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Deriving a clinical prediction rule for coronary artery disease in primary care: improving internal and external validity by pooling individual patient data from five international sites

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Abstract (250 words)

Objective: To construct a clinical prediction rule for coronary artery disease (CAD) presenting with chest pain in primary care.

Study Design: Meta-Analysis using 3099 patients from 5 studies. To identify candidate predictors, we used random forest trees, multiple imputation of missing values and logistic regression within individual studies. To generate a prediction rule on the pooled data, we applied a regression model that took account of the differing standard data sets collected by the 5 studies.

Results: The most parsimonious rule included six equally weighted predictors: age>55 (males) or >65 (females)(+1); attending physician suspected a serious diagnosis(+1); history of CAD(+1); pain brought on by exertion(+1); pain feels like "pressure"(+1); pain reproducible by palpation(-1). CAD was considered absent if the prediction score is <2. The AUC was 0.84. We applied this rule to a study setting with a CAD prevalence of 13.2% using a prediction score cut-off of <2 (i.e., -1, 0, or +1). When the score was <2, the probability of CAD was 2.1%(95%CI:1.1-3.9%); when the score was ≥2, it was 43.0%(95% CI:35.8-50.4%).

Conclusions: Clinical prediction rules are a key strategy for individualizing care. Large data sets based on electronic health records from diverse sites creates opportunities for improving their internal and external validity. Our patient-level meta-analysis from 5 primary care sites should improve external validity. Our strategy for addressing site-to-site systematic variation in missing data should improve internal validity. Using principles derived from decision theory, we also discuss the problem of setting the cut-off prediction score for taking action.

Keywords [MeSH] Chest Pain, individual patient data meta-analysis, Myocardial Ischemia, Medical History Taking, Symptom Assessment, Primary Health Care, Sensitivity and Specificity

1 Introduction

Applying individual patient meta-analysis to create clinical prediction rules is methodologically difficult when primary studies, acting independently, do not collect the same standard data sets. Methods to summarize the measures of prediction (e.g. regression coefficients) across studies must account for the data that individual studies did not try to collect. We encountered this problem when we used data from 5 independent studies of chest pain to develop a clinical prediction rule for initial assessment of patients presenting to a primary care setting. Chest pain is an important diagnostic problem in primary care, where 0.7% to 2.7% of patient encounters are due to chest pain [1–3], and coronary artery disease is the cause of chest pain in 8.6 to 14.6 % of patients [3, 4]. Clinical prediction rules developed in emergency departments, specialty clinics, or hospitals may not apply to primary care because diagnostic test results (e.g., an electrocardiogram) are incorporated in the prediction rule in those settings.

2 Methods

2.1 Data Sources and Study Selection

We conducted a systematic literature search to identify studies potentially suitable for inclusion in a patient-level meta-analysis [5]. We describe the search and selection process in Appendix 1. We defined primary care as an outpatient or clinic setting other than an emergency department. We identified studies that had prospectively obtained data on symptoms and signs and established a

final diagnosis of CAD in consecutive adult patients presenting with chest pain in primary care. We excluded studies if the patients received care in a hospital emergency department or had been pre-selected for evaluation because of suspected CAD.

Included studies:

We identified eight potentially eligible studies. We did not include 3 studies because individual patient data were not available [6], we could not contact the principal investigators [7], or the study was ongoing when we conducted our analysis [8] (see Supplement Figure 1). The 5 included studies had a total enrollment of 3099 patients [2, 4, 9–11]. Table 1 summarizes characteristics of the 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, and study physicians used the clinical course and results of tests to establish the cause of the index episode of chest pain. This delayed-type reference standard can be an acceptable and valid alternative when a single reference test is not possible [12]. The five studies differed in the length of follow-up. The physicians making the final study diagnosis were not blinded to the initial history and physical examination findings.

- Table 1 about here -

2.2 Data management

Principal investigators of the eligible primary studies were invited to join the INTERCHEST collaboration and to provide the raw data and information on inclusion criteria, patient recruitment, data collection, and diagnostic reference standard. If necessary, we translated the original questionnaires or case report forms into English and created a synopsis of definitions of all variables used in each study. We excluded symptoms and signs that only one study obtained routinely. We recoded the variables in the individual datasets so that each variable corresponded to

a common definition across the 5 data sets. The authors of each study verified that the meaning of each variable was consistent with its counterpart in their study.

