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# Chest pain rules in general practice: a systematic review

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*Contributors*

REH and WAML conceived of the study and were responsible for the design and search strategy. REH and SCL were responsible for conducting the search. REH, SCL and JCLH conducted the data analysis and produced the tables and graphs. HCPMvW provided input into the data analysis and interpretation. The initial draft of the manuscript was prepared by REH and SCL then circulated among the coauthors for critical revision. All authors helped to evolve analysis plans, interpret data and critically revise successive drafts of the manuscript.

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*Competing interests / conflict of interests:*

None

*Data sharing statement:*

There are no additional data available.

**Abstract**

*Objective*
To identify and assess the performance of clinical decision rules (CDR) for intermittent and acute chest pain in general practice.

*Methods*
We systematically searched PubMed, Embase (OVID), CINAHL, and Google Scholar for original, prospective studies. We separately assessed CDRs for intermittent chest pain and for rule-out of acute coronary syndrome (ACS). Methodological quality was assessed using QUADAS-2 for diagnostic studies.

*Results*
Eight studies comprising 5 CDRs met the inclusion criteria. Three CDRs are designed for rule-out of coronary disease in intermittent chest pain (Gencer-rule, Marburg Heart Score, INTERCHEST), and two for rule-out of ACS (Grijseels-rule, Bruins-Slot-rule). Studies that examined the Marburg Heart Score had the highest methodological quality with consistent sensitivity (86-91%), specificity (61-81%), positive and negative predictive values (PPV=23-35%, NPV=97-98%). The diagnostic performance of Gencer (PPV:20-34%, NPV:95-99% and INTERCHEST PPV:35-43%, NPV:96-98%) appears comparable, but requires further validation. The Marburg Heart Score was more sensitive in detecting coronary disease than the clinical judgement of the general practitioner. The diagnostics performance of CDRs that focused on rule-out of ACS were: Grijseels-rule (sensitivity: 91%, specificity:37%, PPV:57%, NPV:82%) and Bruins-Slot (sensitivity: 97%, specificity: 10%, PPV: 23%, NPV:92%). Compared to clinical judgement the Bruins-Slot-rule appeared to be safer than clinical judgement alone, but the study was limited in sample size.

*Conclusions*
In general practice there is currently no clinical decision aid that can safely rule-out ACS. For intermittent chest pain, several rules exist, of which the Marburg Heart Score has been most extensively tested and appears to outperform clinical judgement alone.

*Word count: 248 (abstract)*
Key words: chest pain, general practice, primary care, clinical evaluation, decision aids, prediction rules

**Article summary**

*Article focus*

- Chest pain presents a diagnostic dilemma in general practice, leading to a low threshold for referral and a burden on the emergency services. Clinical decision rules ("chest pain rules") have been coined as an idea to aid in the diagnostic process and to make more efficient referral decisions for general practitioners.

*Key messages*

- Five clinical decision rules have been developed for rule-out of coronary artery disease in intermittent-type chest pain, in which the Marburg Heart Score is most extensively evaluated and appears to be better than clinical judgement alone.
- Two clinical decision rules have been developed specifically for rule-out of acute coronary syndrome in a general practice setting. These rules have not been extensively validated, but also lack sufficient sensitivity for safe rule-out of ACS in a general practice setting.
- The study supports the use of the Marburg Heart Score for intermittent chest pain in low-risk general practice settings. Further refinement of chest pain rules – for instance by including point-of-care-based cardiac biomarkers – is warranted, as well as outcomes-based randomized studies that compare with unaided clinical judgement.

*Strengths and limitations*

- We applied a comprehensive literature search to retrieve the published evidence on chest pain rules, applying stringent inclusion criteria and assessed the methodological quality of the studies systematically.
- The published studies had moderate methodological quality and level of reporting. The majority of studies found a high risk of bias in the reference standard, as the assessors who determined the final diagnosis (delayed-type) were not blinded to the index test results

## INTRODUCTION

Chest pain is a common symptom for contacting the general practitioner (GP). During office-hours, 1.5 percent of all consultations and 4 percent of all new episodes are related to chest pain. (1-5) The highest frequency of chest pain consultations is in the age category 45 to 64 years, with notable differences between men and women in its presentation. (1, 3, 4, 6) The initial task for GPs is differentiating less frequent, but urgent diagnoses of chest pain, such as acute coronary syndrome, or pulmonary embolism, from more common, but less urgent diagnoses (such as gastro-esophageal reflux, musculoskeletal pain or anxiety). (1-5) To make this important differentiation, GPs mainly depend on history taking, past medical history, physical examination and past experience to establish a working hypothesis/diagnosis. The most prevalent reason for referral is rule out of acute coronary syndrome (ACS) in patients with acute-onset chest pain as well as rule out of coronary artery disease (CAD) in patients who present with intermittent-type chest pain.

The GPs' evaluation of chest pain patients, based on symptoms and signs alone ("clinical gestalt") is unfortunately insufficient for diagnosing or excluding stable angina and particularly ACS reliably (sensitivity of 69% and specificity of 89%). (7) GPs are very well aware of their own limitations and therefore apply a low referral threshold. A validated clinical risk score could aid GPs in decision-making by calculating the risk of an unfavorable diagnosis based on patient characteristics, symptoms, and other readily available information. In this systematic review we aim to identify and assess the performance of existing clinical decision aids/rules for stable angina and/or acute coronary syndrome in patients with chest pain that are applicable and have been validated in low-resource general practice or equivalent settings.

## METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to undertake this review. (8)

*Data sources and searches*

We searched PubMed, Embase, CINAHL and Google Scholar from database inception through to the search date October 17th 2018. We searched for studies written in English, Dutch or German. We used keywords: chest pain, coronary artery disease, acute coronary syndrome, general practice, primary care practice, prediction rule, decision model, or decision aid. Supplement Aof the supplemental data document displays the full search strategy.

*Study selection*

Two investigators (REH, SCL) identified potentially eligible studies, with a third (WAML) to resolve any disagreements. We used an online systematic review platform (Covidence, Veritas Health Innovation Ltd, Melbourne, Australia) for this purpose. In addition to the language (English, Dutch, German) and human research restrictions, the following inclusion criteria for eligible studies were applied: 1) original studies in adults (>=18 years of age) with enrollment in a primary care setting; 2) chest pain either acute or intermittent-type; 3) ascertainment of the diagnosis of coronary artery disease or acute coronary syndrome at follow-up; 4) predictive tool based on multivariable analysis; 5) predictive tool derived from findings that are applicable in primary care setting. These findings may include: (past) medical history, physical examination, electrocardiogram, or previously documented laboratory findings (such as lipid levels). We excluded studies with a retrospective study design and studies that used a prediction rule that was based on serial biomarker testing (i.e. sequential troponin testing at 2-3 hour time interval), required advanced computer algorithms or advanced diagnostic testing (cardiac imaging, coronary angiography).

*Clinical decision rules and outcomes of interest*
The clinical decision aids may include items from history taking, physical examination, laboratory and electrocardiographic data. The outcomes of interest are diagnostic test characteristics of included rules , including: sensitivity, specificity, likelihood ratios, negative and positive prediction values.

*Reference diagnosis*
The clinical outcomes that we used as reference diagnosis were 1) any form of coronary artery or heart disease (CAD/CHD); or 2) a more restricted form including unstable angina or myocardial infarction (referred to as acute coronary syndrome) in patients with acute chest pain. We applied no restrictions on minimum or maximum time of follow-up. The assessment of applicability of the reference standard for each study is assessed by the QUADAS-2 tool, which can be found as supplemental data in Supplement B.

*Study population*
We included studies with adult populations that present at a GP office or out-of-office setting (i.e. patient visits when making house calls). In-hospital, emergency department, and/or preselected outpatient populations are not eligible.

*Data extraction and quality assessment*
Two investigators (REH, SCL) extracted data elements from each study, with a third investigator (WAML) independently reviewing these data for accuracy. The quality of the studies was assessed by three investigators (REH, SCL, WAML) using the QUADAS-2 tool for assessing risk of bias in diagnostic accuracy studies. This tool comprises four key domains, namely: patient selection, index test, reference standard, and flow and timing. (9) We assessed whether a clinical decision rule was ready for application in clinical practice based on the level of evidence for each rule using the definitions of the Mount Sinai Evidence-Based Medicine Working group. (10)

*Data synthesis and analysis*
The extracted data on study and patient characteristics, outcome measures and follow-up information of the included studies will be displayed in tables. Subsequently we extracted data on the discriminatory properties (C-statistic) of the decision rule from each studies, as well as. data on sensitivitiy, specificity, positive and negative predictive values, true and false positives and negatives . We constructed a summary receiver operating characteristic curve based on 2x2 tables from the individual study data using Review Manager (RevMan version 5.3. The Cochrane Collaboration, Copenhagen, Denmark).

*Patient and public involvement*
This study did not involve direct patient involvement. For the current analysis we did not *a priori* consult with representatives of patient organizations. After peer-review and acceptance of publication we will share the findings of our research with the Dutch Heart Foundation, relevant patient organizations, as well as general practitioners within our academic network.

## RESULTS

*Search results*
Our search resulted in 3,105 unique studies of which we assessed 94 in full-text. Of those, 8 studies met the inclusion criteria of our study, in which 5 different CDRs were evaluated. All studies were written in English. The flowchart of our search strategy and reasons for exclusions can be found as *Figure 1*.

*Quality assessment*

The overall quality of the studies was moderate as graphically displayed in *figure 2.* In 6 out of 8 studies, we found a high risk of bias in the reference standard, as the assessors who determined the final diagnosis (delayed-type) were not blinded to the index test results. In 3 studies, we found a high risk of bias in patient selection as a significant proportion of patients were excluded prior to enrollment. (11-13) Also in 4 studies a high risk of bias was found in flow and timing, due to relatively high drop-out rates of patients. (7, 12-14) In one study >15% of participating GPs stopped recruiting prematurely. (7) Quality concerns of the pooled-individual data study (INTERCHEST) included possible bias due to missing data in >20% of the study population and unverifiable risks of bias regarding patient selection. (14) Details of the quality assessment can be found in *appendix B* of the supplement.

*Study and patient characteristics*

As shown in *table 1*, a total of 7 single cohort studies were included involving 6,959 patients and 1 pooled-individual data study from 5 cohorts (INTERCHEST) involving 3,099 patients. The sample size of the individual cohort studies ranged from 289 to 1249 patients. Studies were conducted in Europe and the United States and were published 1995 and 2017. All studies were conducted in general practice, with two studies mandating immediate work-up of all patients at the emergency department. (12, 13) The prevalence of CAD, with a variable diagnostic follow-up period of up to 1 year, ranged from 8.0 to 15.0%. In 3 studies concentrating on acute onset chest pain the prevalence of ACS ranged from 22.0 to 47.8%. (11-13) The reported mean age of patients ranged from 41 to 67 years, with women comprising 44 to 58% of the population. In studies that reported the prevalence of comorbidities, hypertension (45-50%) and dyslipidemia (31-41%) were common, and diabetes was present in approximately 13%. The in- and exclusion criteria as well as the definitions that were used for the reference diagnoses for each of the studies can be found as *supplement C and D* in the supplemental file.

**Clinical decision rules**

We identified a total of 5 CDRs, namely the Gencer-rule (7), the Marburg Heart Score (15-17), INTERCHEST (14), Grijseels-rule (12, 13) and Bruins-Slot-rule (11). As shown in *table4*, the CDRs have been developed based on readily available clinical information, such as patient characteristics, (past) medical history, and physical examination. The Grijseels-rule also requires an electrocardiogram. The former three scores (Gencer, Marburg Heart Score and INTERCHEST) were developed for rule-out of CAD, whereas the Grijseels and Bruins-Slot rules were constructed for rule out of ACS.

*Decision rules for stable coronary artery disease in patients with intermittent chest pain*

As shown in *table 2*, the decision aid that was most extensively tested is the Marburg Heart Score. This study has good overall discrimination (C-statistic of 0.84-0.90), with a sensitivity of 86-89%, specificity of 64-81%, with a positive predictive value of 23-40% and a negative predictive value of 97-98%. The diagnostic properties of the Marburg Heart Score are visualized in *Figure 3*, illustrating its consistent diagnostic performance in terms of sensitivity and specificity As shown in *table 3*, The Marburg Heart Score was found to outperform unaided clinical judgement. When used as an decision aid both the sensitivity (+8.0%) and specificity were higher (+5.8%). Moreover, when the Marburg Heart Score was used for an initial triage tool it led to higher specificity (+11.6%) with similar sensitivity (-1.5%) compared with unaided clinical judgement. Based on the combined body of evidence the level of evidence is 2 for the Marburg Heart Score, which implicates that this rule can be used in a general practice setting of low-risk patients with intermittent chest pain with confidence in its accuracy.

The other two CDRs for rule-out of stable CAD were the INTERCHEST rule and the Gencer rule. The INTERCHEST rule which was derived from a pooled data analysis also shows promise (C-statistic of 0.84, sensitivity 82-88%, specificity 74-82%, positive predictive value of 35-43% and negative predictive value of 96-98%), but has a number of quality concerns, and has not been compared with unaided clinical

judgement. As such the INTERCHEST rule should not be considered ready for clinical application (level of evidence is 4). The Gencer rule was developed and externally validated in only one study (*c* statistic: 0.75-0.95, sensitivity 87-98%, specificity 42-71%). Given the limited evidence, the Gencer rule can only be used with caution (level of evidence for its use is 3).

*Decision rules designed for acute coronary syndrome*

Grijseels *et al* developed a decision rule for ruling out ACS in general practice in the late 1990s that was later updated by Bruins Slot *et al*. These studies show that the discrimination of these decision rules was mediocre (*c*-statistic of 0.66 and 0.72). Unaided clinical judgment provided a better overall fit (*c*statistic of 0.75) with a 51% agreement in risk estimation. Other diagnostic properties are listed in *Table 3*. Although the study by Bruins Slot is limited by sample size, it appears that the CDR was safer that clinical judgement alone, as four patients that were considered low-risk by the GP (8.2%) were correctly identified as high risk by the decision aid. The INTERCHEST score was also assessed among 169 patients with acute chest pain, the authors found a reasonable overall performance (*c*-statistic of 0.79). However, data on its test characteristics were lacking, and as such we are unable to assess its safety andaccuracy. Overall, neither the Grijseels, Bruins Slot or INTERCHEST rules ought to be recommended for rule-out of ACS in a general practice setting.

