3*).

For the update of the NTS protocol, items from the Safety First model replaced existing items in the NTS decision tree. This meant that four new criteria were introduced to the NTS protocol, which were: age, gender, calling at night and a family history of acute cardiac death <50 years of age.[14] Existing questions on the duration, character and presence of radiation were preserved, while those on severity, location, and course of the pain were omitted. Of the accompanying symptoms, only sweating was retained.

Although the newly included characteristics were selected based on their predictive value, the final composition of the updated protocol was determined through expert consensus. Importantly, the updated protocol was implemented without prior validation, meaning its reliability and effectiveness were not tested in practice before it was rolled out, and there is no guarantee that these changes will improve triage accuracy.

Using our prospective TRACE sample, we conducted exploratory analyses of the updated NTS protocol. These analyses raised safety concerns as the updated protocol missed more major events and ACS cases (**Chapter 7**). This finding may partly reflect misclassification due to missing data. Nevertheless, it underscores the urgent need for rigorous external validation of the updated protocol to confirm its safety and efficiency in routine triage practice.

Table 3. Diagnostic accuracy parameters of the NTS, MHS, INTERCHEST score and Safety First Prediction Rule for major events and ACS.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Major events				
NTS*				
Retrospective cohort	82.5-83.0 (76.9-87.6)	42.3-42.6 (39.5-45.2)	21.4-22.0 (20.1-23.3)	92.7-92.8 (90.5-94.5)
MHS				
Retrospective cohort	82.1 (76.6-86.8)	58.8 (55.9-61.6)	28.1 (26.3-30.0)	94.4 (92.7-95.7)
INTERCHEST				
Retrospective cohort	81.7 (76.2-86.4)	61.6 (58.8-64.4)	29.5 (27.5-31.4)	94.5 (92.9-95.8)
Safety First rule				
Retrospective cohort	93.3 (89.2-96.2)	44.9 (42.0-47.8)	24.2 (23.1-25.4)	97.3 (95.6-98.3)
ACS				
NTS*				
Retrospective cohort	85.7-86.3 (77.2-92.5)	39.9-40.4 (37.3-43.1)	9.5 (8.7-10.3)	97.4-97.6 (95.9-98.5)
MHS				
Retrospective cohort	78.6 (69.1-86.2)	54.3 (51.6-57.0)	11.2 (10.1-12.5)	97.2 (95.9-98.1)
INTERCHEST				
Retrospective cohort	88.8 (80.8-94.3)	57.7 (55.0-60.4)	13.3 (12.3-14.5)	98.6 (97.6-99.2)
Safety First rule				
Retrospective cohort	95.8 (89.6-98.8)	41.3 (38.7-44.1)	10.6 (10.0-11.2)	99.3 (98.1-99.7)

The table shows performance parameters for both the retrospective and prospective evaluation of the NTS protocol for chest pain, the MHS and INTERCHEST score, and the Safety First Prediction Rule. Results are shown for the prediction of major events (i.e. a composite of all-cause mortality and urgent conditions, including ACS, requiring hospital admittance or urgent in-hospital treatment), and ACS alone. Test properties are displayed as percentages with the 95% confidence interval in parentheses.

* In this table, NTS performance includes results of both Chapter 6 and Chapter 8, expressed as a range. The variation in the results between these chapters are caused by the exclusion of 29 additional patients with missing Safety First predictor data in Chapter 8.

Abbreviations: ACS, acute coronary syndrome; MHS, Marburg Heart Score; PPV, positive predictive value; NPV, negative predictive value; NTS, Netherlands Triage Standard.

Decision support for chest pain evaluation across primary care

In recent years, substantial research has been conducted to improve risk stratification for chest pain across primary care. Using a systematic review,

we assessed the evidence on available risk stratification tools for acute chest pain in this setting (**Chapter 9**). Fourteen studies were included, nine of which validated seven different clinical decision rules (Grijseels/Bruins Slot rule, Willemsen CDR, Marburg Heart Score, INTERCHEST score, Gencer rule, HEART-score variants, and the Safety First Prediction Rule), and five that evaluated strategies using point-of-care troponin measurements.[13,15-27] Most of the clinical decision rules without troponin consist of patient and symptom characteristics. The Grijseels rule, Willemsen CDR and HEART-score variants also include an ECG. If possible, strategies were compared to unaided GP assessment, defined as the physician's clinical judgement without the aid of risk stratification tools.

While some clinical decision rules without troponin improved safety, none demonstrated superiority over unaided GP assessment. Only the modified HEART-scores approached optimal diagnostic accuracy (i.e. NPV ≥99% and specificity ≥50%). Among strategies with troponin testing, those using high-sensitivity troponin assays performed best with sensitivities of 83.3-100% and NPV's of 98.8-100%. These findings indicate that clinical decision rules without troponin, or with conventional troponin measurements lack sufficient sensitivity to rule out ACS in primary care, and should not be used as standalone tools. In contrast, high-sensitivity troponin testing showed clear potential, although further validation is required before its implementation in primary care can be recommended.

Building on these insights, several research initiatives in the Netherlands are currently exploring the use of point-of-care high-sensitivity troponin testing in primary care. First, in OOH-PC, the HEART-GP study is underway and investigates the combination of high-sensitivity troponin with clinical assessment, as well as integrated with the HEART score, INTERCHEST score and MHS, to rule out ACS in patients with acute chest pain.[28] Patient enrollment was recently completed and results are pending. Additionally, the 'Pijn op de borst-HELP' (POB HELP) study examines the use of the MHS combined with a high-sensitivity troponin measurement in daytime primary care.[29] Similarly, patient enrollment was completed recently, and results are expected within the following months.

These studies are crucial for advancing the integration of high-sensitivity troponin testing into primary care. However, the organizational structures of primary care vary across countries, which may influence the generalizability of findings.[30,31] Therefore, consideration of international research on troponin-based strategies is important as well.

In Norway, patients with acute symptoms are initially assessed in primary care outpatient clinics. These clinics differ from emergency departments by having fewer diagnostic resources, but unlike Dutch OOH-PC, they do have an observation unit, enabling short-term monitoring and serial troponin measurements. In this setting, Johannessen *et al.* evaluates the 0/1-hour algorithm for high-sensitivity troponin measurements in combination with clinical assessment and an ECG in the OUT-ACS study.[32] Preliminary analyses showed encouraging results with a NPV of 99.9%, sensitivity of 98.4%, and specificity of 79.4%.

In New Zealand, researchers implemented an accelerated diagnostic pathway (ADP) in rural general practices to rule out major adverse cardiovascular events among patients with chest pain who would otherwise be referred to hospital care.[33] The ADP included high-sensitivity troponin testing at 0 and 2 hours after presentation and proved safe, with a sensitivity and NPV of 100% and a specificity of 50.7%.[34]

Together, these international studies demonstrate that strategies using high-sensitivity troponin testing in primary care can meet benchmarks for diagnostic accuracy. However, their implementation in Dutch OOH-PC is currently not feasible, as both the Norwegian and New Zealand strategies require patient observation, which is not available in the Dutch system.

Sex differences in triage of chest pain

In **Chapter 5** we evaluated sex-related differences in symptom characteristics, triage management, and subsequent outcomes among patients with chest pain in OOH-PC. We found that women had a lower a priori cardiovascular risk and were less likely to have a major event (12.8 vs 20.8%) or ACS (5.4 vs 8.4%) compared to men. These differences were not incorporated in the triage protocol at that time, neither as a predictive factor, nor in the content of triage assessment. In our study, symptom characteristics and actions following triage were largely similar between women and men. Thus, despite women's lower risk, they were triaged the same way, which resulted in relatively more cautious management for women, with a higher proportion of unnecessary high urgency levels. Two other Dutch studies in OOH-PC reported overall higher incidences of ACS (8.4-8.6% in women and 14.0-15.0% in men), yet their findings on symptom presentation and triage actions were consistent with ours, showing more similarities than differences between sexes.[35,36]

Despite the lower a priori risk of ACS in women, incorporating sex as a triage predictor may be unsafe, as it could increase the risk of undertriage in women who do present with an ACS. Current evidence indicates that symptom overlap

outweighs sex-based differences, limiting the predictive value of sex in acute triage settings.[37-41]

Nevertheless, with the NTS' update in October 2024, sex was incorporated as a predictive factor.[14] In this update, symptom characteristics are not made sex-specific, but the patient's sex does influence the urgency allocation. Since the updated NTS protocol was implemented without prior validation, the impact of these changes on the safety and efficiency of triage for both women and men remains uncertain.