2.3 Data analysis

Overview of Methods

Our objective was a clinical prediction rule for estimating the probability that CAD is the cause of a patient's chest pain. Here, we give a short overview of our methods. Figure 1 provides a schematic depiction.

- Figure 1 about here –

In all analyses, the dependent variable was a CAD diagnosis (both stable and acute forms) for the index episode of chest pain, as determined by a study clinician or an expert panel at least several months after the index visit, taking all available information into account (Table 1). We excluded cases that lacked a final diagnosis. Items of the medical history or clinical examination were the predictor variables. We imputed data that a study collected routinely but were missing in an individual patient, generating five imputed data sets for each original study. We identified the best predictors within each study, using random forest trees and logistic regression. We created five imputed meta-data sets, each including one imputed data set from each original study, and, for each imputed meta-data set, fitted a logistic regression model in which the independent variables were the best predictors in each study and the dependent variable was a CAD diagnosis. We combined the results from each model (see below for details) and, to derive an easy-to-use clinical prediction rule from this model, reduced the number of predictors to six by removing the weakest predictors and by replacing the regression coefficients by 1 (if $\beta > 0$) and -1 (if $\beta < 0$), respectively. We calculated the area under the ROC curve to measure how well the models discriminated

between patients with and without a final diagnosis of CAD. We calculated sensitivity, specificity, likelihood ratios and predictive values for all studies that provided data on all predictors included in the final, simplified model. To test for over-fitting the model, we performed an internal validation using a three-fold cross-validation approach [13]. To test the performance of the rule in patients with acute and non-acute pain, we calculated likelihood ratios for each variable in the rule in both sub-groups, plotted the ROC curve and calculated the AUC. [14]

Details of the methods:

Missing values – A study that combines retrospective data from several sources can have 2 sources of missing data: *within-study* missingness and *between-study* missingness. If a study routinely recorded a specific predictor, but its value was missing for individual patients within the study (*within-study* missingness), we considered these as missing at random and performed multiple imputation. As imputed data are not truly observed data and are random on their own, multiple imputation is needed in order to get valid inference at the final stage of analysis (five imputation are considered sufficient, see [15, 16]). Using imputation by chained equations [17], we created five [18] imputed datasets for each of the studies, selected the candidate predictors across studies (see below) and then merged them into 5 imputed meta-datasets, each of which included a different imputed dataset from each of the five studies (see Figure 1).

The regression analyses of the meta-data took into account *between-study* missingness: some of the selected candidate predictors had been recorded routinely in some studies but were not obtained in other studies (*between-study* missingness). In fact, only two predictors had been obtained routinely in all 5 studies. The regression models fitted on the meta-data took account of the differing sets of predictors that the individual studies had routinely collected (see formula 1 in

Supplement 3). The estimation of the effects of the two predictors common to all 5 studies was based on data from all studies, whereas the effects of the other predictors were estimated using data from the studies that collected data on these predictors [19].

Selection of candidate predictors – This section describes a two-step process for identifying candidate predictors from each individual study. in step 1, we used a random forest algorithm to identify the most important predictors in each study. The random forest algorithm cycles many times through a process of constructing a classification tree by random selection (with replacement) of cases from a study (the set of all such trees is a forest). The tree is constructed by testing a random subset of predictors at each node to determine which one provides the best discrimination. The most commonly occurring predictor among the set of predictors at all terminal nodes of each tree is the classifying predictor for the tree. The candidate predictors for the forest are the classifying predictors appearing most frequently over all the trees in the forest [20]. In step 2, we fitted logistic regression models using the forest candidate predictors as the independent variables and a CAD diagnosis as the dependent variable. As noted above, we repeated this process for each of the 5 imputed data sets of each original study. All statistically significant predictors ($\alpha \leq 0.05$) in the logistic models from at least one of the imputed datasets from each original study were included in the candidate predictor list for the patient-level meta-analysis.

Meta-analysis and derivation of the diagnostic model - We fitted a logistic regression model to each imputed meta-dataset (created as described in the section on missing values). We used a fixed effects regression model with study-specific intercepts β_{0i} and study-specific dummy indicators I_{ki} (formula 1). The study-specific intercepts account for the different CAD prevalences across studies while accounting for the effect of the predictors. The study-specific dummy indicators account for the different predictor sets across studies, with the indicator I_{ki}taking value 1 if data on predictor *k* were obtained for study *i,* and 0 otherwise. Regression coefficients and their standard errors from

the five imputed datasets were combined according to the rules of multiple imputation, as proposed by Rubin [15, 16]. All predictors that were significant ($\alpha \leq 0.05$) were combined into one linear score to be used for classifying patients (see Supplement 3 in Appendix).