**DISCUSSION**

Chest pain presents a diagnostic dilemma in general practice. Advances in therapeutic options, the aging of our populations and associated increase in patients with chest pain, as well as the fear of medico-legal consequences, has led to a dramatic increase in the number of referrals that threaten to overwhelm the emergency services. (18, 19) CDRs have been coined as an idea to aid in the diagnostic process and to make safe and efficient referral decisions. A prior systematic review on this topic showed that CDRs are not sensitive enough to safely rule out CAD in primary care patients. (20) We performed an updated systematic review in which we included both derivation, validation and comparative studies with clinical judgement ("gestalt"). Moreover, we made a clear distinction between intermittent-type and acute-onset chest pain, as the diagnostic demands for CDR vary between these two clinical presentations. In summary, we found 5 primary care based CDRs that have been developed to differentiate cardiac from non-cardiac chest pain. Three CDRs were developed for ruling-out CAD in patients with intermittent chest pain, and two CDRs were developed for patients with symptoms suggestive of ACS. Overall, the Marburg Heart Score holds most promise for ruling out CAD in patients with intermittent chest pain with a consistent, high sensitivity and acceptable specificity and a negative predictive value of 97.3-98.7% in multiple prospective studies. Moreover, the Marburg Heart Score was more accurate in differentiating CAD from non-CAD than the GP's own clinical judgement, an important argument for implementation into clinical practice. As such, the Marburg Heart score can be used for rule-out of CADin low-risk general practice populations with intermittent-type chest pain (level of evidence of 2). The other CDRs for CAD or ACS lack sufficient validation in external populations or lack sufficient safety or overall accuracy (level of evidence of 3 and 4).

In order for a CDR to be useful in GP settings, it should consist of readily available and/or easy to measure elements. The Marburg Heart Score with its 5-item check list is both user friendly and seems to do an acceptable job in ruling-out CAD in (low-risk) patients with intermittent chest pain. Because of its consistent performance a point-of-care guide issued by the *American Family Physician* proposes to integrate the Marburg Heart Score into an algorithm for the evaluation of patients with chest pain in primary care. (1) It proposes that low risk patients (score 0 or 1) should not receive further cardiac follow-up, whereas high-risk patients (>3) should be referred for cardiac evaluation. In the

intermediate/moderate risk group (score 2 or 3), the algorithm proposes the use of the electrocardiogram and when negative to consult with the cardiologist for further work-up or to order a sequential troponin test. When the troponin test is negative the risk of a cardiac event is deemed <1 percent within the next 30 days. The guide also states that certain anamnestic elements, including the character of chest pain, should be factored in when making this decision.

While this algorithm may seem appealing it should be noted that the supportive evidence for the Marburg Heart Score is only applicable for patients with intermittent chest pain in a general practice setting. As such, while risk stratification may be of use to guide referral and diagnostic work-up decisions (i.e. exercise testing, etc), there are no data to support the Marburg Heart Score as an ACS rule-out tool. This is unfortunate, because it is particularly in the setting of acute-onset chest pain that GPs feel a great need for a CDR. In a recent survey conducted among GPs in the Netherlands, the vast majority of respondents would accept a <1.0% risk for missing a diagnosis of ACS in a patient and would accept no more than 25 (in hindsight) unnecessary referrals (21). The currently available Grijseels (NPV 82.4%, PPV 56.9%) and Bruins-Slot (NPV 91.7%, PPV 23.4%) rules fall short of both these targets. The question is whether a CDR based on anamnestic elements will be sufficient to reach a >99% NPV. Perhaps the additional use of point-of-care tests for cardiac markers, may increase the safety of a CDR. Studies in general practice found a negative predictive value for troponin and heart-fatty acid binding protein of 94-96% for ACS and 99.0-99.7% for myocardial infarction, respectively. (22-26) As such, current research efforts focus on whether combining these tests (as point-of-care kits) with a CDR could enhance safety and still provide an effective decision aid. This could be particularly helpful for patients with acute onset of chest pain. Similarly for those with intermittent chest pain, the use of the Marburg Heart Score as a primary-cared derived clinical risk assessment tool similar to the Diamond-Forrester chest pain rule (27) is appealing. However, whether such a strategy is cost-effective compared to usual care should be further evaluated.

*Strengths and limitations*

We performed a rigorous systematic search and quality assessment of the included articles involving chest pain rules in primary care. We avoided bias in the selection of studies by two reviewers individually identifying eligible studies, with a third to resolve any disagreements. While not being the first systematic review on this topic, this review is to our knowledge the first that examines the results of the CDRs while taking into account the results of the derivation, validation, and compared the performance of the CDR with the unaided clinical judgement of the GP.

Our study also has a number of limitations. First, we accepted a final diagnosis of coronary artery disease based on a delayed-type reference diagnosis based on consensus of a panel of experts using available symptom-related data and work-up. Such a strategy is valid, as mandating the use of coronary angiography as the reference standard would not be feasible in primary care. (28) A second limitation is the substantial heterogeneity in the prevalence of ACS among studies of CDRs for acute chest pain (range of 22-47.8%), which could indicate that GPs may have preselected patients.

Furthermore we should acknowledge that while we searched for clinical prediction rules for chest pain to rule out CAD or specifically ACS, a minority of patients may present with non-chest pain symptoms (i.e. dyspnea, jaw pain) but do have myocardial ischemia, these patients (which are more frequently elderly, women and diabetics) may not be properly represented in the included studies (29-31). A third limitation is that not all included studies reported sufficient data to allow construction of two-by-two contingency tables. Therefore, we cannot accurately assess the performance data of these CDRs. Finally, the CDRs were derived over a span of 22 years. Since the criteria for CAD, the prevalence of risk factors and prevalence of CAD may have changed over the years, some CDRs might be outdated.

## CONCLUSION

Chest pain is a common symptom in primary care, but there is only one validated clinical decision rule (Marburg Heart Score) that appears to outperform clinical judgement when applied in patients with intermittent chest pain in a low-risk setting. For ruling out acute coronary syndrome, none of the clinical decision rules was sensitive enough. Future research is warranted for the role of implementing point-of-care cardiac marker tests into clinical decision rules for acute chest pain, as well as the cost-effectiveness of a Marburg Heart Score work-up strategy for intermittent chest pain.

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**Figure legends.**

**Figure 1.** Flow chart of systematic search of the literature

**Figure 2**. Quality assessment by QUADAS-2

**Figure 3**. Summary receiver operating characteristic curve of specificity and sensitivity of the Marburg Heart Score across the individual studies

**Table 1**. Characteristics of the study design and study population

| 1st author, Year | Country | Type | Patients, *n* | Mean age, *y* | Female, *%* | Prevalence of CAD/ACS, *%* | Follow-up period |
|---|---|---|---|---|---|---|---|
| **CORONARY ARTERY DISEASE** | | | | | | | |
| *Gencer-rule* | | | | | | | |
| Gencer, 2010 (7) | Switzerland | Derivation | 661 | 55.4 | 52.5 | 12.9 | 1 year |
| | Germany | External validation | 774 | N/A | 58.0 | 14.7 | 6 months |
| *Marburg Heart Score* | | | | | | | |
| Bösner, 2010 (15) | Germany | Derivation | 1249 | 59 | 43.9 | 14.4 | 6 months |
| | Switzerland | External validation | 672 | 55 | 47.6 | 12.6 | 1 year |
| Haasenritter, 2012 (16) | Germany | External validation | 844 | 59.5 | 51.5 | 10.9 | 6 months |
| Haasenritter, 2015 (17) | Germany | External validation | 578 | 60.2 | 51.7 | 12.1 | 6 months |
| *INTERCHEST* [A] | | | | | | | |
| Aerts, 2017 (14) | USA, Belgium, Sweden, Switzerland, Germany | Derivation | 3099 | N/A | N/A | 12.5 | N/A |
| | Switzerland | Validation in study 1 | 644 | 55.4 | 52.3 | 13.2 | 1 year |
| | Germany | Validation in study 2 | 1238 | 59.4 | 56.2 | 14.5 | 6 months |
| **ACUTE CORONARY SYNDROME** | | | | | | | |
| *Grijseels-rule* | | | | | | | |
| Grijseels, 1995 (13) | The Netherlands | Derivation | 906 | 67 | 46 | 16.2 | 30 days |
| Grijseels, 1996 (12) | The Netherlands | Validation | 977 | 65.6 | 47 | 17.8 | 30 days |
| *Bruins-Slot-Rule* | | | | | | | |
| Bruins-Slot, 2011 (11) | The Netherlands | Derivation | 298 | 66 | 52 | 32 | 30 days |
| Aerts, 2017 (14) | USA, Belgium, Sweden, Switzerland, Germany | Sensitivity analysis | 169 | N/A | N/A | N/A | N/A |

*Abbreviations:* CAD, coronary artery disease; ACS, acute coronary syndrome

[A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'.

**Table 2**. Diagnostic performance data of the clinical decision rules for coronary artery disease♦

| 1st author, Year | Type | AUC | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|---|---|
| **Performance of decision** | | | | | | |
| *Gencer-rule* | | | | | | |
| Gencer, 2010 (7) | Derivation* | 0.95 (0.92-0.97) | 97.6 | 71.3 | 33.5 | 99.5 |
| | External validation | 0.75 (0.72-0.80) | 86.8 | 41.5 | 20.4 | 94.8 |
| *Marburg Heart Score* | | | | | | |
| Bösner, 2010 (15) | Derivation* | 0.87 (0.83-0.91) | 86.4 (78.5-91.7) | 75.2 (71.8-78.3) | 34.9 (29.3-40.9) | 97.3 (95.5-98.4) |
| | External validation | 0.90 (0.87-0.93) | 87.1 (79.9-94.2) | 80.8 (77.6-83.9) | 39.6 (32.6-46.6) | 97.7 (96.4-99.1) |
| Haasenritter, 2012 (16) | External validation | 0.84 (0.80-0.88) | 89.1 (81.1-94.0) | 63.5 (60.0-66.9) | 23.3 (19.2-28.0) | 97.9 (96.2-98.9) |
| Haasenritter, 2015 (17) | External validation | N/A | 91.4 (82.5-96.0) | 60.6 (56.3-64.8) | 24.2 (19.5-29.8) | 98.1 (95.9-99.1) |
| *INTERCHEST* [A] | | | | | | |
| Aerts, 2017 (14) | Derivation** | 0.84 | N/A | N/A | N/A | N/A |
| | Validation in study 1 | N/A | 88.2 (79.5-93.6) | 82.2 (78.7-85.2) | 43.0 (35.8-50.4) | 97.9 (96.1-98.9) |
| | Validation in study 2 | N/A | 82.0 (75.1-87.3) | 73.8 (70.9-76.4) | 34.7 (30.2-39.5) | 96.0 (94.3-97.2) |
| **Performance of decision rule versus Clinical judgement** | | | | | | |
| *Marburg Heart Score* [X] | | | | | | |
| Haasenritter, 2015 (17) | GP's unaided clinical judgement | N/A | 82.9 (72.4-89.9) | 61.0 (56.7-65.2) | 22.7 (18.0-28.2) | 96.3 (93.6-97.9) |
| | Marburg Heart Score (external validation) | N/A | 91.4 (82.5-96.0) | 60.6 (56.3-64.8) | 24.2 (19.5-29.8) | 98.1 (95.9-99.1) |
| | Marburg Heart Score as triage test *** | N/A | 81.4 (70.8-88.8) | 72.6 (68.6-76.3) | 29.1 (23.2-35.8) | 96.6 (94.3-98.0) |
| | GP's aided clinical judgement | N/A | 90.9 (72.2-97.5) | 66.8 (60.5-72.6) | 20.6 (13.8-29.7) | 98.7 (95.5-99.6) |

*Abbreviations:* AUC, area under the ROC-curve; PPV, positive predictive value; NPV, negative predictive value

♦ We calculated the sensitivity, specificity, PPV, and NPV using two-by-two contingency tables. We used the lowest probability category as "test negative".

* Internal validation by means of bootstrapping techniques was performed ** Internal validation by using a three-fold cross-validation approach *** Patients with definite Marburg Heart Score results were counted as negative (score ≤2 points) or positive (score ≥4 points). In patients with an intermediate score (3 points), the final test result was

determined by the GP's unaided clinical judgement. [A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'. [X] The GP's unaided clinical judgement was compared to: (1) the Marburg Heart Score; (2) using the Marburg Heart Score as triage test; (3) the GP's clinical judgement aided by the Marburg Heart Score

**Table 3**. The clinical judgement of the general practitioner

| 1st author, Year | Type | AUC | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|---|---|
| **Performance of decision** | | | | | | |
| Bruins-Slot, 2011 (11) | Derivation* | 0.66 (0.58-0.73) | 97.0 | 9.5 | 23.4 | 91.7 |
| Aerts, 2017 (14) | Sensitivity analysis | 0.79 | N/A | N/A | N/A | N/A |
| **Performance of decision rule versus Clinical judgement** | | | | | | |
| Grijseels, 1996 (12) | Validation | 0.70 | 91.4 | 36.7 | 56.9 | 82.4 |
| | GP's aided clinical judgement | N/A | 97.6 | 21.0 | 53.1 | 90.7 |
| Bruins-Slot, 2011 (11) | Derivation | 0.66 (0.58-0.73) | 97.0 | 9.5 | 23.4 | 91.7 |
| | GP's unaided clinical judgement | 0.75 (0.68-0.82) | 93.9 | 19.4 | 24.9 | 91.8 |

*Abbreviations:* AUC, area under the ROC-curve; PPV, positive predictive value; NPV, negative predictive value; GP, general practitioner