Moving past the triage process, meaningful sex differences do emerge in the management and outcomes of (suspected) ACS. Evidence indicates that men and women benefit equally from invasive and non-invasive management strategies, leaving no rationale for different treatment policies in chest pain or suspected ACS.[42] Nevertheless, growing evidence shows that women, especially those of a younger age, are less likely to receive guideline-directed care, experience more complications, and face higher mortality compared with men.[43-49] Women also tend to delay seeking care more often.[42,50,51]

Furthermore, while chest pain is the predominant symptom of ACS in up to 90% of both women and men, other presenting complaints such as dyspnea, nausea, or localized complaints outside the chest are also reported.[38,40,51,52] Some studies found that such non-chest pain presentations occur more frequently in women and may contribute to misdiagnosis.[37,40,53] Public campaigns often draw specifically on these findings and emphasize the differences, portraying women's symptoms as 'atypical'. Although well-intended, this framing may inadvertently reinforce disparities in care. Instead, the key challenge lies in ensuring equitable management after triage so women receive the same expeditious diagnostics and treatment for ACS as men.

METHODOLOGICAL CONSIDERATIONS

Conducting research in primary care comes with inherent challenges. Because patient data are usually stored at individual GP practices, large-scale studies require extensive collaboration and data sharing. The introduction of the GDPR in 2018 added additional barriers for researchers, particularly when assessing routine-care data. From a privacy perspective, explicit patient consent is preferred, but this is often not feasible for retrospective research. In such cases, providing an individual and easily accessible opt-out option may serve as a suitable alternative.[54] For the retrospective part of the TRACE project, we implemented such an approach by informing patients about the study and offering the possibility to withdraw from participation. This strategy

allowed inclusion of a large, consecutive sample, minimizing selection bias. Nevertheless, a number of patients were lost to follow-up because some GPs expressed liability concerns, despite the legal validity of the opt-out procedure. For the prospective study, triage assistants obtained initial verbal consent, which was subsequently confirmed by the research team. This enabled more comprehensive data collection, but also resulted in a smaller sample size. Such procedures, while ethically and legally robust, may render large-scale OOH-PC research increasingly difficult to conduct in the future. Thus, sustaining research in this context will require clear national frameworks.

In the design of the retrospective and prospective phase of the TRACE project, there was a risk of outcome misclassification. In both study designs, only patients referred to secondary care underwent a full diagnostic work-up, introducing potential verification bias. This was mitigated by an extended 6-week follow-up period, as most events (i.e. 98.4%) occur within that time frame.[55] Nevertheless, some delayed events may have been missed. Additional misclassifications may have arisen from inaccuracies in the diagnostic coding of routine care data. In primary care, the International Classification of Primary Care (ICPCC) system is used, and its application in daily practice is susceptible to variability and human error. In an exploratory analysis we found that almost a quarter of codes were incorrect, with potentially relevant miscoding in 7.5%.

In addition to these general challenges, both retrospective and prospective approaches brought specific strengths and limitations. The retrospective design allowed us to study a large, unselected population over an entire year, offering a robust reflection on how chest pain is triaged in daily practice. Although this approach relied on digital triage reports rather than original recordings (which limited completeness of symptom data), it captured routine care as it truly occurs, without influencing triage behavior. Conversely, the prospective study enabled a more comprehensive assessment of decision rules, since triage assistants were explicitly instructed to collect predefined elements. This improved internal validity but at the cost of a smaller and more selective sample, as patients had to agree to participation, and study questions were more often completed for patients with a higher a-priori risk of cardiovascular disease.

Ideally, research on triage and diagnostic decision-making should be based on cohorts of unselected, consecutive patients to reflect clinical reality. A preferred strategy would be to integrate research modules directly within existing triage software, allowing additional data to be collected automatically, without influencing the urgency allocation or patient management. Such an approach would facilitate prospective evaluation of new triage elements under real-world conditions before their formal implementation.

While methodological and design choices shape how triage performance is studied, the actual functioning of triage in practice is equally influenced by human factors. The experience and training of triage assistants play a decisive role in the reliability of telephone triage.[4] Prior research has shown that assistants sometimes override the protocol's suggested urgency, or 'tinker' with symptom characteristics to align the computer-generated recommendation with their own clinical judgment.[56] While this complicates the evaluation of the NTS as a stand-alone tool, it illustrates the importance of human oversight in safeguarding patient safety. In Dutch OOH-PC, triage is further supported by the supervising GP, whose additional assessment (i.e. without supportive tools or preselection) has demonstrated strong performance, with a reported NPV of 93.2%.[57] The layered structure of triage thus complicates the disentanglement of algorithmic and human contributions, yet it accurately reflects the reality of clinical practice.

Finally, broader considerations affect both the scope and the generalizability of our findings. We evaluated only patients presenting with chest pain, although a proportion of ACS patients present with other complaints such as dyspnea or fatigue. In addition, while our cohort was likely representative for Dutch OOH-PC, we did not specifically account for ethnic minorities, despite evidence that cardiovascular risk and symptom presentation may differ between groups.[58-60] Another limitation relates to the governance of the triage system itself. The NTS is developed and maintained by a privately held company. Although we made several efforts to establish collaboration, engagement with the developers proved challenging, which limited transparency and independent validation. This raises questions about accountability in a system that has a profound influence on urgent care delivery in the Netherlands.

FUTURE OF CHEST PAIN TRIAGE

The primary aim of any future triage innovation for acute chest pain must remain patient safety. Only when an adequate level of safety is assured, can efforts be directed towards improving efficiency, for instance by reducing unnecessary referrals. This would benefit both the patient, and the healthcare system by alleviating pressure on resources and reducing costs. Future triage tools should explicitly prioritize sensitivity and NPV, while still considering their feasibility in routine practice. Likely, such advancements will require a multi-pronged approach, as no single strategy will serve as the 'holy grail' for ruling out major events or ACS. Instead, optimization should be sought across the different layers of the assessment of patients with acute chest pain in OOH-PC:

telephone triage, clinical judgment of the attending GP, and potential point-of-care diagnostic tools, such as high-sensitivity troponin measurements. These components are complementary, rather than interchangeable, and the optimal balance between them may differ depending on the clinical and organizational context.

Point-of-care troponin testing may represent a particularly promising step forward. It could be integrated within existing OOH-PC workflows, with relatively little structural change, providing rapid biochemical risk stratification to improve both safety and efficiency. As current evidence suggests that clinical decision rules without troponin fail to achieve improved diagnostic performance, future research efforts should focus on the validation and practical implementation of troponin testing in primary care.

The integration of an observation unit in OOH-PC, as seen in several international studies, could theoretically improve safety and efficiency by allowing short-term monitoring of low- to intermediate-risk patients. However, in the Dutch context, with a high population density, short travel distances, and already high workload of primary care professionals, this would likely add logistical and organizational strain rather than relieve it.

The role and training of triage assistants also deserve further attention. Although the NTS was originally designed to assess urgency rather than to establish diagnoses, effective triage of chest pain inevitably involves some degree of diagnostic reasoning. Expanding training to include diagnostic aspects could therefore enhance both the quality and professionalism of telephone triage.

Greater involvement of GPs in the triage process, by returning some of the responsibilities to physicians or by even directing towards shared control rooms with ambulance services, could further enhance triage accuracy. However, such changes require substantial reorganizations and are unlikely to be feasible in the short term.

Emerging technologies may further shape the future of pre-hospital triage. Artificial intelligence-driven triage systems, preferably trained on large datasets that combine clinical information with diagnostic outcomes, could potentially lead to more accurate and consistent triage decisions. In addition to data-driven risk assessment tools, AI-driven voice analyzers are increasingly being developed to support telephone triage by detecting subtle vocal or speech patterns that may signal underlying clinical severity. Whether such tools can be safely embedded in OOH-PC workflows without compromising

accessibility and human oversight remains an important question for future research.