Prediction rule sensitivity, specificity, and discrimination: In applying the classification rule to a specific patient, the clinician can ascertain the value of each predictor (present or absent); since all predictors are available, all availability-indicators would be equal to 1. For the application of the rule on our original data set, we need to include the indicator in formula in Supplement 3 as we need to compute the score for all patients in our five studies and not all predictors are available for all studies. We applied the rule to all the patients in the five studies, each of which had been classified as having a CAD diagnosis or not. Using different cut-off values of the chest pain score, we calculated sensitivity and specificity and the area under the ROC curve.

Internal validation - We randomly partitioned the entire sample of patients into three sub-samples. We performed the steps of the meta-analysis, model derivation and model simplification three times, taking one of the sets as the test sample, the other two as learning samples.[21].

Sensitivity analyses: We performed two sensitivity analyses. One measured the sensitivity, specificity, likelihood ratios, and discrimination (AUC) of the chest pain rule in patients with acute chest pain and patients with chronic chest pain (see Supplement 5 in the Appendix). The other compared these performance measures after deleting one predictor variable (physician is concerned that chest pain is serious) (see Supplement 6 in the Appendix)).

We used R 2.13.2 (R Foundation for Statistical Computing, Vienna, Austria) using Mice [17], randomForest [22], and pROC [23] packages.

3 Results

As candidate predictors, we considered 61 medical history and physical examination items that at least two studies had collected routinely (see Supplement 2). No two studies collected the exact same set of predictors. The predictors 'sex' and 'age' were the only ones that all studies obtained. Based on the random forest tree analysis and the study-specific logistic regression analyses, we entered 19 candidate variables in a logistic regression model that we fitted to each of the five imputed meta-data sets.

- Table 2 about here –

The clinical prediction rule: In this patient-level meta-analysis, eleven of the 19 candidate predictors were statistically significant predictors of the final diagnosis ($\alpha \leq 0.05$) (Table 2). The corresponding chest pain rule I discriminated well between patients with and without a CAD final diagnosis (area under the ROC curve, AUC, = 0.87) (table 3); the discrimination was only slightly lower (AUC=0.85) after eliminating the five statistically weakest predictors (chest pain rule II). The rule discriminated essentially equally well after we further simplified the calculation of the score by assigning a value of 1.0 or -1.0 to the six regression coefficients (chest pain rule III, AUC= 0.84).

– Table 3 about here –

The final chest pain rule III included six predictors: older age, physician initially suspected a serious condition (the very first impression or gut feeling), chest pain feels like "pressure", chest pain is related to effort, history of CAD, and chest pain reproduced by chest wall palpation. With one exception, the presence of a predictor increased the likelihood of CAD; chest pain reproducible by chest wall palpation decreased the likelihood. Two of the five studies [2, 11] had collected data on all predictors included in the final chest pain rule III. Figure 2 shows the distribution of chest pain

scores in these two studies; the score values range from -1 to 5 points; most of the patients had scores of 1 or less. Using the same two studies, we calculated the diagnostic accuracy of this clinical prediction rule for a chest pain score threshold of 2 points (CAD considered unlikely if score < 2) (Table 4). We applied this rule to one of the two study settings (4) with a CAD prevalence of 13.2% using a prediction score cut-off of <2 (i.e., -1, 0, or +1). When the score was <2, the probability of CAD was 2.1% (95%CI: 1.1-3.9%); when the score was ≥2, it was 43.0% (95% CI: 35.8-50.4%). These post-test probabilities are equivalent to a negative predictive value of 97.9 and a positive predictive value of 43%, as shown in Table 4.

We performed three internal cross-validations, which all yielded a model with the same predictors and similar estimates of their discriminatory power (see Supplement 4; Supplement Tables 2, 3, and 4).