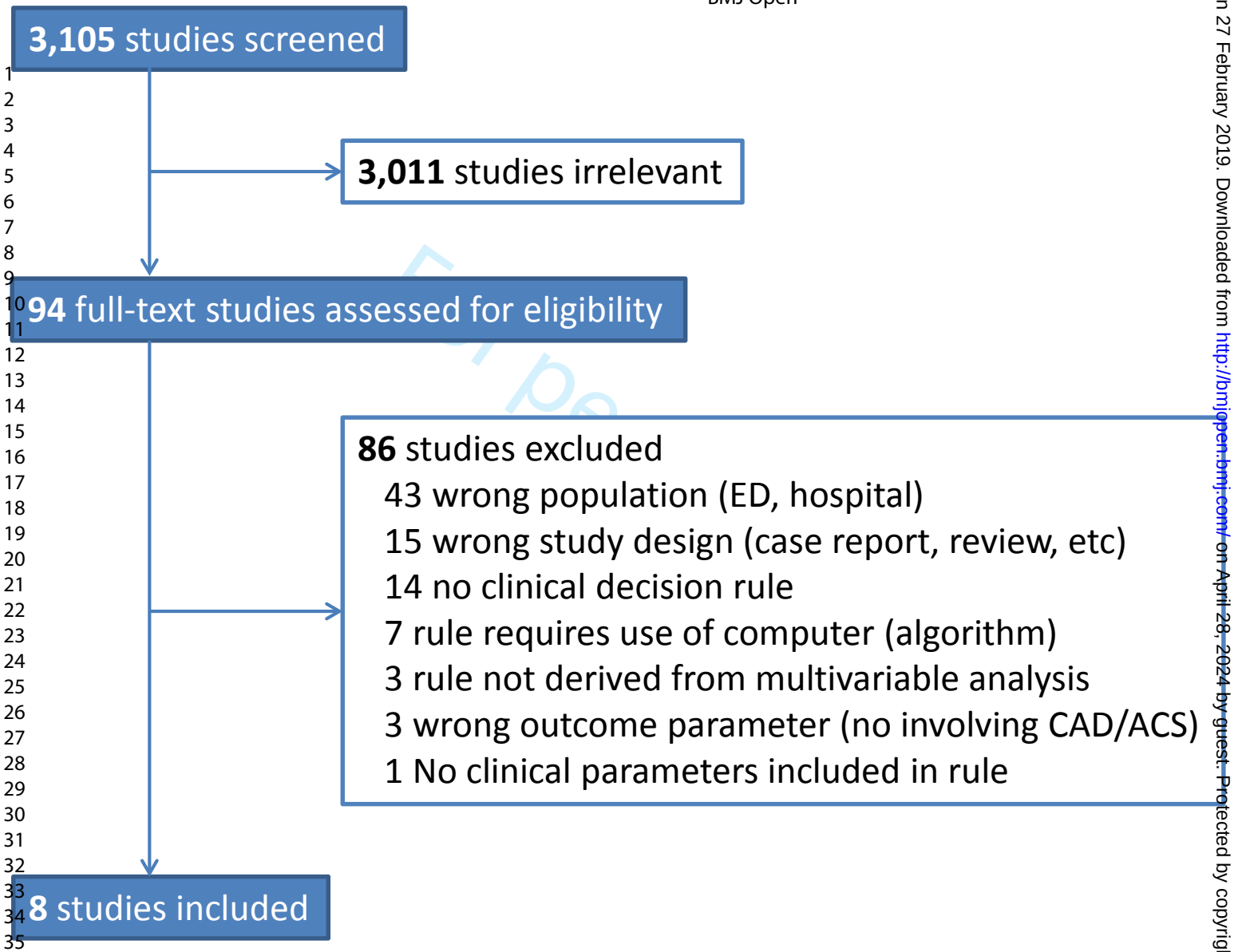
**Table 4.** Components of the clinical decision rules

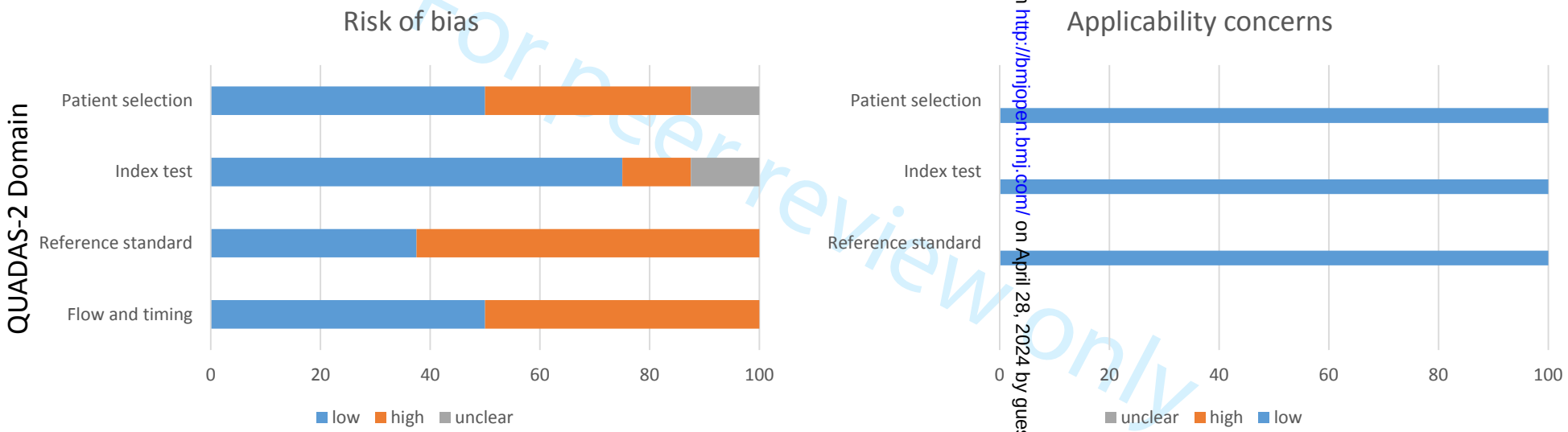
| | | |
|---|---|---|
| **CORONARY ARTERY DISEASE** | | |
| *Gencer-rule (7)* | | |
| History of CVD | 2 | *Score ranges from 0 to 11 points*<br>0-4 points: low risk<br>5-7 points: moderate risk<br>8-11 points: high risk |
| Age/sex (F ≥ 65y or M ≥ 55y) | 2 | |
| Increased pain with exercise | 1 | |
| Pain not reproducible by palpation | 1 | |
| CVD risk factor* | 2 | |
| Duration of pain 1-60 minutes | 1 | |
| Substernal location of pain | 2 | |
| *Marburg Heart Score (15-17)* | | |
| Known clinical vascular disease** | 1 | *Score ranges from 0 to 5 points*<br>0-2 points: negative result<br>3-5 points: positive result |
| Age/sex (F ≥ 65y or M ≥ 55y) | 1 | |
| Increased pain with exercise | 1 | |
| Pain not reproducible by palpation | 1 | |
| Patient assumes pain is of cardiac origin | 1 | |
| *INTERCHEST (14)* | | |
| History of CAD | +1 | *Score ranges from -1 to +5 points*<br><2 points: CAD negative<br>2-5 points: CAD positive |
| Age/sex (F ≥ 65y or M ≥ 55y) | +1 | |
| Increased pain with exercise | +1 | |
| Pain reproducible by palpation | -1 | |
| Physician assumes cardiac origin | +1 | |
| Pain feels like "pressure" | +1 | |
| **ACUTE CORONARY SYNDROME** | | |
| *Grijseels-rule (12, 13)* | | |
| History of CAD<br>Male sex<br>Presence of radiation of pain<br>Presence of nausea/sweating<br>Abnormal ECG | | <table><tr><th>Variables present</th><th>Normal ECG</th><th>Possible/minor MI on ECG</th><th>Major MI on ECG</th></tr><tr><td>0</td><td>Home</td><td>Possible referral</td><td rowspan="4">Always referral and start treating as ACS</td></tr><tr><td>1</td><td>Home</td><td>Referral</td></tr><tr><td>2</td><td>Possible referral</td><td>Referral</td></tr><tr><td>>=3</td><td>Referral</td><td>Referral</td></tr></table> |
| *Bruins-Slot-rule (11)* | | |
| History of CAD | 2 | *Score ranges from 0 to 20 points*<br>Cut-off values for low-, intermediate- and high-risk groups were not reported |
| Male sex | 5 | |
| Presence of radiation of pain | 8 | |
| Presence of nausea/sweating | 5 | |

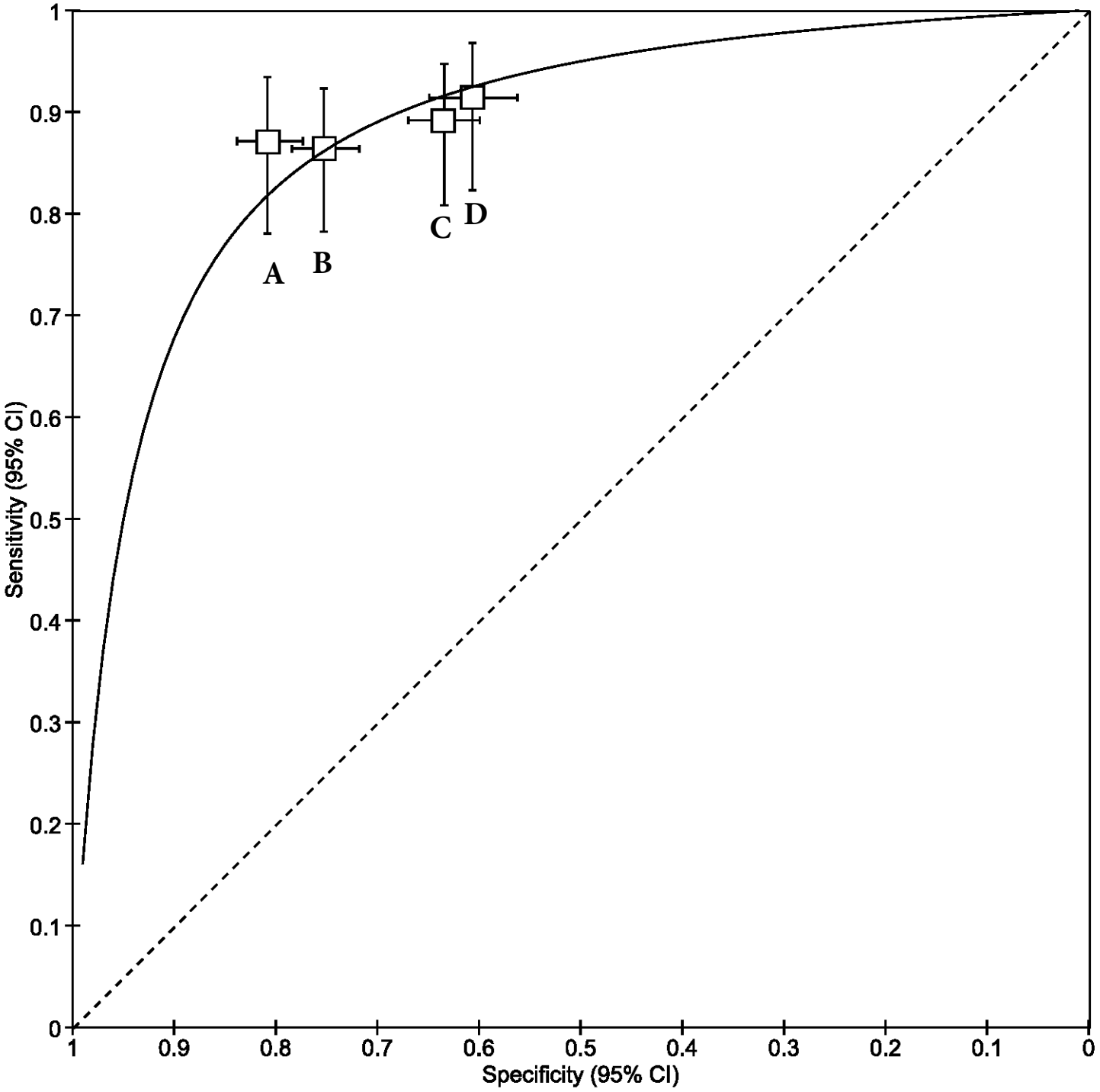
*Abbreviations:* CVD, cardiovascular disease; CAD, coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction

* Family history of CVD, diabetes mellitus, (treated) hypertension, (treated) hyperlipidaemia, smoking or obesity (Body Mass Index ≥ 30)

** CAD, occlusive vascular disease or cerebrovascular disease








| Study | 1st Author | Sensitivity | Specificity | TP | FP | FN | TN |
|---|---|---|---|---|---|---|---|
| A | Bösner 2010 (val) | 0.87 [0.79-0.94] | 0.81 [0.78-0.84] | 74 | 113 | 11 | 474 |
| B | Bösner 2010 (der) | 0.86 [0.79-0.92] | 0.75 [0.72-0.78] | 89 | 166 | 14 | 504 |
| C | Haasenritter 2012 | 0.89 [0.81-0.94] | 0.64 [0.60-0.67] | 82 | 270 | 10 | 470 |
| D | Haasenritter 2015 | 0.91 [0.83-0.96] | 0.61 [0.56-0.65] | 64 | 200 | 6 | 308 |

**Supplemental data**

**Supplement A**

PubMed search was last performed on October 17th 2018. Two search strategies were combined (#1 and #2) resulting in 1599 hits. We excluded 64 non-human studies and 159 studies that were not published in English, Dutch or German. Of the remaining 1376 studies there was 1 duplicate pair, as such there were a total of 1375 publications left to be screened. The Embase (OVID) search was subsequently performed resulting in 1751 hits. When combining the Pubmed (1375 hits) and Embase (1751 hits) search there were 114 duplicates; leading to a total of 3,009 publications that required screening. Thereafter we searched CINAHL and Google Scholar, which after excluding duplicates led to a total of 3,098 included studies. Finally we also hand-searched the references of articles eligible for full-manuscript review resulting in 7 more studies for review; resulting in a total of 3,105 studies.

| Database/search engine | Search | Query | Items found |
|---|---|---|---|
| **PubMed** | #5 | Search (#1) OR #2 Filters: Humans; Dutch; English; German | 1376 |
| | #4 | Search (#1) OR #2 Filters: Humans | 1535 |
| | #3 | Search (#1) OR #2 | 1599 |
| | #2 | Search ((((“Chest pain”[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]) AND (“Myocardial ischemia”[MeSH] OR “myocardial ischemia” OR “acute coronary syndrome” 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 ((“General practitioners”[MeSH] OR general practitioner*[tiab] OR general practice physician*[tiab]) OR (“General practice”[MeSH] OR general practice*[tiab] OR family practice*[tiab]) OR (“Primary health care”[MeSh] OR primary health care[tiab] OR primary healthcare[tiab] OR primary care[tiab]) OR (“Physicians, primary care”[MeSH] OR primary care physician*[tiab]) OR (“Physicians, family”[MeSH] OR family physician*[tiab])))) | 1232 |
| | #1 | Search ((((“Chest pain”[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]) AND (“Myocardial ischemia”[MeSH] OR “myocardial ischemia” OR “acute coronary syndrome” 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 aid*[tiab] OR | 405 |

| Database/search engine | Search | Query | Items found |
|---|---|---|---|
| | | clinical prediction rule*[tiab] OR decision model*[tiab])) | |
| **Embase (OVID)** | | ((General practice (all fields) OR primary care (all fields)) AND (chest pain (all fields)) AND ((prediction rule (all fields) or (decision aid) (all fields)). Limits were: human and English. | 1751 |
| **CINAHL** | #5 | S1 AND S2 AND S3 AND S4 | 66 |
| | #4 | ( (MH "Coronary Arteriosclerosis") OR (MH "Coronary Disease+") OR (MH "Coronary Stenosis+") OR "acute coronary syndrome OR coronary artery disease" OR (MH "Myocardial Ischemia+") OR (MH "Myocardial Infarction+") OR (MH "Acute Coronary Syndrome") ) OR TX acute coronary syndrome OR TX coronary artery disease OR TX coronary heart disease | 112,169 |
| | #3 | ( (MH "Physicians, Family") OR (MH "Family Practice") OR (MH "Primary Health Care") OR "primary care OR family medicine OR general practice" ) OR TX general practice OR TX primary care OR TX family medicine | 269,632 |
| | #2 | ( (MH "Decision Support Techniques+") OR (MH "Decision Support Systems, Clinical") OR (MH "Decision Support Systems, Management") OR (MH "Decision Trees") OR (MH "Decision Making, Clinical") OR (MH "Decision-Making Support (Iowa NIC)") ) OR TX prediction rule OR TX decision aid | 36,621 |
| | #1 | ( (MH "Chest Pain+") OR (MH "Angina Pectoris+") OR (MH "Angina, Stable") OR (MH "Angina, Unstable") OR "chest pain OR angina OR angina pectoris" ) OR TX chest pain | 26,387 |
| **Google Scholar** | | ("chest pain" OR "angina") AND ("acute coronary syndrome" OR "coronary artery disease") AND ("primary care" OR "family medicine" OR "general practice") AND ("prediction rule" OR "decision aid" OR "prediction rule" or "decision rule")<br>Filters: “articles”, excluding: patents and citations | 149 |