REFERENCES

1. Harskamp R, van Peet P, Bont J, Ligthart S, Lucassen W, van Weert H. The conundrum of acute chest pain in general practice: a nationwide survey in The Netherlands. *BJGP Open*. Dec 2018;2(4):bjgpopen18X101619. doi:10.3399/bjgpopen18X101619
2. Than M, Herbert M, Flaws D, et al. What is an acceptable risk of major adverse cardiac event in chest pain patients soon after discharge from the Emergency Department?: a clinical survey. *International journal of cardiology*. 2013;166(3):752–754.
3. Wouters LT, Rutten FH, Erkelens DC, De Groot E, Damoiseaux RA, Zwart DL. Accuracy of telephone triage in primary care patients with chest discomfort: a cross-sectional study. *Open heart*. 2020;7(2):e001376.
4. Moll HA. Challenges in the validation of triage systems at emergency departments. *Journal of clinical epidemiology*. 2010;63(4):384–388.
5. Kuriyama A, Urushidani S, Nakayama T. Five-level emergency triage systems: variation in assessment of validity. *Emerg Med J*. Nov 2017;34(11):703–710. doi:10.1136/emermed-2016-206295
6. Dippenaar E. Triage systems around the world: a historical evolution. *International Paramedic Practice*. 2019;9(3):61–66.
7. Nishi FA, Maia FdOM, de Souza Santos I. Assessing sensitivity and specificity of the Manchester Triage System in the evaluation of acute coronary syndrome in adult patients in emergency care: a systematic review. *JBI Evidence Synthesis*. 2017;15(6):1747–1761.
8. Van der Wulp I, Van Baar M, Schrijvers A. Reliability and validity of the Manchester Triage System in a general emergency department patient population in the Netherlands: results of a simulation study. *Emergency Medicine Journal*. 2008;25(7):431–434.
9. International Working Group on Chest Pain in Primary Care (INTERCHEST), Aerts M, Minalu G, et al. Pooled individual patient data from five countries were used to derive a clinical prediction rule for coronary artery disease in primary care. *Journal of Clinical Epidemiology*. 2017;81:120–128. doi:10.1016/j.jclinepi.2016.09.011
10. Bösner S, Haasenritter J, Becker A, et al. Ruling out coronary artery disease in primary care: development and validation of a simple prediction rule. *CMAJ*. Sep 7 2010;182(12):1295–300. doi:10.1503/cmaj.100212
11. Haasenritter J, Bösner S, Vaucher P, et al. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. *British Journal of General Practice*. 2012;62(599):e415–e421. doi:10.3399/bjgp12X649106
12. Harskamp RE, Laeven SC, Himmelreich JC, Lucassen WAM, van Weert H. Chest pain in general practice: a systematic review of prediction rules. *BMJ Open*. Feb 27 2019;9(2):e027081. doi:10.1136/bmjopen-2018-027081
13. Wouters LT, Zwart DL, Erkelens DC, et al. Development and validation of a prediction rule for patients suspected of acute coronary syndrome in primary care: a cross-sectional study. *BMJ open*. 2022;12(10):e064402.

14. Utrecht JCU, Standaard NT. Revision of the protocol for chest pain - supporting document and background information. Original title: Aanpassing ingangsklacht "pijn/druk thorax" - Begeleidend document & inhoudelijke achtergrond 2024.

15. Bruins Slot M, Rutten F, van der Heijden GJ, Geersing G, Glatz J, Hoes AW. Diagnosing acute coronary syndrome in primary care: comparison of the physicians' risk estimation and a clinical decision rule. *Family Practice*. 2011;28(3):323–328.

16. Grijseels E, Deckers eJ, Hoes A, et al. Implementation of a pre-hospital decision rule in general practice: Triage of patients with suspected myocardial infarction. *European heart journal*. 1996;17(1):89–95.

17. Grijseels E, Deckers J, Hoes A, et al. Pre-hospital triage of patients with suspected myocardial infarction. Evaluation of previously developed algorithms and new proposals. *European heart journal*. 1995;16(3):325–332.

18. Willemsen RT, Winkens B, Kietselaer BL, et al. Evaluating possible acute coronary syndrome in primary care: the value of signs, symptoms, and plasma heart-type fatty acid-binding protein (H-FABP). A diagnostic study. *BJGP open*. 2019;3(3)

19. Schols AM, Willemsen RT, Bonten TN, et al. A nationwide flash-mob study for suspected acute coronary syndrome. *The Annals of Family Medicine*. 2019;17(4):296–303.

20. Kleton M, Manten A, Smits I, Rietveld R, Lucassen WA, Harskamp RE. Performance of risk scores for coronary artery disease: a retrospective cohort study of patients with chest pain in urgent primary care. *BMJ open*. 2021;11(12):e045387.

21. Manten A, De Clercq L, Rietveld R, Lucassen W, Moll van Charante E, Harskamp R. Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care. *Netherlands Heart Journal*. 2022:1–7.

22. Harskamp RE, Kleton M, Smits IH, et al. Performance of a simplified HEART score and HEART-GP score for evaluating chest pain in urgent primary care. *Neth Heart J*. 2021;doi:10.1007/s12471-020-01529-4

23. Planer D, Leibowitz D, Paltiel O, Boukhobza R, Lotan C, Weiss TA. The diagnostic value of troponin T testing in the community setting. *International journal of cardiology*. 2006;107(3):369–375.

24. Tomonaga Y, Gutzwiller F, Lüscher TF, et al. Diagnostic accuracy of point-of-care testing for acute coronary syndromes, heart failure and thromboembolic events in primary care: a cluster-randomised controlled trial. *BMC family practice*. 2011;12(1):12.

25. Nilsson S, Andersson PO, Borgquist L, et al. Point-of-care troponin T testing in the management of patients with chest pain in the Swedish primary care. *International journal of family medicine*. 2013;2013(1):532093.

26. Andersson PO, Karlsson J-E, Landberg E, Festin K, Nilsson S. Consequences of high-sensitivity troponin T testing applied in a primary care population with chest pain compared with a commercially available point-of-care troponin T analysis: an observational prospective study. *BMC research notes*. 2015;8(1):210.

27. Johannessen TR, Atar D, Vallersnes OM, Larstorp ACK, Mdala I, Halvorsen S. Comparison of a single high-sensitivity cardiac troponin T measurement with the HEART score for rapid rule-out of acute myocardial infarction in a primary care emergency setting: a cohort study. *BMJ open*. 2021;11(2):e046024.

28. Melessen IMB, Himmelreich JC, Manten A, et al. HEART-GP - Decision support for chest pain Accessed 22-08-2025, https://www.heartgp.nl/Home/

29. Van Den Bulk S, Petrus AH, Willemsen RT, et al. Ruling out acute coronary syndrome in primary care with a clinical decision rule and a capillary, high-sensitive troponin I point of care test: study protocol of a diagnostic RCT in the Netherlands (POB HELP). *BMJ open*. 2023;13(6):e071822.

30. Franks P, Clancy CM, Nutting PA. Gatekeeping revisited—protecting patients from overtreatment. Mass Medical Soc; 1992. p. 424–429.

31. Steeman L, Uijen M, Plat E, Huibers L, Smits M, Giesen P. Out-of-hours primary care in 26 European countries: an overview of organizational models. *Family practice*. 2020;37(6):744–750.

32. Johannessen TR, Vallersnes OM, Halvorsen S, Larstorp ACK, Mdala I, Atar D. Pre-hospital One-Hour Troponin in a Low-Prevalence Population of Acute Coronary Syndrome: OUT-ACS study. *Open Heart*. 26 May 2020 2020;7(e001296) doi:10.1136/openhrt-2020-001296

33. Norman T, Young J, Jones JS, et al. Implementation and evaluation of a rural general practice assessment pathway for possible cardiac chest pain using point-of-care troponin testing: a pilot study. *BMJ open*. 2022;12(4):e044801.

34. Miller R, Nixon G, Pickering JW, et al. A prospective multi-centre study assessing the safety and effectiveness following the implementation of an accelerated chest pain pathway using point-of-care troponin for use in New Zealand rural hospital and primary care settings. *European Heart Journal: Acute Cardiovascular Care*. 2022;11(5):418–427.

35. Wouters LT, Zwart DL, Erkelens DC, et al. Gender-stratified analyses of symptoms associated with acute coronary syndrome in telephone triage: a cross-sectional study. *BMJ open*. 2021;11(6):e042406.

36. van der Meer MG, Appelman Y, Rutten KH, et al. Are there gender disparities in symptom presentation or triage of patients with chest discomfort at primary care out-of-hours services? An observational study. *BMJ open*. 2019;9(11):e031613.

37. Canto JG, Goldberg RJ, Hand MM, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. *Archives of internal medicine*. 2007;167(22):2405–2413.

38. DeVon HA, Rosenfeld A, Steffen AD, Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. *Journal of the American Heart Association*. 2014;3(2):e000586.

39. DeVon HA, Ryan CJ, Ochs AL, Shapiro M. Symptoms across the continuum of acute coronary syndromes: differences between women and men. *American journal of critical care*. 2008;17(1):14–24.

40. Ferry AV, Anand A, Strachan FE, et al. Presenting symptoms in men and women diagnosed with myocardial infarction using sex-specific criteria. *Journal of the American Heart Association*. 2019;8(17):e012307.

41. Rubini Gimenez M, Reiter M, Twerenbold R, et al. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. *JAMA Intern Med*. Feb 1 2014;174(2):241–9. doi:10.1001/jamainternmed.2013.12199

42. Byrne RA, Rossello X, Coughlan J, et al. 2023 ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal: Acute Cardiovascular Care*. 2024;13(1):55–161.