- Figure 2 about here -

- Table 4 about here -

Sensitivity analyses: we divided the study population into those with acute chest pain and those with non-acute chest pain and applied the simplified rule. Five of the six variables in the simplified rule had the same likelihood ratio in the two subgroups (see Supplement 5; Supplement Table 5). The variable 'history of CAD' was a weaker predictor in the acute chest pain subgroup. We applied the simplified rule (chest pain rule III) to the five imputed data sets from the two participating studies [2][11] that routinely collected data on all 6 variables in both subgroups. In both studies the simplified rule predicted a CAD reference diagnosis equally well in the two subgroups. When we applied the chest pain rule to the 5 imputed data sets of the study by Bösner et al. [11], the AUC ranged from 0.79 to 0.80 (patients with acute pain) and from 0.86 to 0.87 (patients with non-acute pain) (see Supplement 5, Supplement Table 6 and Figure 2); p values of DeLong's test for whether

the two ROC curves differed ranged from 0.08 to 0.12. In the study of Verdon et al. [2], the difference in the AUC of each subgroup was even smaller.

We were concerned that some clinical sites would be reluctant to use a prediction rule that used the predictor variable "physician initially suspected a serious condition," which requires a highly subjective judgement. In a second sensitivity analysis, we deleted this variable from chest pain rule III and tested the resulting rule on the five imputed data sets derived from the Bösner et al. [11] and the Verdon et al. [2] respectively. Omitting the variable reduced the sensitivity of the rule, increased its specificity, and did not change its discrimination (AUC) (Supplement 6 in the Appendix).

4 Discussion

The present systematic review and meta-analysis is the first, to our knowledge, to pool the patient data from all completed studies of chest pain signs and symptoms in a primary care setting, which is where most patients with chest pain first seek care. Our individual patient meta-analysis enhances internal validity in several ways. First, the large number of patients improves statistical precision, especially for subgroup analyses, and reduces the likelihood of a Type II error in comparing subgroups of patients. Furthermore, the diverse primary care settings in different countries enhances external validity.

Second, we used a statistical modeling strategy that deals with several difficulties encountered in individual patient meta-analyses based on observational studies. These include heterogeneity across studies (different populations, different sets of routinely collected predictors) and within studies (missing observations). The logistic regression meta-analytic model assumes that the effects of predictors on the probability of CAD are the same in all 5 studies, even if a particular

predictor is not available in a particular study. In our modeling strategy, only studies with data on a particular predictor contribute to the estimation of that predictor's effect, and consequently different studies contribute differently to the estimation of predictive effects. In this way, albeit under the reasonable assumption of a common effect for all predictors in the final clinical prediction rule, the model optimizes the contribution of all studies. The use of different intercepts for each study adjusts for the heterogeneity between the 5 studies (because we had only 5 studies, we used fixed models). To deal with missing observations for a patient within a study, we used multiple imputation.

Our meta-analysis has several limitations. First, the exact meaning of history items used in the studies may vary due to semantic and cultural differences, adding statistical uncertainty to measures of discrimination. Second, unlike a study of a recursive partitioning algorithm for diagnosing myocardial infarction [24],we did not do a prospective external validation in a consecutive series of patients from an independent clinical setting [25]. However, each prediction rules generated by our cross-validation identified the same predictors and each had sensitivity, specificity and likelihood ratios similar to the original prediction rule, suggesting that over-fitting to our study data sets is less likely. Our limited approach to validation is another limitation. We did not do an internal validation study of the clinical diagnosis of CAD using an objective diagnostic reference standard on a randomly selected subset of patients from the pooled study populations. Such a study would be subject to concerns that the results of applying an objective diagnostic reference standard to patients referred for it would not be the same as the source population (test-referral bias). Our cross-validation study provides an internal validity check that our model was not over-fitted to the data. We did not do a prospective external validation study in a consecutive series of patients from an independent clinical setting, as is considered best practice. Ideally, an

external validation study should be entirely independent of the original study: new patients, different clinical settings, and different clinicians [25, 26]. We suggest that an individual patient meta-analysis based on data pooled from studies done at different times, with different patients and clinicians, and using different diagnostic reference standards provides partial assurance of external validity.

The choice of a diagnostic reference standard in studies of chest pain in primary care poses a special dilemma. We used a clinical diagnostic reference standard based on follow-up data rather than a uniform objective measure, such as coronary arteriography. This is a limitation because some diagnostic misclassification probably occurred and because clinical findings obtained at the index visit may have influenced the final diagnosis, which could lead to biased estimates of the likelihood ratios of clinical findings. Using coronary angiography as the diagnostic reference standard is not feasible in primary care settings. The alternative, using receipt of coronary angiography as a study inclusion criterion, would result in referral bias and possibly a serious systematic error when applying the results to a primary care population [27]. Despite these observations, a clinical diagnosis after follow-up may be a good diagnostic reference standard for primary care, since the clinician is initially uncertain of the diagnosis and hopes to choose the best interventions for the eventual diagnosis as established by testing, response to empirical treatment, and the passage of time.