**Supplement B :** QUADAS-2 results for included studies

| | Risk of bias | | | | Applicability concerns | | |
|---|---|---|---|---|---|---|---|
| 1st author | **Patient selection** | **Index test/score** | **Reference standard** | **Flow and timing** | **Patient selection** | **Index test** | **Reference standard** |
| Gencer, 2010 | **Low risk** Unselected patients from 59 family practitioners ' offices | **Low risk** Variables are clearly described, sound statistical methods to construct the risk score | **High risk** delayed diagnosis; assessors in derivation cohort were not blinded to index tests | **High risk** Very few missing subjects (n=11), but eleven physicians stopped recruiting prematurely | **Low risk** Unselected population | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Bösner, 2010 | **Low risk** Unselected patients from 74 family practitioners ' offices | **Low risk** Variables are clearly described, sound statistical methods to construct the risk score | **High risk** Delayed diagnosis, assessors in were not blinded to index tests | **Low risk** Few missing subjects (<5%), no physician drop-outs. | **Low risk** Consecutive patients | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Haasenritter, 2012 | **Low risk** Unselected patients from 56 family practitioners ' offices | **Low risk** Previously developed score (Bösner, 2010); now externally validated | **High risk** Delayed diagnosis, assessors in were not blinded to index tests | **Low risk** Few missing subjects due to f/u, no physician drop-outs | **Low risk** Consecutive patients | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Haasenritter, 2015 | **Low risk** Unselected patients from 56 family practitioners ' offices | **Low risk** Previously developed score (Bösner, 2010); now validated as clinical pathway | **High risk** Delayed diagnosis, assessors in were not blinded to index tests | **Low risk** Few missing subjects due to f/u, no physician drop-outs | **Low risk** Consecutive patients | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Aerts, 2017 | **Unclear risk** | **High risk** Various datasets | **High risk** All use a delayed | **High risk** Imputation was | **Unclear risk** Cannot be | **Low risk** The index test is | **Low risk** The reference |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Data is obtained from various apparently unselected primary care patient cohorts; but this is not documented for all sources | were used in which variables or proxy variables were constructed and multiple imputation was required to account for missing data | reference standard with a multi-disciplinary group to establish the final diagnosis. It is unclear whether they were blinded. | used to adjust for missing index tests; which was a very significant proportion of the study population | verified for all studies | applicable in clinical practice | standard is an acceptable and therefore applicable standard in clinical practice |
| Bruins Slot, 2011 | **High risk** Data is obtained from consecutive patients with suspicion of ACS among various primary care patient cohorts. This inclusion criterium is subjective and therefore selection bias cannot be verified. | **Unclear risk** The authors updated the prediction rule of Grijseels, 1995; and used bootstrapping for internal validation. No data is presented on this. | **Low risk** All patients received laboratory and ECG work-up and accepted ACS criteria were used (one could argue that unstable angina could have been missed, but (N)STEMI certainly not) | **Low risk** Well conducted study. The patient drop-out (11%), mainly due to protocol violation (non-acute chest pain) or refusal of informed consent | **Low risk** Patients with acute chest pain symptoms | **Low risk** Prediction rule is applicable. | **low risk** Follows current work-up for ACS. Similar to usual care, one could miss unstable angina cases (in which ECG and laboratory work-up are negative) |
| Grijseels, 1995 | **High risk** Only patients who were referred by the primary | **Low risk** Variables are clearly described, sound statistical methods to | **Low risk** Rigorous assessment of all included patients for clearly defined | **High risk** Only 35% of all eligible patients were included for a number of reasons | **High risk** Only applies to patients with acute chest pain symptoms who referral is | **Low risk** Prediction rule is applicable. (but ECG should be present) | **High risk** using outcome definitions now considered outdated |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | care physicians to the hospital were included | construct the risk score | cardiac conditions | | considered and ECG is available | | |
| Grijseels, 1996 (validation cohort) | **High risk** Only patients who were referred by the primary care physicians to the hospital were included | **Low risk** Previously developed score (Grijseels, 1995); now externally validated (in new patient cohort but in same catchment area) | **Low risk** Rigorous assessment of all included patients for clearly defined cardiac conditions | **High risk** Significant number of eligible patients were excluded for a number of reasons | **High risk** Only applies to patients with acute chest pain symptoms who referral is considered and ECG is available | **Low risk** Prediction rule is applicable. (but ECG should be present) | **High risk** using outcome definitions now considered outdated |

Low risk= smiley
High risk= sad face
Unclear risk= ?

**Supplement C**. Inclusion- and exclusion criteria of studies

| 1st author, Year | Type | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| **CORONARY ARTERY DISEASE** | | | |
| *Gencer-rule* | | | |
| Gencer, 2010 (7) | Derivation | Age ≥ 16 years; any type of chest pain | Patients with anginal equivalents alone (e.g. jaw pain, dyspnea on exertion, arm pain) |
| | External validation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated |
| *Marburg Heart Score* | | | |
| Bösner, 2010 (14) | Derivation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated |
| | External validation | Age ≥ 16 years; any type of chest pain | Patients with anginal equivalents alone (e.g. jaw pain, dyspnea on exertion, arm pain) |
| Haasenritter, 2012 (15) | External validation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated; traumatic chest pains |
| Haasenritter, 2015 (16) | External validation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated; traumatic chest pains |
| *INTERCHEST* [A] | | | |
| Aerts, 2017 (13) | Derivation | Studies that established a final diagnosis of CAD in consecutive adult patients with chest pain in primary care | Patients received care in a hospital emergency department or had been preselected for evaluation because of suspected CAD |
| | Validation in study 1 | N/A | N/A |
| | Validation in study 2 | N/A | N/A |
| **ACUTE CORONARY SYNDROME** | | | |
| *Grijseels-rule* | | | |
| Grijseels, 1995 (12) | Derivation | Symptoms suggestive of acute cardiac pathology; patients transferred to the hospital after GP consultation | No ECG available |
| Grijseels, 1996 (11) | Validation | Symptoms suggestive of acute cardiac pathology; patients in whom a pre-hospital ECG was made | - |
| *Bruins-Slot-Rule* | | | |
| Bruins-Slot, 2011 (10) | Derivation | Patients suspected of ACS | Complaints lasting >24 hours; patients requiring instant hospital emergency room referral |

*Abbreviations:* CAD, coronary artery disease; GP, general practitioner; ECG, electrocardiogram; ACS, acute coronary syndrome

[A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'.

**Supplement D**. Follow-up data collection and definitions of the reference diagnoses as reported in the included studies

| 1st author, Year | Endpoint | Endpoint | |
|---|---|---|---|
| **CORONARY ARTERY DISEASE** | | | |
| *Gencer-rule* | | | |
| Gencer, 2010 (7) | During the initial visit, the suspected diagnosis was noted and then confirmed or modified during (1-year) follow-up. Detailed information on patients' (past medical) history and physical examination, and CRFs included information on further examinations and laboratory assays, referrals to specialists, admissions to emergency wards, hospitalizations, and health events during the follow-up period. The diagnoses retained after 12 months of follow-up were grouped in six categories: chest wall, CHD, psychogenic, respiratory, digestive, and miscellaneous. CHD included angina pectoris, unstable angina, and myocardial infarction (MI). When the diagnosis of chest pain was inconsistent or uncertain through the follow-up, a group of investigators discussed the case. | | |
| *Marburg Heart Score* | | | |
| Bösner, 2010 (14) | A reference panel of one cardiologist, one primary care physician and one research staff member reviewed baseline and follow-up data for every patient. The panel decided on whether coronary artery disease was present or absent at the time of the index consultation. It based its decision on all of the results available after the follow-up period (index questionnaire, the attending physician's provisional diagnosis, coronary angiography, if available, and results of non-invasive tests such as electrocardiography, exercise test and echocardiography). A diagnosis of coronary artery disease was based on recommendations from the German Program for Disease Management Guidelines. | | |
| Haasenritter, 2012 (15) | The reference diagnosis was established using a delayed-type reference standard in combination with an independent expert panel. Study nurses contacted all patients by phone after 6 weeks and 6 months and asked about the course of chest pain, further medical consultations, and treatments including drugs or hospitalisations. Additionally, they contacted all GPs to receive relevant information about further consultations, diagnostic procedures, treatments, and discharge letters from specialists, or hospitals. If necessary, specialists and hospitals were approached directly. An expert panel consisting of two members of the research team (at least one GP and another research staff member) reviewed each patient's data and decided if CHD had been the underlying cause for chest pain, using recommended criteria from European guidelines (ESC, NICE). | | |
| Haasenritter, 2015 (16) | A panel diagnosis was used. All patients included in the study were contacted by phone after 6 weeks and again at 6 months, and asked about their chest pain, further medical consultations, and treatments including drugs or hospitalisations. Additionally, their GPs were contacted — and specialists and hospitals if referred — to obtain relevant information about further consultations, diagnostic procedures, treatments, and discharge letters. An independent expert panel consisting of at least one GP and one research staff member reviewed each patient's data and used recommended criteria from European guidelines (ESC, NICE) to decide whether CHD had been the underlying cause for chest pain. | | |
| *INTERCHEST* [A] | | | |
| Aerts, 2017 (13) | Aerts was based on 5 prospective studies. All studies had investigated prospectively the diagnostic accuracy of symptoms and signs for CAD in consecutive patients with chest pain in a primary care setting. To establish the final diagnosis, study patients were followed up for a defined period (between 2 weeks and 1 year), and study physicians used the clinical course and results of tests to establish the cause of the index episode of chest pain. | | |
| **ACUTE CORONARY SYNDROME** | | | |
| *Grijseels-rule* | | | |
| Grijseels, 1995 (12) | Final discharge diagnoses were gathered from the hospital medical records. Myocardial infarction was diagnosed when patients met standard history, ECG and enzyme criteria (CPK, CPK-MB, aHBDH). Unstable angina was defined as a history of angina wilh increasing frequency and severity of symptoms. In addition, the diagnosis of unstable angina included patients who presented with new recent onset symptoms of angina with subsequent documentation of either ST-T changes at rest, an abnormal stress test or an abnormal coronary arteriogram. | | |
| Grijseels, 1996 (11) | By use of the decision rule, the general practitioner could subsequently decide whether hospitalization was necessary or not. Patients not admitted were visited at home the next working day, at which occasion blood was drawn for follow-up cardiac enzyme determinations (CPK, CPK-MB, aHBDH) and a follow-up ECG was recorded. The results of this follow-up were immediately provided to the general practitioner. Complications were recorded up to 30 days after the original visit of the general practitioner and the ambulance service. The final hospital discharge diagnoses were gathered from the hospital medical records or from the general practitioner. | | |
| *Bruins-Slot-Rule* | | | |

| | |
|---|---|
| Bruins-Slot, 2011 (10) | ACS was defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology. In all patients, irrespective of whether they were referred to the hospital emergency room or not, a venous blood sample was collected between 12 and 36 hours after onset of complaints, for measurement of cardiac biomarkers [troponin, creatinin kinase (CK) and creatinin kinase– myocardial band (CK-MB)]. Also, a 12-lead ECG was obtained in every patient. In referred patients, these measurements were performed as part of routine care. Patients who were not referred to hospital were visited at home by a qualified GP laboratory service personnel for performance of these tests. An expert panel consisting of two cardiologists and one GP established a final diagnosis in each patient. The panel used all available patient information, including signs and symptoms, ECG and biomarker levels (troponin, CK and CK-MB), specialist letters in those who had been referred to hospital and follow-up results up to 1 month after the event. |

*Abbreviations:* CAD, coronary artery disease; GP, general practitioner; ECG, electrocardiogram; ACS, acute coronary syndrome

[A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3,4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3,4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Suppl |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3,4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3,4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3,4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | suppl |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 3,4 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 3,4 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | suppl |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4,5 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 4,5 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 4,5 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 4,5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 4,5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 4,5 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 4,5 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 5 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 6 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 7 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | No funding |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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# Chest pain in general practice: a systematic review of prediction rules



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# Chest pain in general practice: a systematic review of prediction rules

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*Contributors*

REH and WAML conceived of the study and were responsible for the design and search strategy. REH and SCL were responsible for conducting the search. REH, SCL and JCLH conducted the data analysis and produced the tables and graphs. HCPMvW provided input into the data analysis and interpretation. The initial draft of the manuscript was prepared by REH and SCL then circulated among the coauthors for critical revision. All authors helped to evolve analysis plans, interpret data and critically revise successive drafts of the manuscript.

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*Competing interests / conflict of interests:*

None

*Data sharing statement:*

There are no additional data available.

**Abstract**

*Objective*
To identify and assess the performance of clinical decision rules (CDR) for chest pain in general practice.

*Design*
Systematic review of diagnostic studies

*Data sources*
Medline/Pubmed, Embase/Ovid, CINAHL/EBSCO, and Google Scholar up to October 2018.

*Study selection*
Studies that assessed CDRs for intermittent-type chest pain and for rule-out of acute coronary syndrome (ACS) applicable in general practice, thus not relying on advanced laboratory, computer or diagnostic testing.

*Review methods*
Reviewers identified studies, extracted data, and assessed the quality of the evidence (QUADAS-2), independently and in duplicate.