43. Dawson LP, Nehme E, Nehme Z, et al. Sex Differences in Epidemiology, Care, and Outcomes in Patients With Acute Chest Pain. *J Am Coll Cardiol*. Mar 14 2023;81(10):933–945. doi:10.1016/j.jacc.2022.12.025

44. Mehilli J, Presbitero P. Coronary artery disease and acute coronary syndrome in women. . *Heart*. 2020;106:487–492.

45. Mehta LS, Beckie TM, DeVon HA, et al. Acute Myocardial Infarction in Women. A Scientific Statement From the American Heart Association. . *Circulation*. 2016;133:916–947.

46. Redfors B, AngerAas O, RAamunddal T, et al. Trends in gender differences in cardiac care and outcome after acute myocardial infarction in Western Sweden: a report from the Swedish web system for enhancement of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Journal of the American Heart Association*. 2015;4(7):e001995.

47. Anand SS, Xie CC, Mehta S, et al. Differences in the management and prognosis of women and men who suffer from acute coronary syndromes. *Journal of the American College of Cardiology*. 2005;46(10):1845–1851.

48. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non–ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) national quality improvement initiative. *Journal of the American College of Cardiology*. 2005;45(6):832–837.

49. Bugiardini R, Yan AT, Yan RT, et al. Factors influencing underutilization of evidence-based therapies in women. *European heart journal*. 2011;32(11):1337–1344.

50. Wechkunanukul K, Grantham H, Clark RA. Global review of delay time in seeking medical care for chest pain: An integrative literature review. *Australian Critical Care*. 2017;30(1):13–20.

51. Harskamp RE, Fanaroff AC, Zhen SW, Sawe HR, Weber EJ. Recognising acute coronary syndrome. *BMJ*. 2022;377

52. Mackay MH, Ratner PA, Johnson JL, Humphries KH, Buller CE. Gender differences in symptoms of myocardial ischaemia. *European heart journal*. 2011;32(24):3107–3114.

53. van Oosterhout RE, de Boer AR, Maas AH, Rutten FH, Bots ML, Peters SA. Sex Differences in Symptom Presentation in Acute Coronary Syndromes: A Systematic Review and Meta-analysis. *Journal of the American Heart Association*. 2020;9(9):e014733.

54. Ploem C, Harskamp RE, van Dijk N, et al. Privacy legislation and scientific research. *Huisarts & Wetenschap*. 8 januari 2020 2020;

55. Van Den Berg P, Body R. The HEART score for early rule out of acute coronary syndromes in the emergency department: a systematic review and meta-analysis. *European Heart Journal: Acute Cardiovascular Care*. 2018;7(2):111–119.

56. Wouters LT, Zwart DL, Erkelens DC, et al. Tinkering and overruling the computer decision support system: working strategies of telephone triage nurses who assess the urgency of callers suspected of having an acute cardiac event. *Journal of clinical nursing*. 2020;29(7-8):1175–1186.

57. Willemsen RT, Bonten TN, Cals JW, Knottnerus JA, Dinant G-J. The general practitioner is an excellent rapid test for chest pain (Original title: De huisarts is een prima sneltest bij pijn op de borst). *Huisarts & Wetenschap*. 2019;2019, nummer 8:14–17.

58. Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2019. Geneva, World Health Organization. Accessed 25-08-2025, https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death

59. Hummel B, Harskamp RE, Vester A, Galenkamp H, Mommersteeg PM, van Valkengoed IG. Chest pain in a multi-ethnic population: A community-based study on sex differences in chest pain prevalence and care contacts. *International Journal of Cardiology Cardiovascular Risk and Prevention*. 2025;24:200361.

60. Wechkunanukul K, Grantham H, Damarell R, Clark RA. The association between ethnicity and delay in seeking medical care for chest pain: a systematic review. *JBI Evidence Synthesis*. 2016;14(7):208–235.


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME

Appendices

SUMMARY

Chest pain is a common reason for seeking medical care. In the Netherlands, general practitioners (GPs) frequently encounter this complaint as they act as gatekeepers and hold a central position in the healthcare system. During afterhours, GPs maintain this role through out-of-hours primary care (OOH-PC) facilities, which, together with emergency medical services (EMS) serve as the first point of contact in the acute care-chain. Every year, approximately 160,000 individuals contact Dutch OOH-PC for acute chest pain. While most chest pain episodes arise from benign conditions, underlying causes vary greatly and may also include urgent conditions, such as acute coronary syndrome (ACS), that require timely diagnosis and treatment. Distinguishing between high- and low-risk patients is complex and requires careful triage, while the demand on the acute care chain regularly puts pressure on the available capacity.

To efficiently manage the considerable number of chest pain-related contacts, most OOH-PC facilities and EMS use standardized, symptom-based telephone triage protocols from the Netherlands Triage Standard (NTS). The NTS prioritizes calls by assigning an urgency code, linked to a recommended response time and clinical action. Despite its use, some patients with urgent conditions are insufficiently identified, while many patients with benign chest pain are unnecessarily referred for further testing.

This thesis aimed to improve the safety and efficiency of acute chest pain evaluation in OOH-PC by focusing on the process of telephone triage. To this end, we addressed the following research questions:

1. What is the relative volume of chest pain patients that access care through OOH-PC?
2. How does the current NTS triage standard perform in terms of safety and efficiency for ACS as well as a broad range of relevant clinical outcomes, and are there sex-specific differences?
3. Can easy-to-apply, additional decision support tools improve the efficiency and safety of telephone triage for chest pain in OOH-PC?

1. Distribution of chest pain presentations across pre-hospital care settings

The distribution of chest pain patients across pre-hospital care providers remains incompletely characterized. A more comprehensive understanding of the distribution of demand could reveal opportunities to improve care coordination, optimize workflows, and allocate pre-hospital care resources more appropriately. In **Chapter 2**, we explored the relative burden of chest pain-related contacts on OOH-PC. We compared patient volumes across two regions and found that OOH-PC managed more contacts than EMS dispatched ambulances. Temporal analysis from 2019 to 2024 demonstrated an increase in chest pain-related burden across all pre-hospital providers, with patterns suggesting a growing proportion of suboptimal resource utilization. Additional studies are warranted to fully elucidate patient navigation patterns within pre-hospital care pathways for chest pain.

2. Performance evaluation of the Netherlands Triage Standard for chest pain

Telephone triage is the starting point of the evaluation of chest pain in OOH-PC and plays a crucial role in guiding subsequent diagnostic and treatment decisions. We designed the *TRiage of Acute Chest pain Evaluation in primary care* (TRACE) project (**Chapter 3**) to assess the performance of the current NTS triage standard across a broad range of clinical outcomes (i.e. major events, including ACS), and to explore whether additional, easy-to-apply clinical support tools could enhance the overall efficiency. Throughout this thesis, we assessed the diagnostic accuracy of the triage system and additional tools against established benchmarks and their corresponding criteria (i.e. negative predictive value (NPV) ≥99% and specificity ≥50%).

We evaluated the diagnostic accuracy of the NTS protocol for telephone triage of chest pain in two separate patient cohorts, both consisting of patients who contacted a Dutch OOH-PC facility regarding acute chest pain (**Chapters 4** and **7**). In both the retrospective and prospective cohorts, the NTS resulted in a high proportion of overtriage, suggesting a defensive approach. However, miss rates exceeded the accepted threshold. Thus, the NTS protocol did not meet the desired balance between safety and efficiency.

In **Chapter 5**, we evaluated whether sex differences existed in the symptomatology, triage management, and subsequent clinical outcomes among chest pain patients in OOH-PC. We found that women had a lower a priori cardiovascular risk and were less likely to have a major event or ACS compared to men. Despite this lower risk, women were triaged the same way, resulting in relatively more cautious management for women, with a higher

proportion of unnecessary high urgency classifications. Furthermore, symptom characteristics showed more similarities than differences. These results align with current evidence suggesting that symptom overlap outweighs sex-based differences, limiting the predictive value of sex in acute triage settings.

3. Decision support tools to enhance telephone triage performance

Numerous decision support tools have been developed to aid the assessment of chest pain or suspected ACS. Only a proportion of these tools are applicable in a telephone triage setting. We hypothesized that incorporating (elements of) validated clinical decision rules could improve triage accuracy without compromising patient safety. In **Chapters 6** and **7**, we assessed the Marburg Heart Score (MHS) and INTERCHEST score for their ability to predict major events and ACS. Taken together, our results indicate that the MHS and INTERCHEST score are not suitable for telephone triage of acute chest pain complaints as they were unable to meet the benchmarks for safety and efficiency. Compared to the NTS protocol, both scores could improve specificity, but at the cost of reduced sensitivity, which limits their clinical utility in this setting.