Comparison of our prediction rule and previous work is difficult because we studied patients in primary care, whereas prior studies studied them in emergency department and subspecialty clinics. In one large study validating a prediction rule for assessing chest pain in the ED, the target was myocardial infarction, and ECGs were performed routinely [24]. Because that study used a

recursive partitioning algorithm, it is possible to evaluate the role of the ECG findings in identifying patients with myocardial infarction. Four of the 13 nodes in the algorithm used ECG results, and these nodes identified 628 of the 835 patients with myocardial infarction. Only 3 nodes used findings that were included in our prediction rule, and all of them were distal to a high yield ECG-based node, which made it impossible to compare the accuracy of these findings in our study (in which ECGs were done sporadically) and theirs.

A 2012 individual patient meta-analysis of 18 data sets developed a CAD prediction rule in hospitalized patients who were referred to CT angiography, catheter angiography or both [28]. The findings of angiography were used to establish the reference diagnosis. We could not use the results of this study as a validity check on our results because the authors classified the participants' chest pain as non-specific, atypical angina, and typical angina and used these global syndromes as candidate predictors of the results of angiography. We, on the other hand, used the individual characteristics of chest pain (e.g. substernal, brought on by exertion, reproduced by palpating the chest wall) as candidate predictors.

A critical concern for any clinical prediction rule is linking the clinical score to an action, such as referral from primary care to an emergency department. A clinical score above a threshold would lead to further evaluation or treatment for CAD, whereas a score below the threshold would lead to watchful waiting or pursuing other diagnoses. In decision theory, the choice of threshold depends on the prevalence of CAD and the ratio of harms to benefits of the actions to be taken.[29] Given the small harms of treating CAD in patients who do not have CAD and the large benefit of treating CAD in patients who do have CAD, one should prefer a threshold clinical score that provides high sensitivity. A high sensitivity threshold would mean a very low probability of CAD if the clinical score

is below the action threshold. Using the simplified chest pain rule 3, a score value below 2 points resulted in a sensitivity of 88 % and 82%, respectively in the two study sites that were suitable for calculating sensitivity and specificity because they had obtained all of the chest pain rule predictors [2, 11]. While that sensitivity might seem too low for the clinician to rely solely on this prediction rule, especially in acute situations, the prevalence of a CAD diagnosis is low in office-based primary care, as shown in these two studies (13.2% and 14.5%) [2, 11]. Therefore, the negative predictive values (the probability that a patient with a chest pain score < 2 does not have a CAD diagnosis) in these two settings is very high (97.9% and 96.0%, respectively). Given the low probability of a CAD diagnosis with a score <2, clinicians may consider the rule to be suitable for initial triage in a primary care setting, especially if the prevalence of CAD diagnoses was very low (e.g., 7.4% as in the Sox et al. study [4]).

In the past 25 years, five studies have focused on the diagnosis of coronary artery disease in patients with chest pain in the primary care setting, a small number given the importance of the problem. We undertook a systematic review of this experience. By pooling the data from the 5 studies, we hoped to create a prediction rule that was more trustworthy than the clinical prediction rules of the 5 individual studies. Beyond the specifics of the clinical problem, our study suggests a more general model for diagnostic research: the sharing of clinical data to improve the care of the patient [30]. In the coming era of large data sets derived from diverse clinical settings, researchers are eager to pool data and develop clinical prediction rules with high external validity. Our experience with 5 independently derived, heterogeneous data sets, and that described in a recent publication [28], provide reason to hope that individual patient-level meta-analysis can produce promising clinical tools from studies that were performed independently with little or no attention to standardizing data definitions, clinical data sets, and uniform diagnosis protocols.

Authors' contributions: MA and GM performed the statistical analyses and wrote a first draft of manuscript. All other authors commented on this draft and contributed to, and improved the final manuscript. All authors contributed to the study design and analyses. NDB is the principal investigator of the study described in this article. JH coordinated the study.

Conflict of Interest Statement: The authors declare that they have no competing interests.

Disclaimer: Dr. Sox is an employee of the Patient-Centered Outcomes Research Institute (PCORI). This study does not describe any policies of PCORI.