*Results*
Eight studies comprising 5 CDRs met the inclusion criteria. Three CDRs are designed for rule-out of coronary disease in intermittent-type chest pain (Gencer-rule, Marburg Heart Score, INTERCHEST), and two for rule-out of ACS (Grijseels-rule, Bruins-Slot-rule). Studies that examined the Marburg Heart Score had the highest methodological quality with consistent sensitivity (86-91%), specificity (61-81%), positive (23-35%) and negative (97-98%) predictive values. The diagnostic performance of Gencer (PPV:20-34%, NPV:95-99%) and INTERCHEST (PPV:35-43%, NPV:96-98%) appear comparable, but requires further validation. The Marburg Heart Score was more sensitive in detecting coronary disease than the clinical judgement of the GP. The performance of CDRs that focused on rule-out of ACS were: Grijseels-rule (sensitivity: 91%, specificity:37%, PPV:57%, NPV:82%) and Bruins-Slot (sensitivity: 97%, specificity: 10%, PPV: 23%, NPV:92%). Compared to clinical judgement the Bruins-Slot-rule appeared to be safer than clinical judgement alone, but the study was limited in sample size.

*Conclusions*
In general practice there is currently no clinical decision aid that can safely rule-out ACS. For intermittent chest pain, several rules exist, of which the Marburg Heart Score has been most extensively tested and appears to outperform clinical judgement alone.

*Key words:*
chest pain, general practice, primary care, clinical evaluation, decision aids, prediction rules

**Article summary**

*Methodological strengths and limitations*

- The study provides an up-to-date overview on chest pain rules applicable in general practice
- We applied stringent inclusion criteria and standardized quality assessment tools
- Various diagnostic study designs were included (i.e. derivation, validation)
- Chest pain rules that relied on advanced diagnostic testing (i.e. HEART, TIMI or GRACE) were not included
- Decision rules based on exclusively non-chest pain symptoms (i.e. dyspnea) were not part of the literature search

## INTRODUCTION

Chest pain is a common symptom for contacting the general practitioner (GP). During office-hours, 1.5 percent of all consultations and 4 percent of all new episodes are related to chest pain. (1-5) The highest frequency of chest pain consultations is in the age category 45 to 64 years, with notable differences between men and women in its presentation. (1, 3, 4, 6) The initial task for GPs is differentiating less frequent, but urgent diagnoses of chest pain, such as acute coronary syndrome, or pulmonary embolism, from more common, but less urgent diagnoses (such as gastro-esophageal reflux, musculoskeletal pain or anxiety). (1-5) To make this important differentiation, GPs mainly depend on history taking, past medical history, physical examination and past experience to establish a working hypothesis/diagnosis. The most prevalent reason for referral is rule out of acute coronary syndrome (ACS) in patients with acute-onset chest pain as well as rule out of coronary artery disease (CAD) in patients who present with intermittent-type chest pain.

The GPs' evaluation of chest pain patients, based on symptoms and signs alone ("clinical gestalt") is unfortunately insufficient for diagnosing or excluding stable angina and particularly ACS reliably (sensitivity of 69% and specificity of 89%). (7) GPs are very well aware of their own limitations and therefore apply a low referral threshold. A validated clinical risk score could aid GPs in decision-making by calculating the risk of an unfavorable diagnosis based on patient characteristics, symptoms, and other readily available information. In this systematic review we aim to identify and assess the performance of existing clinical decision aids/rules for stable angina and/or acute coronary syndrome in patients with chest pain that are applicable and have been validated in low-resource general practice or equivalent settings.

## METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to undertake this review. (8)

### *Data sources and searches*

We searched PubMed, Embase, CINAHL and Google Scholar from database inception through to the search date October 17th 2018. We searched for studies written in English, Dutch or German. We used keywords: chest pain, coronary artery disease, acute coronary syndrome, general practice, primary care practice, prediction rule, decision model, or decision aid. Supplement A of the supplemental data document displays the full search strategy.

### *Study selection*

Two investigators (REH, SCL) identified potentially eligible studies, with a third (WAML) to resolve any disagreements. We used an online systematic review platform (Covidence, Veritas Health Innovation Ltd, Melbourne, Australia) for this purpose. In addition to the language (English, Dutch, German) and human research restrictions, the following inclusion criteria for eligible studies were applied: 1) original studies in adults (>=18 years of age) with enrollment in a primary care setting; 2) chest pain either acute or intermittent-type; 3) ascertainment of the diagnosis of coronary artery disease or acute coronary syndrome at follow-up; 4) predictive tool based on multivariable analysis; 5) predictive tool derived from findings that are applicable in primary care setting. These findings may include: (past) medical history, physical examination, electrocardiogram, or previously documented laboratory findings (such as lipid levels). We excluded studies with a retrospective study design and studies that used a prediction rule that was based on serial biomarker testing (i.e. sequential troponin testing at 2-3 hour time interval), required advanced computer algorithms or advanced diagnostic testing (cardiac imaging, coronary angiography).

### *Clinical decision rules and outcomes of interest*

The clinical decision aids may include items from history taking, physical examination, laboratory and electrocardiographic data. The outcomes of interest are diagnostic test characteristics of included rules , including: sensitivity, specificity, likelihood ratios, negative and positive prediction values.

*Reference diagnosis*

The clinical outcomes that we used as reference diagnosis were 1) any form of coronary artery or heart disease (CAD/CHD); or 2) a more restricted form including unstable angina or myocardial infarction (referred to as acute coronary syndrome) in patients with acute chest pain. We applied no restrictions on minimum or maximum time of follow-up. The assessment of applicability of the reference standard for each study is assessed by the QUADAS-2 tool, which can be found as supplemental data in Supplement B.

*Study population*

We included studies with adult populations that present at a GP office or out-of-office setting (i.e. patient visits when making house calls). In-hospital, emergency department (ED), and/or preselected outpatient populations are not eligible.

*Data extraction and quality assessment*

Two investigators (REH, SCL) extracted data elements from each study, with a third investigator (WAML) independently reviewing these data for accuracy. The quality of the studies was assessed by three investigators (REH, SCL, WAML) using the QUADAS-2 tool for assessing risk of bias in diagnostic accuracy studies. This tool comprises four key domains, namely: patient selection, index test, reference standard, and flow and timing. (9) We assessed whether a clinical decision rule was ready for application in clinical practice based on the level of evidence for each rule using the definitions of the Mount Sinai Evidence-Based Medicine Working group. (10)

*Data synthesis and analysis*

The extracted data on study and patient characteristics, outcome measures and follow-up information of the included studies will be displayed in tables. Subsequently we extracted data on the discriminatory properties (C-statistic) of the decision rule from each studies, as well as. data on sensitivity, specificity, positive and negative predictive values, true and false positives and negatives . We constructed a summary receiver operating characteristic curve based on 2x2 tables from the individual study data using Review Manager (RevMan version 5.3. The Cochrane Collaboration, Copenhagen, Denmark).

*Patient and public involvement*

This study did not involve direct patient involvement. For the current analysis we did not *a priori* consult with representatives of patient organizations. After peer-review and acceptance of publication we will share the findings of our research with the Dutch Heart Foundation, relevant patient organizations, as well as general practitioners within our academic network.

## RESULTS

*Search results*

Our search resulted in 3,105 unique studies of which we assessed 94 in full-text. Of those, 8 studies met the inclusion criteria of our study, in which 5 different CDRs were evaluated. All studies were written in English. The flowchart of our search strategy and reasons for exclusions can be found as *Figure 1*.

*Quality assessment*

The overall quality of the studies was moderate as graphically displayed in *figure 2.* In 6 out of 8 studies, we found a high risk of bias in the reference standard, as the assessors who determined the

final diagnosis (delayed-type) were not blinded to the index test results. In 3 studies, we found a high risk of bias in patient selection as a significant proportion of patients were excluded prior to enrollment. (11-13) Also in 4 studies a high risk of bias was found in flow and timing, due to relatively high drop-out rates of patients. (7, 12-14) In one study >15% of participating GPs stopped recruiting prematurely. (7) Quality concerns of the pooled-individual data study (INTERCHEST) included possible bias due to missing data in >20% of the study population and unverifiable risks of bias regarding patient selection. (14) Details of the quality assessment can be found as *supplement B* in the supplemental data file.

*Study and patient characteristics*

As shown in *table 1*, a total of 7 single cohort studies were included involving 6,959 patients and 1 pooled-individual data study from 5 cohorts (INTERCHEST) involving 3,099 patients. The sample size of the individual cohort studies ranged from 289 to 1249 patients. Studies were conducted in Europe and the United States and were published 1995 and 2017. All studies were conducted in general practice, with two studies mandating immediate work-up of all patients at the ED. (12, 13) The prevalence of CAD, with a variable diagnostic follow-up period of up to 1 year, ranged from 8.0 to 15.0%. In 3 studies concentrating on acute onset chest pain the prevalence of ACS ranged from 22.0 to 47.8%. (11-13) The reported mean age of patients ranged from 41 to 67 years, with women comprising 44 to 58% of the population. In studies that reported the prevalence of comorbidities, hypertension (45-50%) and dyslipidemia (31-41%) were common, and diabetes was present in approximately 13%. The in- and exclusion criteria as well as the definitions that were used for the reference diagnoses for each of the studies can be found as *supplement C and D* in the supplemental file.

**Clinical decision rules**

We identified a total of 5 CDRs, namely the Gencer-rule (7), the Marburg Heart Score (15-17), INTERCHEST (14), Grijseels-rule (12, 13) and Bruins-Slot-rule (11). As shown in *table 2*, the CDRs have been developed based on readily available clinical information, such as patient characteristics, (past) medical history, and physical examination. The Grijseels-rule also requires an electrocardiogram. The former three scores (Gencer, Marburg Heart Score and INTERCHEST) were developed for rule-out of CAD, whereas the Grijseels and Bruins-Slot rules were constructed for rule out of ACS.

*Decision rules for stable coronary artery disease in patients with intermittent chest pain*

As shown in *table 3*, the decision aid that was most extensively tested is the Marburg Heart Score. This study has good overall discrimination (C-statistic of 0.84-0.90), with a sensitivity of 86-89%, specificity of 64-81%, with a positive predictive value of 23-40% and a negative predictive value of 97-98%. The diagnostic properties of the Marburg Heart Score are visualized in *Figure 3*, illustrating its consistent diagnostic performance in terms of sensitivity and specificity As shown in *table 4*, The Marburg Heart Score was found to outperform unaided clinical judgement. When used as an decision aid both the sensitivity (+8.0%) and specificity were higher (+5.8%). Moreover, when the Marburg Heart Score was used for an initial triage tool it led to higher specificity (+11.6%) with similar sensitivity (-1.5%) compared with unaided clinical judgement. Based on the combined body of evidence the level of evidence is 2 for the Marburg Heart Score, which implicates that this rule can be used in a general practice setting of low-risk patients with intermittent chest pain with confidence in its accuracy.

The other two CDRs for rule-out of stable CAD were the INTERCHEST rule and the Gencer rule. The INTERCHEST rule which was derived from a pooled data analysis also shows promise (C-statistic of 0.84, sensitivity 82-88%, specificity 74-82%, positive predictive value of 35-43% and negative predictive value of 96-98%), but has a number of quality concerns, and has not been compared with unaided clinical judgement. As such the INTERCHEST rule should not be considered ready for clinical application (level of evidence is 4). The Gencer rule was developed and externally validated in only

one study (*c* statistic: 0.75-0.95, sensitivity 87-98%, specificity 42-71%). Given the limited evidence, the Gencer rule can only be used with caution (level of evidence for its use is 3).

*Decision rules designed for acute coronary syndrome*

Grijseels *et al* developed a decision rule for ruling out ACS in general practice in the late 1990s that was later updated by Bruins Slot *et al*. These studies show that the discrimination of these decision rules was mediocre (*c*-statistic of 0.66 and 0.72). Unaided clinical judgment provided a better overall fit (*c* statistic of 0.75) with a 51% agreement in risk estimation. Other diagnostic properties are listed in *Table 4*. Although the study by Bruins Slot is limited by sample size, it appears that the CDR was safer that clinical judgement alone, as four patients that were considered low-risk by the GP (8.2%) were correctly identified as high risk by the decision aid. The INTERCHEST score was also assessed among 169 patients with acute chest pain, the authors found a reasonable overall performance (*c*-statistic of 0.79). However, data on its test characteristics were lacking, and as such we are unable to assess its safety and accuracy. Overall, neither the Grijseels, Bruins Slot or INTERCHEST rules ought to be recommended for rule-out of ACS in a general practice setting.

## DISCUSSION

Chest pain presents a diagnostic dilemma in general practice. Advances in therapeutic options, the aging of our populations and associated increase in patients with chest pain, as well as the fear of medico-legal consequences, has led to a dramatic increase in the number of referrals that threaten to overwhelm the emergency services. (18, 19) CDRs have been coined as an idea to aid in the diagnostic process and to make safe and efficient referral decisions. A prior systematic review on this topic showed that CDRs are not sensitive enough to safely rule out CAD in primary care patients. (20) We performed an updated systematic review in which we included both derivation, validation and comparative studies with clinical judgement ("gestalt"). Moreover, we made a clear distinction between intermittent-type and acute-onset chest pain, as the diagnostic demands for CDR vary between these two clinical presentations. In summary, we found 5 primary care based CDRs that have been developed to differentiate cardiac from non-cardiac chest pain. Three CDRs were developed for ruling-out CAD in patients with intermittent chest pain, and two CDRs were developed for patients with symptoms suggestive of ACS. Overall, the Marburg Heart Score holds most promise for ruling out CAD in patients with intermittent chest pain with a consistent, high sensitivity and acceptable specificity and a negative predictive value of 97.3-98.7% in multiple prospective studies. Moreover, the Marburg Heart Score was more accurate in differentiating CAD from non-CAD than the GP's own clinical judgement, an important argument for implementation into clinical practice. As such, the Marburg Heart score can be used for rule-out of CADin low-risk general practice populations with intermittent-type chest pain (level of evidence of 2). The other CDRs for CAD or ACS lack sufficient validation in external populations or lack sufficient safety or overall accuracy (level of evidence of 3 and 4).

In order for a CDR to be useful in GP settings, it should consist of readily available and/or easy to measure elements. The Marburg Heart Score with its 5-item check list is both user friendly and seems to do an acceptable job in ruling-out CAD in (low-risk) patients with intermittent chest pain. Because of its consistent performance a point-of-care guide issued by the *American Family Physician* proposes to integrate the Marburg Heart Score into an algorithm for the evaluation of patients with chest pain in primary care. (1) It proposes that low risk patients (score 0 or 1) should not receive further cardiac follow-up, whereas high-risk patients (>3) should be referred for cardiac evaluation. In the intermediate/moderate risk group (score 2 or 3), the algorithm proposes the use of the electrocardiogram and when negative to consult with the cardiologist for further work-up or to order a sequential troponin test. When the troponin test is negative the risk of a cardiac event is deemed <1 percent within the next 30 days. The guide also states that certain anamnestic elements, including the character of chest pain, should be factored in when making this decision.