While our research was underway, advances in decision support for chest pain evaluation continued. In this context, in **Chapter 8**, we externally validated the Safety First Prediction Rule, a multivariate regression model developed to rule out ACS and other life-threatening events in an OOH-PC setting in the Netherlands. Compared to the NTS, the Safety First Prediction Rule achieved a higher sensitivity and NPV, indicating improved safety. However, the rule was not able to also optimize triage efficiency.

The Safety First Prediction Rule was later used as the basis for an update of the NTS triage protocol. For this purpose, items from the model replaced existing elements in the NTS decision tree. The final composition of the updated NTS protocol was determined through expert consensus and implemented without prior validation in October 2024. An exploratory analysis of the updated NTS protocol in **Chapter 7** raised safety concerns, as more major events and ACS cases were missed. While these results may partly reflect misclassification due to missing data, they underscore the urgent need for rigorous validation of the updated protocol to confirm its safety and efficiency in routine triage practice.

Beyond telephone triage, various decision support tools exist for in-person assessment of acute chest pain. In **Chapter 9**, we conducted a systematic review to assess the evidence on available risk stratification tools for acute chest pain across primary care. The review included clinical decision rules and strategies using troponin testing. While some of the clinical decision rules improved safety, none outperformed unaided GP assessment, indicating they

should not be used as standalone tools. For studies evaluating strategies using troponin, we found promising results with high-sensitivity troponin assays, though further validation is required before implementation in primary care can be recommended.

Finally, in **Chapter 10**, we reflect on the findings of this thesis in the context of existing literature, discuss methodological considerations, and conclude with implications for clinical practice and future research. Ensuring patient safety remains the primary goal of any triage innovation for acute chest pain. Once safety is adequately addressed, efforts may shift towards improving efficiency, particularly by reducing unnecessary referrals. In this light, the future of telephone triage of acute chest pain in OOH-PC will depend on a balanced, multi-pronged approach, seeking optimization across the entire patient journey. This approach should combine human expertise, potential point-of-care diagnostic tools (such as high-sensitivity troponin measurements), and other emerging technologies.

NEDERLANDSE SAMENVATTING

Pijn op de borst is een veelvoorkomende reden voor patiënten om medische hulp te zoeken. In Nederland zien huisartsen deze klacht vaak, omdat zij als poortwachter een centrale rol in het zorgsysteem vervullen. Ook buiten kantoortijden behouden zij deze rol via de huisartsenspoedpost. Samen met de regionale ambulancediensten vormen deze posten de eerste schakel in de acute-zorgketen. Jaarlijks melden ongeveer 160.000 patiënten zich met pijn op de borst bij een huisartsenspoedpost. De meeste gevallen van pijn op de borst worden veroorzaakt door onschuldige aandoeningen. Toch varieert de onderliggende etiologie sterk en omvat deze ook urgente aandoeningen, zoals een acuut coronair syndroom (ACS), die snelle herkenning en diagnose vereisen. Het onderscheid tussen hoog- en laagrisicopatiënten is daardoor complex en vraagt om zorgvuldige triage, terwijl de zorgvraag in de acute-zorgketen regelmatig het beschikbare aanbod onder druk zet.

Om het grote aantal contacten efficiënt af te handelen, gebruiken de meeste huisartsenspoedposten en ambulancediensten gestandaardiseerde, klacht-gestuurde triageprotocollen van de Nederlandse Triage Standaard (NTS). De NTS prioriteert contacten door een urgentiecode toe te wijzen, welke gekoppeld is aan een aanbevolen reactietijd en klinische actie. Ondanks het gebruik van de NTS worden sommige urgente aandoening niet voldoende onderkent, terwijl veel patiënten met onschuldige pijn op de borst onnodig vervolgonderzoek ondergaan.

Dit proefschrift heeft als doel om de veiligheid en efficiëntie van de beoordeling van acute pijn op de borst op de huisartsenspoedpost te verbeteren, door zich te richten op het proces van telefonische triage. Vanuit dit doel formuleerden we drie onderzoeksvragen:

1. Wat is het relatieve volume van patiënten met pijn op de borst dat zorg zoekt via de huisartsenspoedpost?
2. Hoe presteert de huidige NTS-triagestandaard in termen van veiligheid en efficiëntie voor zowel ACS als andere relevante klinische uitkomsten, en bestaan er sekse-specifieke verschillen?
3. Kunnen eenvoudig toepasbare, aanvullende beslisondersteuningen de efficiëntie en veiligheid van de telefonische triage van pijn op de borst op de huisartsenspoedpost verbeteren?

1. Verdeling van patiënten met pijn op de borst in de prehospitale zorg

De exacte verdeling van patiënten met pijn op de borst in de prehospitale zorg is niet volledig bekend. Meer inzicht in hoe de zorgvraag is verdeeld kan helpen om gerichte interventies te ontwikkelen voor het verbeteren van de samenwerking, het afstemmen van werkprocessen en het efficiënt inzetten van beschikbare middelen. In **Hoofdstuk 2** exploreerden we de relatieve belasting van pijn-op-de-borst-gerelateerde klachten op de huisartsenspoedpost. We vergeleken de prehospitale patiëntenstromen in een tweetal regio's en zagen dat de huisartsenspoedpost meer contacten afhandelde dan er ambulances uitrukten. Temporele trends (2019-2024) lieten een stijgende vraag naar pijn-op-de-borst-gerelateerde zorg zien in de gehele keten, met aanwijzingen voor een inefficiënt gebruik van beschikbare middelen. Verder onderzoek is nodig om volledig te begrijpen hoe patiënten hun weg binnen ons zorgsysteem vinden.

2. Evaluatie van de Nederlandse Triage Standaard voor pijn op de borst

Telefonische triage vormt het startpunt van de beoordeling van pijn op de borst op de huisartsenspoedpost en stuurt de daaropvolgende diagnostische en therapeutische beslissingen. We ontwikkelden het *TRiage of Acute Chest pain Evaluation in primary care* (TRACE) project (**Hoofdstruk 3**) om de prestaties van het de huidige NTS-triagestandaard te beoordelen voor een breed spectrum aan klinische uitkomsten (d.w.z. hoog-urgente aandoeningen, waaronder ACS) en om te onderzoeken of aanvullende klinische beslisondersteuning de efficiëntie kan verbeteren. In dit proefschrift beoordeelden we de diagnostische accuratesse van het triagesysteem en de beslisondersteuningen aan de hand van vastgestelde richtlijnen en bijbehorende normwaarden (d.w.z. negatieve voorspellende waarde (NPV) ≥99% en specificiteit ≥50%).

We evalueerden de diagnostische accuratesse van het NTS-protocol in twee afzonderlijke patiëntcohorten die met acute pijn op de borst contact opnamen met een Nederlandse huisartsenspoedpost (**Hoofdstukken 4** en **7**). In zowel het retrospectieve als het prospectieve cohort leidde de NTS tot een hoog percentage overtriage, wat duidt op een defensieve benadering. Tegelijkertijd overschreed het aantal gemiste ernstige gevallen de aanvaarde veiligheidsdrempel. Het NTS-protocol bereikte daarmee niet de gewenste balans tussen veiligheid en efficiëntie.

In **Hoofdstuk 5** onderzochten we of er sekseverschillen aanwezig zijn in de symptomatologie, het triageproces en de klinische uitkomsten van patiënten

met pijn op de borst op de huisartsenspoedpost. We vonden dat vrouwen een lager a priori cardiovasculair risico hadden en ook minder vaak een hoog-urgente aandoening of ACS hadden dan mannen. Ondanks dit lagere risico werden vrouwen op dezelfde manier getrieerd, wat resulteerde in een relatief defensieve benadering met een hoger percentage onterecht hoge urgentieclassificaties. Verder vertoonden de symptoomkarakteristieken meer overeenkomsten dan verschillen. Deze bevindingen sluiten aan bij de literatuur, waarin symptoomoverlap zwaarder weegt dan sekse-specifieke verschillen. Dit wijst op een beperkte voorspellende waarde van sekse binnen het triageproces.

3. Beslisondersteuning voor de verbetering van de telefonische triage van pijn op de borst

Er zijn vele beslisondersteuningen ontwikkeld voor de beoordeling van pijn op de borst of vermoede ACS. Slechts een deel daarvan is echter toepasbaar tijdens telefonische triage. We stelden de hypothese dat het opnemen van (elementen van) gevalideerde klinische beslisregels de nauwkeurigheid van triage zou kunnen verbeteren zonder de patiëntveiligheid in te perken. In **Hoofdstukken 6** en **7** beoordeelden we de Marburg Heart Score (MHS) en de INTERCHEST score op hun vermogen om hoog-urgente aandoeningen en ACS te voorspellen. Onze resultaten laten zien dat zowel de MHS als INTERCHEST score ongeschikt zijn voor telefonische triage van acute pijn op de borst, omdat zij niet voldeden aan de criteria voor veiligheid en efficiëntie. Hoewel beide scores in vergelijking met het NTS-protocol de specificiteit zouden kunnen verhogen, gaat dit gepaard met een lagere sensitiviteit. Daardoor is de klinische bruikbaarheid in een triagecontext beperkt.