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5 Literature Cited

1. Svavarsdottir AE, Jonasson MR, Gudmundsson GH, Fjeldsted K. Chest pain in family practice. Diagnosis and long-term outcome in a community setting. Can.Fam.Physician 1996; 42:1122–8.

2. Verdon F, Herzig L, Burnand B, Bischoff T, Pecoud A, Junod M et al. Chest pain in daily practice: occurrence, causes and management. Swiss Med Wkly 2008; 138(23-24):340–7.

3. Bösner S, Becker A, Haasenritter J, Abu Hani M, Keller H, Sönnichsen AC et al. Chest pain in primary care: epidemiology and pre-work-up probabilities. Eur J Gen Pract 2009; 15(3):141–6.

4. Sox, H. C., Jr., Hickam DH, Marton KI, Moses L, Skeff KM, Sox CH et al. Using the patient's history to estimate the probability of coronary artery disease: a comparison of primary care and referral practices. American Journal of Medicine 1990; 89(1):7–14.

5. Haasenritter J, Aerts M, Bosner S, Buntinx F, Burnand B, Herzig L et al. Coronary heart disease in primary care: accuracy of medical history and physical findings in patients with chest pain - a study protocol for a systematic review with individual patient data. BMC family practice 2012; 13(1):81.

6. Rosser W, Henderson R, Wood M, Green L. An exploratory report of chest pain in primary care. A report from ASPN. J.Am.Board Fam.Pract. 1990; 3(3):143–50.

7. Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Michigan Research Network. J.Fam.Pract. 1994; 38(4):345–52.

8. Haasenritter J, Bösner S, Vaucher P, Herzig L, Heinzel-Gutenbrunner M, Baum E et al. Ruling out coronary heart disease in primary care: external validation of a clinical prediction rule. Br J Gen Pract 2012; 62(599):415–21.

9. Buntinx F, Truyen J, Embrechts P, Moreel G, Peeters R. Evaluating patients with chest pain using classification and regression trees. Fam Pract 1992; 9(2):149–53.

10. Nilsson S, Scheike M, Engblom D, Karlsson LG, Molstad S, Akerlind I et al. Chest pain and ischaemic heart disease in primary care. Br J Gen Pract 2003; 53(490):378–82.

11. Bösner S, Becker A, Abu Hani M, Keller H, Sönnichsen AC, Haasenritter J et al. Accuracy of symptoms and signs for coronary heart disease assessed in primary care. Br J Gen Pract 2010; 60(575):246–57.

12. Knottnerus JA, Muris JW. Assessment of the accuracy of diagnostic tests: the cross-sectional study. In: Knottnerus JA, Buntinx F, editors. The evidence base of clinical diagnosis. 2nd ed. Oxford, Hoboken NJ: Wiley-Blackwell Pub./BMJ Books; 2009. p. 42–63 .

13. Steyerberg EW, Harrell, F. E., Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001; 54(8):774–81.

14. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988; 44(3):837–45.

15. Rubin DB. Multiple imputations in sample surveys – a phenomenological Bayesian approach to nonresponse. In: U.S. Department of Commerce, editor. Imputation and Editing of Faulty or Missing Survey Data. Washington, DC: U.S. Department of Commerce; 1978. p. 1–23 .

16. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.

17. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. Journal of Statistical Software 2011; 45(3):1–67.

18. Schafer JL. Analysis of incomplete multivariate data. 1. ed., 1. CRC Press reprint. Boca Raton: Chapman & Hall/CRC; 2000. (Monographs on statistics and applied probability; vol 72).

19. Borenstein M, Hedges LV, Higgins, Julian P. T., Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Research Synthesis Methods 2010 [cited 2013 Jul 31:29:43]; 1(2):97–111.

20. Breiman L. Random Forests. Machine Learning 2001; 45:5–32.

21. Hastie T, Tibshirani R, Friedman J. The elements of statistical learning: Data mining, inference, and prediction. 2. ed., (corr. at 5. print.). New York, NY: Springer; 2011. (Springer series in statistics).

22. Liaw A, Wiener M. Classification and Regression by randomForest. R News 2002; 2(3):18–22.

23. Robin X, Turck N, Hainard A, Tiberti N, Lisacek F, Sanchez JC et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. BMC Bioinformatics 2011; 12:77.

24. Goldman L, Cook EF, Brand DA, Lee TH, Rouan GW, Weisberg MC et al. A computer protocol to predict myocardial infarction in emergency department patients with chest pain. N Engl J Med 1988; 318(13):797–803.