While this algorithm may seem appealing it should be noted that the supportive evidence for the Marburg Heart Score is only applicable for patients with intermittent chest pain in a general practice setting. As such, while risk stratification may be of use to guide referral and diagnostic work-up decisions (i.e. exercise testing, etc), there are no data to support the Marburg Heart Score as an ACS rule-out tool. This is unfortunate, because it is particularly in the setting of acute-onset chest pain that GPs feel a great need for a CDR. In a recent survey conducted among GPs in the Netherlands, the vast majority of respondents would accept a <1.0% risk for missing a diagnosis of ACS in a patient and would accept no more than 25 (in hindsight) unnecessary referrals (21). The currently available Grijseels (NPV 82.4%, PPV 56.9%) and Bruins-Slot (NPV 91.7%, PPV 23.4%) rules fall short of both these targets. The question is whether a CDR based on anamnestic elements will be sufficient to reach a >99% NPV. Perhaps the additional use of point-of-care tests for cardiac markers, may increase the safety of a CDR. Studies in general practice found a negative predictive value for troponin and heart-fatty acid binding protein of 94-96% for ACS and 99.0-99.7% for myocardial infarction, respectively. (22-26) As such, current research efforts focus on whether combining these tests (as point-of-care kits) with a CDR could enhance safety and still provide an effective decision aid. This could be particularly helpful for patients with acute onset of chest pain. Similarly for those with intermittent chest pain, the use of the Marburg Heart Score as a primary-cared derived clinical risk assessment tool similar to the Diamond-Forrester chest pain rule (27) is appealing. However, whether such a strategy is cost-effective compared to usual care should be further evaluated.

*Strengths and limitations*

We performed a rigorous systematic search and quality assessment of the included articles involving chest pain rules in primary care. We avoided bias in the selection of studies by two reviewers individually identifying eligible studies, with a third to resolve any disagreements. While not being the first systematic review on this topic, this review is to our knowledge the first that examines the results of the CDRs while taking into account the results of the derivation, validation, and compared the performance of the CDR with the unaided clinical judgement of the GP.

Our study also has a number of limitations. First, we accepted a final diagnosis of coronary artery disease based on a delayed-type reference diagnosis based on consensus of a panel of experts using available symptom-related data and work-up. Such a strategy is valid, as mandating the use of coronary angiography as the reference standard would not be feasible in primary care. (28) A second limitation is the substantial heterogeneity in the prevalence of ACS among studies of CDRs for acute chest pain (range of 22-47.8%), which could indicate that GPs may have preselected patients. Furthermore we should acknowledge that while we searched for clinical prediction rules for chest pain to rule out CAD or specifically ACS, a minority of patients may present with non-chest pain symptoms (i.e. dyspnea, jaw pain) but do have myocardial ischemia, these patients (which are more frequently elderly, women and diabetics) may not be properly represented in the included studies (29-31). A third limitation is that not all included studies reported sufficient data to allow construction of two-by-two contingency tables. Therefore, we cannot accurately assess the performance data of these CDRs. Finally, the CDRs were derived over a span of 22 years. Since the criteria for CAD, the prevalence of risk factors and prevalence of CAD may have changed over the years, some CDRs might be outdated.

*Chest pain rules outside primary care*

Our aim was to research the availability of chest pain rules that are applicable and have been validated in low-resource primary care settings. We, therefore, purposefully restricted the scope of this systematic review and excluded CDRs that rely on advanced laboratory, computer or diagnostic testing for their respective scoring systems. We therefore did not include studies on CDRs that are commonly used in EDs, such as the History, Electrocardiogram, Age, Risk factors, and initial Troponin (HEART) (32), Global Registry of Acute Coronary Events (GRACE) (33) and Thrombolysis in Myocardial Infarction (TIMI) (34) scores as well as the more recent Manchester Acute Coronary Syndromes

(MACS) rule. (35) For a comprehensive overview of chest pain rules recently validated in ED patients, we refer to the systematic review by Liu et al. (36)

*Future directions*

Chest pain represents a diagnostic challenge for doctors, particularly in the GP setting, due to an unselected patient population, fewer diagnostic options and time restraints. CDRs may be of assistance, as long as they rely on readily available information and directly applicable. The existing CDRs should be more rigorously tested and further optimized, perhaps with the use of machine-learning techniques. Thereafter, we ought to conduct a randomized study in which a CDR-assisted strategy is compared with usual care, in which both safety (clinical outcomes) and efficacy (referral rate) should be assessed. Aside from these research activities, we should also put effort into finding consensus among physicians, patients, and other stakeholders in what safety/efficacy balance we are willing to accept when it comes to chest pain. The current trend towards defensive medicine is not sustainable, and as such warrants a discussion on this topic.

## CONCLUSION

Chest pain is a common symptom in primary care, but there is only one validated clinical decision rule (Marburg Heart Score) that appears to outperform clinical judgement when applied in patients with intermittent chest pain in a low-risk setting. For ruling out acute coronary syndrome, none of the clinical decision rules was sensitive enough. Future research is warranted for the role of implementing point-of-care cardiac marker tests into clinical decision rules for acute chest pain, as well as the cost-effectiveness of a Marburg Heart Score work-up strategy for intermittent chest pain.

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**Figure legends.**

**Figure 1.** Flow chart of systematic search of the literature

**Figure 2**. Quality assessment by QUADAS-2

**Figure 3**. Summary receiver operating characteristic curve of specificity and sensitivity of the Marburg Heart Score across the individual studies

**Table 1**. Characteristics of the study design and study population

| 1st author, Year | Country | Type | Patients, *n* | Mean age, *y* | Female, *%* | Prevalence of CAD/ACS, *%* | Follow-up period |
|---|---|---|---|---|---|---|---|
| **CORONARY ARTERY DISEASE** | | | | | | | |
| *Gencer-rule* | | | | | | | |
| Gencer, 2010 (7) | Switzerland | Derivation | 661 | 55.4 | 52.5 | 12.9 | 1 year |
| | Germany | External validation | 774 | N/A | 58.0 | 14.7 | 6 months |
| *Marburg Heart Score* | | | | | | | |
| Bösner, 2010 (15) | Germany | Derivation | 1249 | 59 | 43.9 | 14.4 | 6 months |
| | Switzerland | External validation | 672 | 55 | 47.6 | 12.6 | 1 year |
| Haasenritter, 2012 (16) | Germany | External validation | 844 | 59.5 | 51.5 | 10.9 | 6 months |
| Haasenritter, 2015 (17) | Germany | External validation | 578 | 60.2 | 51.7 | 12.1 | 6 months |
| *INTERCHEST* [A] | | | | | | | |
| Aerts, 2017 (14) | USA, Belgium, Sweden, Switzerland, Germany | Derivation | 3099 | N/A | N/A | 12.5 | N/A |
| | Switzerland | Validation in study 1 | 644 | 55.4 | 52.3 | 13.2 | 1 year |
| | Germany | Validation in study 2 | 1238 | 59.4 | 56.2 | 14.5 | 6 months |
| **ACUTE CORONARY SYNDROME** | | | | | | | |
| *Grijseels-rule* | | | | | | | |
| Grijseels, 1995 (13) | The Netherlands | Derivation | 906 | 67 | 46 | 16.2 | 30 days |
| Grijseels, 1996 (12) | The Netherlands | Validation | 977 | 65.6 | 47 | 17.8 | 30 days |
| *Bruins-Slot-Rule* | | | | | | | |
| Bruins-Slot, 2011 (11) | The Netherlands | Derivation | 298 | 66 | 52 | 22 | 30 days |
| Aerts, 2017 (14) | USA, Belgium, Sweden, Switzerland, Germany | Sensitivity analysis | 169 | N/A | N/A | N/A | N/A |

*Abbreviations:* CAD, coronary artery disease; ACS, acute coronary syndrome

[A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'.

**Table 2.** Components of the clinical decision rules

<table>
<tr><td colspan="3">CORONARY ARTERY DISEASE</td></tr>
<tr><td colspan="3">Gencer-rule (7)</td></tr>
<tr><td>History of CVD</td><td>2</td><td rowspan="8">Score ranges from 0 to 11 points<br>0-4 points: low risk<br>5-7 points: moderate risk<br>8-11 points: high risk</td></tr>
<tr><td>Age/sex (F ≥ 65y or M ≥ 55y)</td><td>2</td></tr>
<tr><td>Increased pain with exercise</td><td>1</td></tr>
<tr><td>Pain not reproducible by palpation</td><td>1</td></tr>
<tr><td>CVD risk factor*</td><td>2</td></tr>
<tr><td>Duration of pain 1-60 minutes</td><td>1</td></tr>
<tr><td>Substernal location of pain</td><td>2</td></tr>
<tr><td colspan="3">Marburg Heart Score (15-17)</td></tr>
<tr><td>Known clinical vascular disease**</td><td>1</td><td rowspan="5">Score ranges from 0 to 5 points<br>0-2 points: negative result<br>3-5 points: positive result</td></tr>
<tr><td>Age/sex (F ≥ 65y or M ≥ 55y)</td><td>1</td></tr>
<tr><td>Increased pain with exercise</td><td>1</td></tr>
<tr><td>Pain not reproducible by palpation</td><td>1</td></tr>
<tr><td>Patient assumes pain is of cardiac origin</td><td>1</td></tr>
<tr><td colspan="3">INTERCHEST (14)</td></tr>
<tr><td>History of CAD</td><td>+1</td><td rowspan="6">Score ranges from -1 to +5 points<br><2 points: CAD negative<br>2-5 points: CAD positive</td></tr>
<tr><td>Age/sex (F ≥ 65y or M ≥ 55y)</td><td>+1</td></tr>
<tr><td>Increased pain with exercise</td><td>+1</td></tr>
<tr><td>Pain reproducible by palpation</td><td>-1</td></tr>
<tr><td>Physician assumes cardiac origin</td><td>+1</td></tr>
<tr><td>Pain feels like “pressure”</td><td>+1</td></tr>
<tr><td colspan="3">ACUTE CORONARY SYNDROME</td></tr>
<tr><td colspan="3">Grijseels-rule (12, 13)</td></tr>
<tr><td>History of CAD<br>Male sex<br>Presence of radiation of pain<br>Presence of nausea/sweating<br>Abnormal ECG</td><td colspan="2"><table>
<tr><td>Variables present</td><td>Normal ECG</td><td>Possible/minor MI on ECG</td><td>Major MI on ECG</td></tr>
<tr><td>0</td><td>Home</td><td>Possible referral</td><td rowspan="4">Always referral and start treating as ACS</td></tr>
<tr><td>1</td><td>Home</td><td>Referral</td></tr>
<tr><td>2</td><td>Possible referral</td><td>Referral</td></tr>
<tr><td>>=3</td><td>Referral</td><td>Referral</td></tr>
</table></td></tr>
<tr><td colspan="3">Bruins-Slot-rule (11)</td></tr>
<tr><td>History of CAD</td><td>2</td><td rowspan="4">Score ranges from 0 to 20 points<br>Cut-off values for low-, intermediate- and high-risk groups were not reported</td></tr>
<tr><td>Male sex</td><td>5</td></tr>
<tr><td>Presence of radiation of pain</td><td>8</td></tr>
<tr><td>Presence of nausea/sweating</td><td>5</td></tr>
</table>

*Abbreviations:* CVD, cardiovascular disease; CAD, coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction

* Family history of CVD, diabetes mellitus, (treated) hypertension, (treated) hyperlipidemia, smoking or obesity (Body Mass Index ≥ 30)

** CAD, occlusive vascular disease or cerebrovascular disease

**Table 3**. Diagnostic performance data of the clinical decision rules for coronary artery disease♦

| 1st author, Year | Type | AUC | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|---|---|
| **Performance of decision** | | | | | | |
| *Gencer-rule* | | | | | | |
| Gencer, 2010 (7) | Derivation* | 0.95 (0.92-0.97) | 97.6 | 71.3 | 33.5 | 99.5 |
| | External validation | 0.75 (0.72-0.80) | 86.8 | 41.5 | 20.4 | 94.8 |
| *Marburg Heart Score* | | | | | | |
| Bösner, 2010 (15) | Derivation* | 0.87 (0.83-0.91) | 86.4 (78.5-91.7) | 75.2 (71.8-78.3) | 34.9 (29.3-40.9) | 97.3 (95.5-98.4) |
| | External validation | 0.90 (0.87-0.93) | 87.1 (79.9-94.2) | 80.8 (77.6-83.9) | 39.6 (32.6-46.6) | 97.7 (96.4-99.1) |
| Haasenritter, 2012 (16) | External validation | 0.84 (0.80-0.88) | 89.1 (81.1-94.0) | 63.5 (60.0-66.9) | 23.3 (19.2-28.0) | 97.9 (96.2-98.9) |
| Haasenritter, 2015 (17) | External validation | N/A | 91.4 (82.5-96.0) | 60.6 (56.3-64.8) | 24.2 (19.5-29.8) | 98.1 (95.9-99.1) |
| *INTERCHEST* [A] | | | | | | |
| Aerts, 2017 (14) | Derivation** | 0.84 | N/A | N/A | N/A | N/A |
| | Validation in study 1 | N/A | 88.2 (79.5-93.6) | 82.2 (78.7-85.2) | 43.0 (35.8-50.4) | 97.9 (96.1-98.9) |
| | Validation in study 2 | N/A | 82.0 (75.1-87.3) | 73.8 (70.9-76.4) | 34.7 (30.2-39.5) | 96.0 (94.3-97.2) |
| **Performance of decision rule versus Clinical judgement** | | | | | | |
| *Marburg Heart Score* [X] | | | | | | |
| Haasenritter, 2015 (17) | GP's unaided clinical judgement | N/A | 82.9 (72.4-89.9) | 61.0 (56.7-65.2) | 22.7 (18.0-28.2) | 96.3 (93.6-97.9) |
| | Marburg Heart Score (external validation) | N/A | 91.4 (82.5-96.0) | 60.6 (56.3-64.8) | 24.2 (19.5-29.8) | 98.1 (95.9-99.1) |
| | Marburg Heart Score as triage test *** | N/A | 81.4 (70.8-88.8) | 72.6 (68.6-76.3) | 29.1 (23.2-35.8) | 96.6 (94.3-98.0) |
| | GP's aided clinical judgement | N/A | 90.9 (72.2-97.5) | 66.8 (60.5-72.6) | 20.6 (13.8-29.7) | 98.7 (95.5-99.6) |

*Abbreviations:* AUC, area under the ROC-curve; PPV, positive predictive value; NPV, negative predictive value

♦ We calculated the sensitivity, specificity, PPV, and NPV using two-by-two contingency tables. We used the lowest probability category as test negative".