Tijdens ons onderzoek vonden er nieuwe ontwikkelingen plaats op het gebied van klinische beslisondersteuning voor de beoordeling van pijn op de borst. In dit kader voerden we in **Hoofdstuk 8** een externe validatie uit van de Safety First-beslisregel, een multivariaat regressiemodel dat werd ontwikkeld om ACS en andere levensbedreigende aandoeningen uit te sluiten op de Nederlandse huisartsenspoedpost. In vergelijking met de NTS behaalde de Safety First-beslisregel een hogere sensitiviteit en NPV, wat wijst op verbeterde veiligheid. De regel slaagde er echter niet in om ook de efficiëntie van triage te optimaliseren.

De Safety Fist-beslisregel vormde later de basis voor een update van het NTS-triageprotocol. Voor deze herziening vervingen predictoren uit het model bestaande elementen in de NTS-beslisboom. De uiteindelijke samenstelling van het nieuwe NTS-protocol werd vastgesteld op basis van expertconsensus en in oktober 2024, zonder voorafgaande validatie, geïmplementeerd. Een exploratieve analyse van deze vernieuwde NTS-triagestandaard in

Hoofdstuk 7 riep zorgen op over de veiligheid, omdat meer hoog-urgente aandoeningen en ACS-gevallen werden gemist. Hoewel deze bevindingen mogelijk mede zijn beïnvloed door misclassificatie door ontbrekende data, benadrukken zij de noodzaak van rigoureuze validatie van het nieuwe NTS-protocol om de veiligheid en efficiëntie in de dagelijkse triagepraktijk te waarborgen.

Naast het gebruik tijdens telefonische triage bestaan er diverse klinische beslisondersteuningen voor de fysieke beoordeling van acute pijn op de borst. In **Hoofdstuk 9** voerden we een systematische review uit naar beschikbare risicostratificatie tools voor de beoordeling van acute pijn op de borst in de eerste lijn. De review omvatte zowel klinische beslisregels als strategieën met troponine testen. Hoewel een aantal klinische beslisregels de veiligheid verbeterden, bleek geen van deze tools beter te presteren dan de eigen beoordeling van de huisarts. Dit suggereert dat deze beslisregels niet als op zichzelf staande tools kunnen worden ingezet. Voor de strategieën die troponine testen gebruikten, vonden we veelbelovende resultaten met hoogsensitief troponine. Verdere validatie is echter nodig voordat implementatie van dergelijke testen in de eerste lijn aanbevolen kan worden.

Tot slot reflecteren we in **Hoofdstuk 10** op de bevindingen van dit proefschrift in de context van de bestaande literatuur, bespreken we methodologische aspecten en sluiten we af met de implicaties voor de klinische praktijk en toekomstig onderzoek. Het waarborgen van patiëntveiligheid blijft het belangrijkste doel van elke triage-innovatie voor acute pijn op de borst. Pas wanneer de veiligheid voldoende is gegarandeerd, kunnen inspanningen zich richten op het verbeteren van de efficiëntie, bijvoorbeeld door het aantal onnodige verwijzingen te verminderen. Vanuit dit perspectief zal de toekomst van telefonische triage van acute pijn op de borst op de huisartsenpost afhangen van een gebalanceerde, trapsgewijze aanpak die optimalisatie nastreeft gedurende het gehele patiënttraject. Deze aanpak zou menselijke expertise moeten combineren met mogelijke point-of-care diagnostische hulpmiddelen (zoals hoogsensitief troponine) en andere opkomende technologieën.

AUTHORS AND AFFILIATIONS

R. Bolijn
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of Public and Occupational Health, Amsterdam Public Health, Amsterdam, the Netherlands

T.N. Bonten
Leiden University Medical Center, Department of Public Health and Primary Care, Leiden, the Netherlands

W.B. Busschers
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

S. van den Bulk
Leiden University Medical Center, Department of Public Health and Primary Care, Leiden, the Netherlands

L. De Clercq
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

C.J.J. Cuijpers
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

R.E. Harskamp
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Amsterdam Cardiovascular Sciences Research Institute, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

J.C.L. Himmelreich
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Amsterdam Cardiovascular Sciences Research Institute, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

B. Hummel

Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of Public and Occupational Health, Amsterdam Public Health, Amsterdam, the Netherlands

I. van Hulst
Huisartsenorganisatie Noord-Kennemerland, Hertog Aalbrechtweg 5A, 1823 DL Alkmaar, the Netherlands

W.A.M. Lucassen
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

I.M.B. Melessen
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

E.P. Moll van Charante
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice and Department of Public & Occupational Health, Amsterdam Cardiovascular Sciences Research Institute, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

F. van de Graaf
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

E. Groot
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

R.P. Rietveld
Huisartsenorganisatie Noord-Kennemerland, Hertog Aalbrechtweg 5A, 1823 DL Alkmaar, the Netherlands

I.G.M. van Valkengoed
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of Public and Occupational Health, Amsterdam Public Health, Amsterdam, the Netherlands

S. Voerman
Huisartsenorganisatie Noord-Kennemerland, Hertog Aalbrechtweg 5A, 1823 DL Alkmaar, the Netherlands

H.C.P.M. van Weert
Amsterdam UMC, University of Amsterdam, Academic Medical Center, Department of General Practice, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands

LIST OF PUBLICATIONS & AUTHOR'S CONTRIBUTION

Publications included in this thesis

Manten A, Melessen IMB, Himmelreich JCL, Moll van Charante EP, Harskamp RE. Comparing ambulance and out-of-hours primary care pathways for acute chest pain in the Netherlands. Submitted to Netherlands Heart Journal.

Author's contribution: A.M. and R.E.H. conceived the study. A.M. carried out data collection and data analysis. A.M. wrote the article, supervised by E.P.M.C. and R.E.H. and in cooperation with all co-authors. All co-authors read and approved the final version of the article.

Manten A*, Cuijpers CJJ*, Rietveld RP, Groot E, van de Graaf F, Voerman S, Himmelreich JCL, Lucassen WAM, van Weert HCPM, Harskamp RE. Rationale and design of a cohort study evaluating triage of acute chest pain in out-of-hours primary care in the Netherlands (TRACE), Prim Health Care Res Dev. 2020 May 8:21:e10. PMID: 32383424.

*Authors contributed equally

Author's contribution: R.E.H., W.A.M.L. and H.C.P.M.W. devised the project and the main conceptual ideas. Additionally, C.J.J.C, J.C.L.H, E.G., F.G. and A.M. contributed to the rationale, design and implementation of the research. R.R. and S.V. provided input on the cooperation with the HONK organization and affiliated PCPs. A.M. and C.J.J.C took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research and manuscript.

Manten A, Rietveld RP, De Clerq L, van Hulst I, Lucassen WAM, Moll van Charante EP, Harskamp RE. Evaluation of telephone triage among chest pain patients in out-of-hours primary care in the Netherlands (TRACE), Fam Pract. 2023 Feb 9;40(1):23-29. PMID: 35849343

Author's contribution: R.E.H. conceived the study. R.P.R. and I.H. contributed to the design and implementation of the research. A.M. processed the data, performed the analysis, drafted the manuscript and designed the figures. L.D.C. provided critical assistance in analyzing the data. W.A.M.L., E.P.M.C. and R.E.H. supervised the project. All authors read and approved the final version of the article.

Manten A, Hummel B, Bolijn R, Rietveld RP, van Valkengoed IGM, Moll van Charante EP, Harskamp RE. Sex differences in chest pain presentation, triage assessment, and outcomes in urgent primary care: findings from the TRACE cohort study, Prim Health Care Res Dev. 2025 Jul 3:26:e53. PMID: 40605786

Author's contribution: A.M. and R.E.H. conceived the study. A.M. carried out data analysis. B.H., R.B. and I.G.M.V. contributed to the interpretation of

the results. A.M. wrote the article, supervised by E.P.M.C. and R.E.H. and in cooperation with all co-authors. All authors read and approved the final version of the article.

Manten A, De Clercq L, Rietveld RP, Lucassen WAM, Moll van Charante EP, Harskamp RE. Evaluation of the Marburg Heart Score and INTERCHEST score compared to current telephone triage for chest pain in out-of-hours primary care, Neth Heart J. 2023 Apr;31(4):157-165. PMID: 36580267

Author's contribution: A.M., R.E.H. and W.A.M.L. conceived the study. A.M. carried out data analysis. L.D.C. provided critical assistance in analyzing the data. A.M. wrote the article, supervised by W.A.M.L., E.P.M.C. and R.E.H. and in cooperation with all co-authors. All authors read and approved the final version of the article.

Manten A, Melessen IMB, Himmelreich JCL, Moll van Charante EP, Harskamp RE. Marburg Heart Score and INTERCHEST score for telephone triage of acute chest pain: a prospective, diagnostic accuracy study in out-of-hours primary care. Under review at BMJ Open.

Author's contribution: A.M. and R.E.H. designed the study, with contributions of all the authors. A.M. directed the project, processed the data, performed analyses, and drafted the manuscript. I.M.B.M., J.C.L.H. E.P.M.C. and R.E.H. aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript. All authors read and approved the final version of the article.

Manten A, Harskamp RE, Busschers WB, Moll van Charante EP, Himmelreich JCL. Telephone triage of chest pain in out-of-hours primary care: external validation of a symptom-based prediction rule to rule out acute coronary syndromes, Fam Pract. 2024 Oct 8;41(5):832-840. PMID: 38801727

Author's contribution: A.M., R.E.H. and J.C.L.H. designed the study, with contributions of all the authors. A.M. processed the data and performed analyses, supervised by J.C.L.H. W.B.B. provided critical assistance in analyzing the data. A.M. wrote the article, supervised by J.C.L.H. and in cooperation with all co-authors. All authors read and approved the final version of the article.

Van den Bulk S*, **Manten A***, Bonten TN, Harskamp RE. Chest pain in primary care: a systematic review of risk stratification tools to rule out acute coronary syndrome, Ann Fam Med. 2024 Sep-Oct;22(5):426-436. PMID: 39313342

*Authors contributed equally

Author's contribution: S.B. and A.M. designed the study, carried out data collection and data analysis, with contributions of all the authors. R.E.H. independently reviewed the extracted data and quality assessment for

accuracy. S.B. and A.M. wrote the manuscript and designed the tables and figures, supervised by T.N.B. and R.E.H. All authors read and approved the final version of the article.

Publications not included in this thesis

Harskamp RE, Kleton M, Smits IH, **Manten A**, Himmelreich JCL, van Weert HCPM, Rietveld RP, Lucassen WAM. Performance of a simplified HEART score and HEART-GP score for evaluating chest pain in urgent primary care, Neth Heart J. 2021 Jun;29(6):338-347. PMID: 33405015

Kleton M, **Manten A**, Smits IH, Rietveld RP, Lucassen WAM, Harskamp RE. Performance of risk scores for coronary artery disease: a retrospective cohort study of patients with chest pain in urgent primary care, BMJ Open. 2021 Dec 8;11(12):e045387. PMID: 34880006

Manten A, van den Bulk S, Rutten FH, Willemsen RTA, Bonten TN, Harskamp RE. Acute pijn op de borst op de huisartsenpost, Ned Tijdschr Geneeskd. 2023;167:D7379. PMID: 37565468

Hummel B, **Manten A**, van Apeldoorn JAN, Harskamp RE, van Valkengoed IGM. Psychosociale factoren voor het opstellen van een cardiovasculair risicoprofiel: aandacht voor diversiteit, Huisarts Wet 2024;67(2):21-25.

Harskamp RE, Melessen IMB, **Manten A**, De Clercq L, den Elzen WPJ, Himmelreich JCL. Troponin testing in routine primary care: observations from a dynamic cohort study in the Amsterdam metropolitan area, Diagnosis (Berl). 2024 Jan 29;11(2):171-177. PMID: 38281102

Johannessen TR, Melessen IMB, Vallersnes OM, **Manten A**, Halvorsen S, Atar D, Harskamp RE. Adequately identifying low-risk chest pain in emergency primary care: evaluating the performance of preHEAR(T) based on two European cohorts, Open Heart. 2025 Jul 27;12(2):e003362. PMID: 40716792

PHD PORTFOLIO

PhD student: Amy Manten

PhD supervisors: Dr. Ralf E. Harskamp

Prof. Dr. Eric P. Moll van Charante

PhD co-supervisors: Dr. Jelle C.L. Himmelreich

PhD period: September 2020 – December 2025

Total amount of ECT: 44.75

PhD training		
	Year	**ECT**
General courses		
The Amsterdam UMC World of Science	2020	0.7
Research Data Management	2020	0.89
Practical biostatistics	2021	1.14
Scientific Writing in English	2021	1.5
E-BROK ('Basiscursus Regelgeving Klinisch Onderzoek')	2021	1.5
E-BROK re-registration	2024	0.3
Specific courses		
Clinical epidemiology: Systematic Reviews	2022	0.71
Qualitative Health Research	2023	1.9
Clinical Epidemiology: Observational Epidemiology	2025	0.6
Clinical Epidemiology: Evaluation of Medical Tests	2025	0.9
Seminars, workshops and master classes		
Monthly department seminars, dep. General practice	2020-2025	2.6
Weekly research group meetings, dep. General practice, Cardiovascular	2020-2025	4.2
Amsterdam Public Health, annual meeting	2024, 2025	0.56
AIOTO-dag, annual meeting	2022, 2023, 2024, 2025	1.12
(Inter)national conferences visited		
WONCA Europe, online attendance	2021	0.2

European Society of Cardiology conference, online attendance, Amsterdam	2021, 2023	1.6
Nederlands Huisartsen Genootschap (NHG) conference, Den Haag, Groningen, Rotterdam, Amsterdam	2022, 2023, 2024, 2025	0.8
HartVaatHAG dubbelcongres	2022	0.2
ZonMW HGOG dag, annual meeting	2023, 2024, 2025	0.84
DCVA-NLHI Translational Cardiovascular Research concference	2023	0.2
Academisch Netweg Huiartsgeneeskune Amsterdam UMC	2025	0.1
ZonMW HGOG dag, communication in research	2025	0.84
WONCA World, Lisbon	2025	1.1
Oral presentations at (inter)national conferences		
WONCA Europe, online attendance	2021	0.5
HartVaatHAG dubbelcongres	2022	0.5
Nederlands Huisartsen Genootschap (NHG) conference, Groningen, Rotterdam	2023, 2024	1.0
Poster presentations		
European Society of Cardiology conference, online attendance	2021	0.5
Teaching		
	Year	**ECT**
Tutoring, Mentoring, Supervising		
Grading Essays, BSc Medicine	2021-2022	0.7
Grading PICOs, BSc Medicine	2022	0.4
Intern, PA in training	2022	2.25
Intern, Bsc Medicine	2023	0.5
Intern, Msc Medicine	2023	1.5
Peer reviewing		
BMC Cardiovascular Disorders	2025	0.1
Other		
Providing information at the Cycle NL event, Hartstichting Nederland	2023	0.3
Other		
	Year	**ECT**

Huisarts & Wetenschap: journaalschrijver	2023-2025	3.0
LOVAH Werkgroep Wetenschap: algemeen lid	2024-2025	5.0
Huisarts & Wetenschap: lid gastredactie, themanummer ‘Buiten de lijntjes’	2025	3.0
Nederlands Huisartsen Genootschap (NHG) Richtlijnherziening Slechthorendheid	2025-2026	1.0

DANKWOORD

Dit proefschrift is het resultaat van een zesjarig AIOTO-traject dat ik in september 2020 begon. De afgelopen jaren heb ik ervaren als een ontzettend mooie en afwisselende periode, waarin ik de kans heb gekregen me te ontwikkelen tot een wetenschappelijk geëngageerde huisarts in spe. In dit hoofdstuk wil ik graag iedereen bedanken die direct betrokken is geweest bij de totstandkoming van dit proefschrift of mij op welke andere manier dan ook heeft gesteund gedurende dit traject.

Mijn promotieteam, bestaande uit Dr. **Ralf Harskamp**, Prof. Dr. **Eric Moll van Charante** en Dr. **Jelle Himmelreich**, verdient de eerste woorden van dank. Jullie begeleiding was precies wat ik nodig had. Dankzij jullie betrokken supervisie, altijd opbouwende kritiek en onuitputtelijke stroom nieuwe ideeën ligt er nu een proefschrift waar ik apetrots op ben.

Ralf, in 2019 begon ons avontuur. Toen nog als begeleider en wetenschappelijke stagestudent. Mijn hele PhD heeft gevoeld als iets wat we samen deden en jouw deur stond altijd open om even te sparren. Ik bewonder je eindeloze creativiteit en positivisme en hoop dat er nog mooie projecten zullen volgen.

Eric, ik heb de afgelopen jaren ontzettend veel geleerd van jouw nauwkeurigheid en reflectie. Jouw weloverwogen feedback bracht mijn stukken altijd naar een hoger niveau. De manier waarop jij steeds weer de vraag weet te stellen die tot de kern snijdt is een groot talent, en ik hoop dat ik ten minste een fractie van die scherpte heb opgepikt.