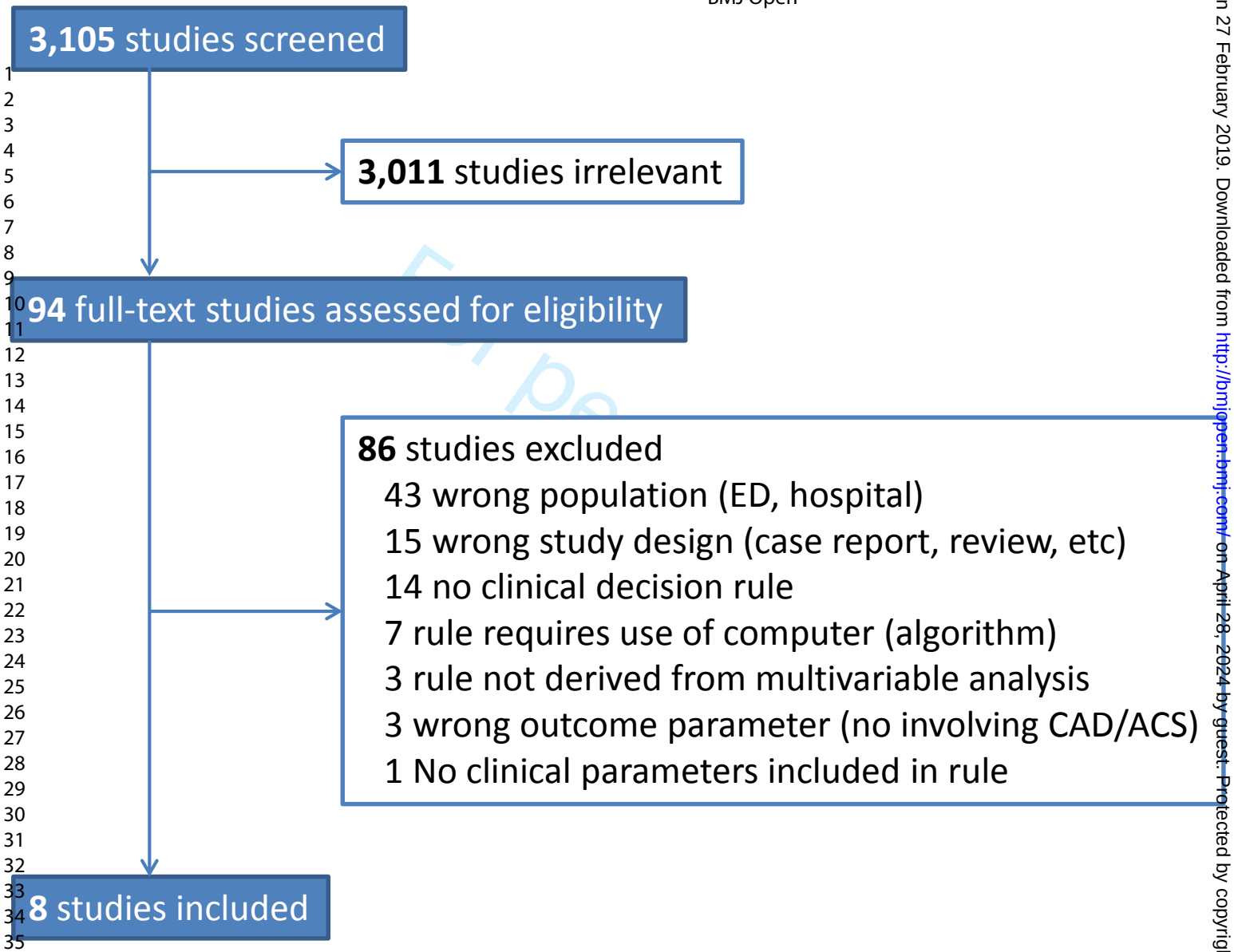
* Internal validation by means of bootstrapping techniques was performed ** Internal validation by using a three-fold cross-validation approach *** Patients with definite Marburg Heart

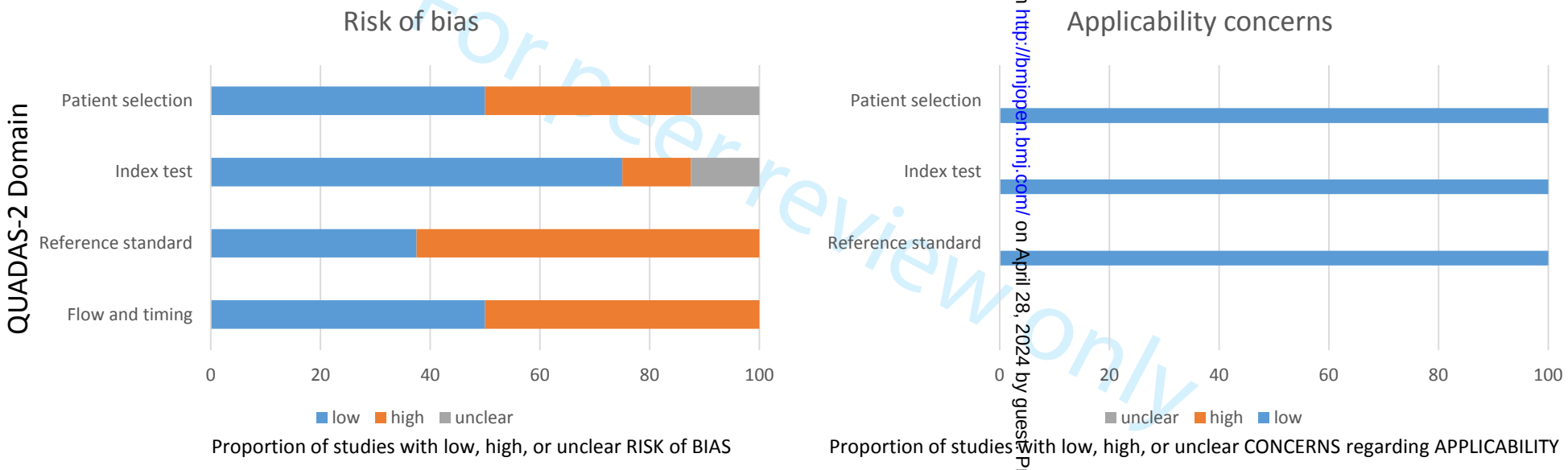
Score results were counted as negative (score ≤2 points) or positive (score ≥4 points). In patients with an intermediate score (3 points), the final test result was determined by the GP's unaided clinical judgement. [A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'. [X] The GP's unaided clinical judgement was compared to: (1) the Marburg Heart Score; (2) using the Marburg Heart Score as triage test; (3) the GP's clinical judgement aided by the Marburg Heart Score

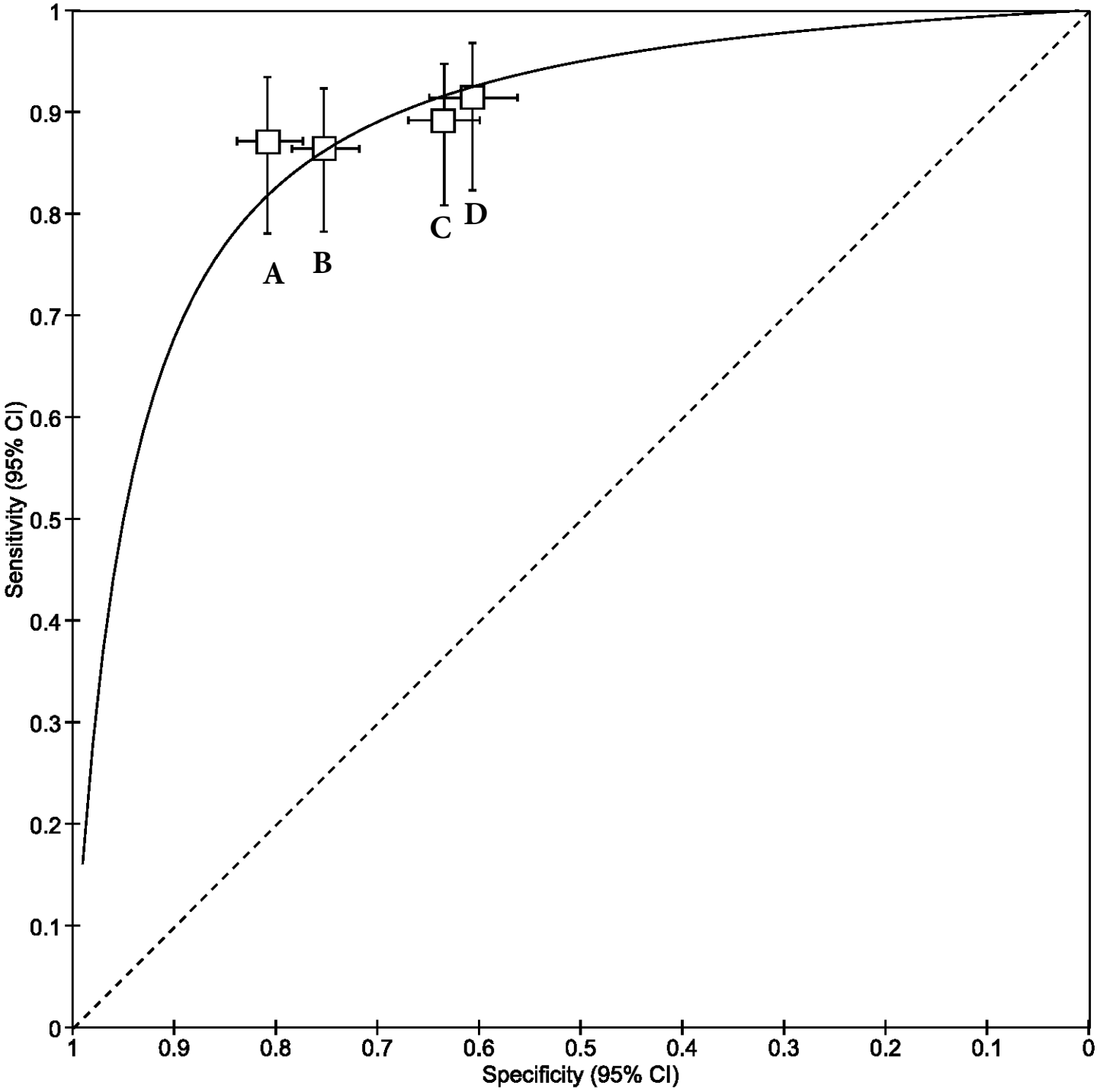
**Table 4**. The clinical judgement of the general practitioner

| 1st author, Year | Type | AUC | Sensitivity, % | Specificity, % | PPV, % | NPV, % |
|---|---|---|---|---|---|---|
| **Performance of decision** | | | | | | |
| Bruins-Slot, 2011 (11) | Derivation* | 0.66 (0.58-0.73) | 97.0 | 9.5 | 23.4 | 91.7 |
| Aerts, 2017 (14) | Sensitivity analysis | 0.79 | N/A | N/A | N/A | N/A |
| **Performance of decision rule versus Clinical judgement** | | | | | | |
| Grijseels, 1996 (12) | Validation | 0.70 | 91.4 | 36.7 | 56.9 | 82.4 |
| | GP's aided clinical judgement | N/A | 97.6 | 21.0 | 53.1 | 90.7 |
| Bruins-Slot, 2011 (11) | Derivation | 0.66 (0.58-0.73) | 97.0 | 9.5 | 23.4 | 91.7 |
| | GP's unaided clinical judgement | 0.75 (0.68-0.82) | 93.9 | 19.4 | 24.9 | 91.8 |

*Abbreviations:* AUC, area under the ROC-curve; PPV, positive predictive value; NPV, negative predictive value; GP, general practitioner








| Study | 1st Author | Sensitivity | Specificity | TP | FP | FN | TN |
|---|---|---|---|---|---|---|---|
| A | Bösner 2010 (val) | 0.87 [0.79-0.94] | 0.81 [0.78-0.84] | 74 | 113 | 11 | 474 |
| B | Bösner 2010 (der) | 0.86 [0.79-0.92] | 0.75 [0.72-0.78] | 89 | 166 | 14 | 504 |
| C | Haasenritter 2012 | 0.89 [0.81-0.94] | 0.64 [0.60-0.67] | 82 | 270 | 10 | 470 |
| D | Haasenritter 2015 | 0.91 [0.83-0.96] | 0.61 [0.56-0.65] | 64 | 200 | 6 | 308 |

**Supplemental data**

**Supplement A**

PubMed search was last performed on October 17th 2018. Two search strategies were combined (#1 and #2) resulting in 1599 hits. We excluded 64 non-human studies and 159 studies that were not published in English, Dutch or German. Of the remaining 1376 studies there was 1 duplicate pair, as such there were a total of 1375 publications left to be screened. The Embase (OVID) search was subsequently performed resulting in 1751 hits. When combining the Pubmed (1375 hits) and Embase (1751 hits) search there were 114 duplicates; leading to a total of 3,009 publications that required screening. Thereafter we searched CINAHL and Google Scholar, which after excluding duplicates led to a total of 3,098 included studies. Finally we also hand-searched the references of articles eligible for full-manuscript review resulting in 7 more studies for review; resulting in a total of 3,105 studies.

| Database/search engine | Search | Query | Items found |
|---|---|---|---|
| **PubMed** | #5 | Search (#1) OR #2 Filters: Humans; Dutch; English; German | 1376 |
| | #4 | Search (#1) OR #2 Filters: Humans | 1535 |
| | #3 | Search (#1) OR #2 | 1599 |
| | #2 | Search ((((“Chest pain”[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]) AND (“Myocardial ischemia”[MeSH] OR “myocardial ischemia” OR “acute coronary syndrome” 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 ((“General practitioners”[MeSH] OR general practitioner*[tiab] OR general practice physician*[tiab]) OR (“General practice”[MeSH] OR general practice*[tiab] OR family practice*[tiab]) OR (“Primary health care”[MeSh] OR primary health care[tiab] OR primary healthcare[tiab] OR primary care[tiab]) OR (“Physicians, primary care”[MeSH] OR primary care physician*[tiab]) OR (“Physicians, family”[MeSH] OR family physician*[tiab])))) | 1232 |
| | #1 | Search ((((“Chest pain”[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]) AND (“Myocardial ischemia”[MeSH] OR “myocardial ischemia” OR “acute coronary syndrome” 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 aid*[tiab] OR clinical prediction rule*[tiab] OR decision model*[tiab]))) | 405 |

| Database/search engine | Search | Query | Items found |
|---|---|---|---|
| **Embase (OVID)** | | ((General practice (all fields) OR primary care (all fields)) AND (chest pain (all fields)) AND ((prediction rule (all fields) or (decision aid) (all fields)). Limits were: human and English. | 1751 |
| **CINAHL** | #5 | S1 AND S2 AND S3 AND S4 | 66 |
| | #4 | ( (MH "Coronary Arteriosclerosis") OR (MH "Coronary Disease+") OR (MH "Coronary Stenosis+") OR "acute coronary syndrome OR coronary artery disease" OR (MH "Myocardial Ischemia+") OR (MH "Myocardial Infarction+") OR (MH "Acute Coronary Syndrome") ) OR TX acute coronary syndrome OR TX coronary artery disease OR TX coronary heart disease | 112,169 |
| | #3 | ( (MH "Physicians, Family") OR (MH "Family Practice") OR (MH "Primary Health Care") OR "primary care OR family medicine OR general practice" ) OR TX general practice OR TX primary care OR TX family medicine | 269,632 |
| | #2 | ( (MH "Decision Support Techniques+") OR (MH "Decision Support Systems, Clinical") OR (MH "Decision Support Systems, Management") OR (MH "Decision Trees") OR (MH "Decision Making, Clinical") OR (MH "Decision-Making Support (Iowa NIC)") ) OR TX prediction rule OR TX decision aid | 36,621 |
| | #1 | ( (MH "Chest Pain+") OR (MH "Angina Pectoris+") OR (MH "Angina, Stable") OR (MH "Angina, Unstable") OR "chest pain OR angina OR angina pectoris" ) OR TX chest pain | 26,387 |
| **Google Scholar** | | ("chest pain" OR "angina") AND ("acute coronary syndrome" OR "coronary artery disease") AND ("primary care" OR "family medicine" OR "general practice") AND ("prediction rule" OR "decision aid" OR "prediction rule" or "decision rule")<br>Filters: “articles”, excluding: patents and citations | 149 |

**Supplement B :** QUADAS-2 results for included studies

| | Risk of bias | | | | Applicability concerns | | |
|---|---|---|---|---|---|---|---|
| 1st author | **Patient selection** | **Index test/score** | **Reference standard** | **Flow and timing** | **Patient selection** | **Index test** | **Reference standard** |
| Gencer, 2010 | **Low risk** Unselected patients from 59 family practitioners' offices | **Low risk** Variables are clearly described, sound statistical methods to construct the risk score | **High risk** delayed diagnosis; assessors in derivation cohort were not blinded to index tests | **High risk** Very few missing subjects (n=11), but eleven physicians stopped recruiting prematurely | **Low risk** Unselected population | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Bösner, 2010 | **Low risk** Unselected patients from 74 family practitioners' offices | **Low risk** Variables are clearly described, sound statistical methods to construct the risk score | **High risk** Delayed diagnosis, assessors in were not blinded to index tests | **Low risk** Few missing subjects (<5%), no physician drop-outs. | **Low risk** Consecutive patients | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Haasenritter, 2012 | **Low risk** Unselected patients from 56 family practitioners' offices | **Low risk** Previously developed score (Bösner, 2010); now externally validated | **High risk** Delayed diagnosis, assessors in were not blinded to index tests | **Low risk** Few missing subjects due to f/u, no physician drop-outs | **Low risk** Consecutive patients | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Haasenritter, 2015 | **Low risk** Unselected patients from 56 family practitioners' offices | **Low risk** Previously developed score (Bösner, 2010); now validated as clinical pathway | **High risk** Delayed diagnosis, assessors in were not blinded to index tests | **Low risk** Few missing subjects due to f/u, no physician drop-outs | **Low risk** Consecutive patients | **Low risk** The index test is applicable in clinical practice | **Low risk** The reference standard is an acceptable and therefore applicable standard in clinical practice |
| Aerts, 2017 | **Unclear risk** Data is | **High risk** Various datasets | **High risk** All use a delayed | **High risk** Imputation was | **Unclear risk** Cannot be | **Low risk** The index test is | **Low risk** The reference |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | obtained from various apparently unselected primary care patient cohorts; but this is not documented for all sources | were used in which variables or proxy variables were constructed and multiple imputation was required to account for missing data | reference standard with a multi-disciplinary group to establish the final diagnosis. It is unclear whether they were blinded. | used to adjust for missing index tests; which was a very significant proportion of the study population | verified for all studies | applicable in clinical practice | standard is an acceptable and therefore applicable standard in clinical practice |
| Bruins Slot, 2011 | **High risk** Data is obtained from consecutive patients with suspicion of ACS among various primary care patient cohorts. This inclusion criterium is subjective and therefore selection bias cannot be verified. | **Unclear risk** The authors updated the prediction rule of Grijseels, 1995; and used bootstrapping for internal validation. No data is presented on this. | **Low risk** All patients received laboratory and ECG work-up and accepted ACS criteria were used (one could argue that unstable angina could have been missed, but (N)STEMI certainly not) | **Low risk** Well conducted study. The patient drop-out (11%), mainly due to protocol violation (non-acute chest pain) or refusal of informed consent | **Low risk** Patients with acute chest pain symptoms | **Low risk** Prediction rule is applicable. | **low risk** Follows current work-up for ACS. Similar to usual care, one could miss unstable angina cases (in which ECG and laboratory work-up are negative) |
| Grijseels, 1995 | **High risk** Only patients who were referred by the primary care physicians to the hospital were | **Low risk** Variables are clearly described, sound statistical methods to construct the risk score | **Low risk** Rigorous assessment of all included patients for clearly defined cardiac conditions | **High risk** Only 35% of all eligible patients were included for a number of reasons | **High risk** Only applies to patients with acute chest pain symptoms who referral is considered and ECG is available | **Low risk** Prediction rule is applicable. (but ECG should be present) | **High risk** using outcome definitions now considered outdated |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | included | | | | | | |
| Grijseels, 1996 (validation cohort) | **High risk** Only patients who were referred by the primary care physicians to the hospital were included | **Low risk** Previously developed score (Grijseels, 1995); now externally validated (in new patient cohort but in same catchment area) | **Low risk** Rigorous assessment of all included patients for clearly defined cardiac conditions | **High risk** Significant number of eligible patients were excluded for a number of reasons | **High risk** Only applies to patients with acute chest pain symptoms who referral is considered and ECG is available | **Low risk** Prediction rule is applicable. (but ECG should be present) | **High risk** using outcome definitions now considered outdated |

Low risk= smiley
High risk= sad face
Unclear risk= ?

**Supplement C**. Inclusion- and exclusion criteria of studies

| 1st author, Year | Type | Inclusion criteria | Exclusion criteria |
|---|---|---|---|
| **CORONARY ARTERY DISEASE** | | | |
| *Gencer-rule* | | | |
| Gencer, 2010 (7) | Derivation | Age ≥ 16 years; any type of chest pain | Patients with angina equivalents alone (e.g. jaw pain, dyspnea on exertion, arm pain) |
| | External validation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated |
| *Marburg Heart Score* | | | |
| Bösner, 2010 (14) | Derivation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated |
| | External validation | Age ≥ 16 years; any type of chest pain | Patients with angina equivalents alone (e.g. jaw pain, dyspnea on exertion, arm pain) |
| Haasenritter, 2012 (15) | External validation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated; traumatic chest pains |
| Haasenritter, 2015 (16) | External validation | Age ≥ 35 years; chest pain localized on the anterior chest wall | Chest pain ≥ 1 month; pain already investigated; traumatic chest pains |
| *INTERCHEST* [A] | | | |
| Aerts, 2017 (13) | Derivation | Studies that established a final diagnosis of CAD in consecutive adult patients with chest pain in primary care | Patients received care in a hospital emergency department or had been preselected for evaluation because of suspected CAD |
| | Validation in study 1 | N/A | N/A |
| | Validation in study 2 | N/A | N/A |
| **ACUTE CORONARY SYNDROME** | | | |
| *Grijseels-rule* | | | |
| Grijseels, 1995 (12) | Derivation | Symptoms suggestive of acute cardiac pathology; patients transferred to the hospital after GP consultation | No ECG available |
| Grijseels, 1996 (11) | Validation | Symptoms suggestive of acute cardiac pathology; patients in whom a pre-hospital ECG was made | - |
| *Bruins-Slot-Rule* | | | |
| Bruins-Slot, 2011 (10) | Derivation | Patients suspected of ACS | Complaints lasting ≥ 24 hours; patients requiring instant hospital emergency room referral |

*Abbreviations:* CAD, coronary artery disease; GP, general practitioner; ECG, electrocardiogram; ACS, acute coronary syndrome

[A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'.

**Supplement D**. Follow-up data collection and definitions of the reference diagnoses as reported in the included studies

| 1st author, Year | Endpoint | Endpoint | |
|---|---|---|---|
| **CORONARY ARTERY DISEASE** | | | |
| *Gencer-rule* | | | |
| Gencer, 2010 (7) | During the initial visit, the suspected diagnosis was noted and then confirmed or modified during (1-year) follow-up. Detailed information on patients' (past medical) history and physical examination, and CRFs included information on further examinations and laboratory assays, referrals to specialists, admissions to emergency wards, hospitalizations, and health events during the follow-up period. The diagnoses retained after 12 months of follow-up were grouped in six categories: chest wall, CHD, psychogenic, respiratory, digestive, and miscellaneous. CHD included angina pectoris, unstable angina, and myocardial infarction (MI). When the diagnosis of chest pain was inconsistent or uncertain through the follow-up, a group of investigators discussed the case. | | |
| *Marburg Heart Score* | | | |
| Bösner, 2010 (14) | A reference panel of one cardiologist, one primary care physician and one research staff member reviewed baseline and follow-up data for every patient. The panel decided on whether coronary artery disease was present or absent at the time of the index consultation. It based its decision on all of the results available after the follow-up period (index questionnaire, the attending physician's provisional diagnosis, coronary angiography, if available, and results of non-invasive tests such as electrocardiography, exercise test and echocardiography). A diagnosis of coronary artery disease was based on recommendations from the German Program for Disease Management Guidelines. | | |
| Haasenritter, 2012 (15) | The reference diagnosis was established using a delayed-type reference standard in combination with an independent expert panel. Study nurses contacted all patients by phone after 6 weeks and 6 months and asked about the course of chest pain, further medical consultations, and treatments including drugs or hospitalisations. Additionally, they contacted all GPs to receive relevant information about further consultations, diagnostic procedures, treatments, and discharge letters from specialists, or hospitals. If necessary, specialists and hospitals were approached directly. An expert panel consisting of two members of the research team (at least one GP and another research staff member) reviewed each patient's data and decided if CHD had been the underlying cause for chest pain, using recommended criteria from European guidelines (ESC, NICE). | | |
| Haasenritter, 2015 (16) | A panel diagnosis was used. All patients included in the study were contacted by phone after 6 weeks and again at 6 months, and asked about their chest pain, further medical consultations, and treatments including drugs or hospitalisations. Additionally, their GPs were contacted — and specialists and hospitals if referred — to obtain relevant information about further consultations, diagnostic procedures, treatments, and discharge letters. An independent expert panel consisting of at least one GP and one research staff member reviewed each patient's data and used recommended criteria from European guidelines (ESC, NICE) to decide whether CHD had been the underlying cause for chest pain. | | |
| *INTERCHEST* [A] | | | |
| Aerts, 2017 (13) | Aerts was based on 5 prospective studies. All studies had investigated prospectively the diagnostic accuracy of symptoms and signs for CAD in consecutive patients with chest pain in a primary care setting. To establish the final diagnosis, study patients were followed up for a defined period (between 2 weeks and 1 year), and study physicians used the clinical course and results of tests to establish the cause of the index episode of chest pain. | | |
| **ACUTE CORONARY SYNDROME** | | | |
| *Grijseels-rule* | | | |
| Grijseels, 1995 (12) | Final discharge diagnoses were gathered from the hospital medical records. Myocardial infarction was diagnosed when patients met standard history, ECG and enzyme criteria (CPK, CPK-MB, aHBDH). Unstable angina was defined as a history of angina wilh increasing frequency and severity of symptoms. In addition, the diagnosis of unstable angina included patients who presented with new recent onset symptoms of angina with subsequent documentation of either ST-T changes at rest, an abnormal stress test or an abnormal coronary arteriogram. | | |
| Grijseels, 1996 (11) | By use of the decision rule, the general practitioner could subsequently decide whether hospitalization was necessary or not. Patients not admitted were visited at home the next working day, at which occasion blood was drawn for follow-up cardiac enzyme determinations (CPK, CPK-MB, aHBDH) and a follow-up ECG | | |

| | |
|---|---|
| | was recorded. The results of this follow-up were immediately provided to the general practitioner. Complications were recorded up to 30 days after the original visit of the general practitioner and the ambulance service. The final hospital discharge diagnoses were gathered from the hospital medical records or from the general practitioner. |
| *Bruins-Slot-Rule* | |
| Bruins-Slot, 2011 (10) | ACS was defined in accordance with guidelines from the European Society of Cardiology and the American College of Cardiology. In all patients, irrespective of whether they were referred to the hospital emergency room or not, a venous blood sample was collected between 12 and 36 hours after onset of complaints, for measurement of cardiac biomarkers [troponin, creatinin kinase (CK) and creatinin kinase– myocardial band (CK-MB)]. Also, a 12-lead ECG was obtained in every patient. In referred patients, these measurements were performed as part of routine care. Patients who were not referred to hospital were visited at home by a qualified GP laboratory service personnel for performance of these tests. An expert panel consisting of two cardiologists and one GP established a final diagnosis in each patient. The panel used all available patient information, including signs and symptoms, ECG and biomarker levels (troponin, CK and CK-MB), specialist letters in those who had been referred to hospital and follow-up results up to 1 month after the event. |

*Abbreviations:* CAD, coronary artery disease; GP, general practitioner; ECG, electrocardiogram; ACS, acute coronary syndrome

[A] Derivation used pooled individual patient data from five studies. The INTERCHEST was applied to two of these five studies to measure its diagnostic performance. We referred to this as 'validation in study 1 and 2'.

# PRISMA 2009 Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 2 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 3 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 3,4 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | N/A |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 3 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 3,4 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Suppl |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 3,4 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 3,4 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 3,4 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | suppl |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 3,4 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 3,4 |

# PRISMA 2009 Checklist



| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | suppl |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 4,5 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 4,5 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 4,5 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 4,5 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 4,5 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 4,5 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 4,5 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 5 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 6 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 7 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | No funding |

*From:* Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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