Jelle, bedankt voor je enthousiasme en je gave om anderen daarin mee te nemen, zeker wanneer het gaat om de potentie van een nieuwe dataset. Dank voor al je ondersteuning en betrokkenheid in de afgelopen jaren.

Wim Lucassen, ook jij hoort in dit rijtje thuis. In de eerste jaren van mijn PhD vervulde jij een belangrijke superviserende rol. Jouw precisie en oog voor detail zijn van grote waarde geweest voor het TRACE-project.

Mijn dank gaat ook uit naar de leden van de promotiecommissie, voor de tijd en aandacht die zij hebben gestoken in het beoordelen van dit proefschrift en voor hun bereidheid om hierover met mij van gedachten te wisselen tijdens mijn verdediging.

Dan de mensen zonder wie het onderzoek zelf niet mogelijk was geweest. Allereerst alle patiënten die hun data beschikbaar stelden: dank u wel.

Ook de medewerkers van Huisartsenorganisatie Noord-Kennemerland (**HONK**) verdienen veel lof. In het bijzonder wil ik **Sandra Voerman**, **Inge van Hulst**, **Ingrid van den Ende**, **Esther Koopman-Beelen**, **Saskia van der Molen** en **Saine Sinnecker** in het zonnetje zetten. Jullie speelden een cruciale rol in de coördinatie, communicatie en kwaliteit van het onderzoek. Daarnaast ben ik alle huisartsen in de regio Noord-Kennemerland dankbaar voor hun gastvrijheid en medewerking.

Lieve **Ellen** en **Tessa**, mijn paranimfen. Dat jullie naast mij staan op die speciale dag voelt precies goed.

Ellen, vriendinnen en onafscheidelijk sinds die ene avond Kip Siam op de Spaklerweg in 2014. Sindsdien volgden vele avonden gebocheld boven schilderen-op-nummer, drankjes in de stad, vakanties en weekendjes weg. Jij bent er al vanaf het begin van mijn medische carrière bij geweest. Dat jij nu mijn paranimf bent voelt als de kers op de taart.

Tessa, samen hebben we ons ondanks alle AIOTO-perikelen, COVID-ongezelligheden en afdelingsverhuizingen staande gehouden. Onze motivatie was gelukkig altijd weer op te krikken met een goede dosis chemisch snoepgoed en af en toe een wandelingetje rond het AMC. Ik hoop dat de toekomst nog een mooi gezamenlijk onderzoeksproject voor ons in petto heeft.

Lieve **Eda**, mijn onofficiële derde paranimf. Jij hield altijd een oogje in het zeil, bracht orde waar dat nodig was en zorgde voor een warmte op de afdeling die allesbehalve vanzelfsprekend is. Ik mis je al sinds het moment dat mijn onderzoeks-tijd erop zat.

Graag bedank ik ook al mijn collega's van de afdeling Huisartsgeneeskunde. Mijn directe collega's van de cardiovasculaire onderzoeksgroep - **Eric**, **Ralf**, **Jelle**, **Eda**, **Tessa**, **Indra** en **Mink -** zorgden voor een echt groepsgevoel in wat soms een solitair traject kan zijn. **Indra**, jij bent werkelijk overal voor te porren; bedank voor je al enthousiasme. **Mink**, dank voor je warmte, ik ken weinig mensen die zo sociaal zijn als jij. In het verlengde daarvan mogen de dementie-promovendi zeker niet ontbreken. **Jakob**, **Joshua**, **Josephine** en **Anne-Roos**: jullie gezelligheid gaf kleur aan de kantoordagen. **Jakob**, weinig mensen verzetten zo veel werk in korte tijd; op die manier heb je helemaal geen plan-skills nodig. **Joshua**, dank voor de dagvullende opsomming van alle woorden die beginnen met Amy. **Josephine**, bedankt voor het faciliteren van het meest wilde congres verhaal (lees: Berlijn) dat ik ooit heb gehoord. **Anne-Roos**, stiekem vind ik het heel jammer dat ik je later niet als collega-huisarts heb, maar je wordt een fantastische een neuroloog.

Simone, ook jou wil ik specifiek bedanken voor de fijne samenwerking bij het schrijven van onze systematic review. Wie had gedacht dat we daar nog zo'n gezellig project van konden maken?

Een AIOTO-traject bestaat uit meer dan alleen onderzoek. Veel dank aan mijn opleiders en collega's uit de huisartsenpraktijken waar ik met heel veel plezier mijn opleidingsjaren deed en doe. **Erik Jan** en alle medewerkers van Huisartsenpraktijk Hartendorp in Schoorl, en **Anne-Karine**, **Carla**, **Bas** en collega's van praktijk de Buitenhof in Amsterdam.

Ook buiten werk heb ik veel steun gekregen.

Bente, **Esmee**, **Megan** en **Tess**, bedankt voor de gezellige borrel- en spelletjesavonden, Harry Potter-marathons en all-you-can-eat sushi dates. **Bent**, mijn honeybooboo en bestie, je bent amazing en verdient uiteraard een dubbele vermelding hier.

Lauré, **Anna**, **Melanie** en **Ida**, ik denk met heel veel plezier terug aan onze vaste plek in de collegebank en alle Vjeze furs in de Epstein Bar. Fijn dat jullie er ook nu nog altijd voor me zijn.

Tijdens de corona-jaren was onderzoek doen niet altijd even leuk. Gelukkig had ik een hele gezellige covidbubbel. Lieve leden van de **Daytime Dwinking**: bedankt voor alle borrelmiddagen, toen en nu.

Desiree, **Suzanne**, **Lex** en **Roos**, samen crossfitten was altijd mijn favoriete uitlaatklep. Dat je tijdens het sporten zulke fijne nieuwe vrienden kunt maken, voelt als iets heel bijzonders.

Rob, **Anneke**, **Nina**, **Thomas** en **Sybren**: jullie zijn een warm nest waar ik mij zo ontzettend thuis voel. Ik geniet er altijd van om bij jullie te zijn.

Lieve **pap** en **mam**, zonder jullie had ik dit niet gekund. Jullie hebben me van jongs af aan gestimuleerd om mijn best te doen, zonder te pushen of hoge verwachtingen op te leggen. Daardoor heb ik kunnen groeien en bloeien met de kennis dat jullie altijd trots op mij waren. Die onvoorwaardelijke liefde en steun hebben mij altijd het vertrouwen gegeven om nieuwe uitdagingen aan te gaan. Lieve **Mitch**, **Myrthe** en natuurlijk **Nora**, bedankt voor al jullie interesse, steun en enthousiasme in de afgelopen jaren.

Lieve **Bas**, de manier waarop wij ieder onze PhD aanpakken is vrij typerend voor onze verschillende karakters. Dankzij jouw nuchtere blik en stabiliteit heb ik mijn drang om alles te willen regelen meer dan eens los kunnen laten. Bedankt voor je eerlijke blik en aanmoediging tijdens dit traject. Het leven met jou is heerlijk!

ABOUT THE AUTHOR

Amy Manten was born on June 24, 1994 in Breukelen, the Netherlands. After graduating from RSG Broklede in 2012, she studied Medicine at the University of Amsterdam, obtaining her Master's degree cum laude in July 2019. During a research internship at the Department of General Practice at the Academic Medical Center (AMC), Amy developed a strong interest in integrating clinical work with research, particularly in primary care settings. Under the supervision of Dr. R. Harskamp, she contributed to the foundational work of the TRACE project, which evaluates telephone triage of acute chest pain in out-of-hours primary care. Following graduation, Amy gained clinical experience as a resident (ANIOS) in the Internal Medicine department at Tergooi Hospital from January to September 2020. She then returned to research, beginning her combined trajectory as a general practitioner (GP) trainee and PhD student (AIOTO) at the AMC. During her PhD, Amy continued her work on the TRACE project and performed exploratory analyses of chest pain patient flow in pre-hospital settings. Alongside her AIOTO-trajectory, she has been active in several extracurricular roles, including membership in the LOVAH Science Working Group, regular contributions to *Huisarts & Wetenschap*, and completion of a focused course in management and policy as part of her GP training.

Amy completed her PhD in 2026 under the supervision of Dr. R. Harskamp, Prof. Dr. E.P. Moll van Charante, and Dr. J.C.L. Himmelreich. After graduating as a GP in November 2026, she intends to continue combining clinical practice with research.

Amy lives in Utrecht with her husband, Sebastiaan Moggré. Outside her professional work, she enjoys sports, spending time with family and friends, and sewing, sharing her creations on Instagram (@naaimant).


CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME
CALL ME


CALL ME