25. Wasson JH, Sox HC, Neff RK, Goldman L. Clinical prediction rules. Applications and methodological standards. N Engl J Med 1985; 313(13):793–9.

26. Laupacis A, Sekar N, Stiell IG. Clinical prediction rules. A review and suggested modifications of methodological standards. JAMA 1997; 277(6):488–94.

27. Knottnerus JA, Leffers P. The influence of referral patterns on the characteristics of diagnostic tests. J Clin Epidemiol 1992; 45(10):1143–54.

28. Genders TS, Steyerberg EW, Hunink MG, Nieman K, Galema TW, Mollet NR et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. BMJ 2012; 344:e3485.

29. Sox, Harold C., Jr., Higgins MC, Owens DK. Medical Decision Making. 2nd ed. Oxford: Wiley-Blackwell; 2013.

30. Peng RD, Dominici F, Zeger SL. Reproducible epidemiologic research. Am J Epidemiol 2006; 163(9):783–9.

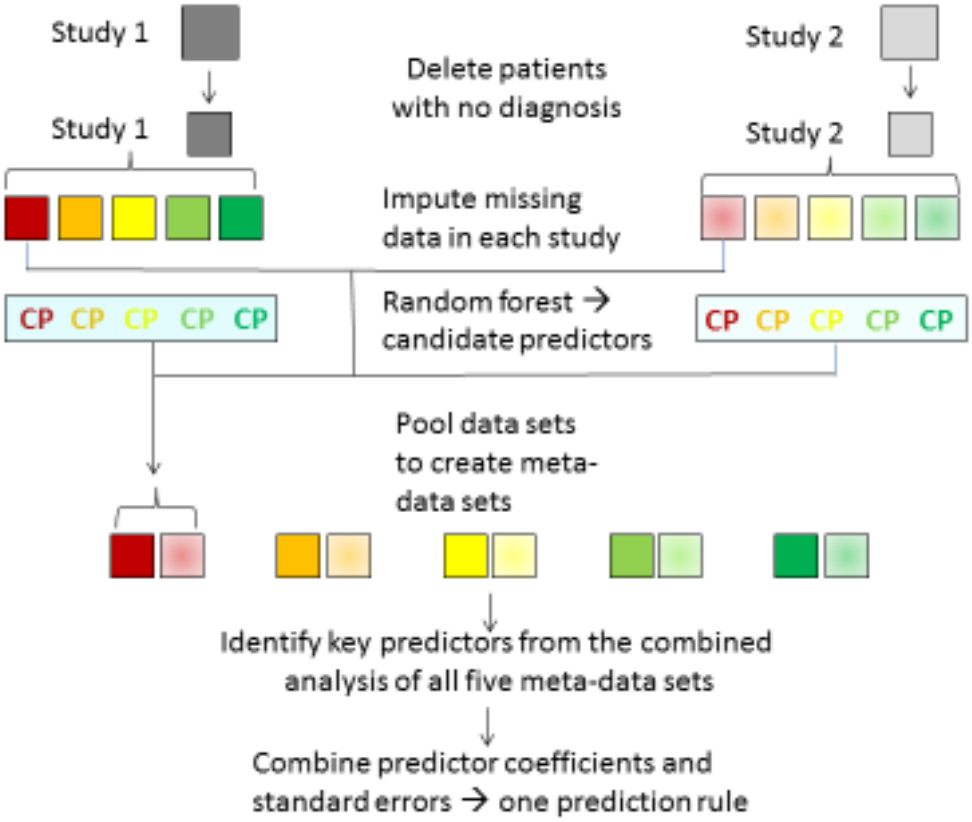


Figure 1: Schematic depiction of methods: This figure shows two studies (Study 1 and Study 2) to represent the process for all five studies. Imputation of within- study data missing at random generates five imputed data sets for each study, each containing all patients in the study but differing because of the randomly imputed values for the missing data. Five imputed meta-data sets are constructed by pooling one of the five imputed data sets from each study (shown here as pooling the first imputed datasets across all five studies, next pooling the second ones, and so on). The predictors were selected as follows. For each imputed data set and for each study: first, the random forest method identified candidate predictors; next, a logistic regression model using these candidate predictors was fitted. All statistically significant predictors (at level ≤0.05) in the logistic regression models from at least one of the imputed datasets across all studies were included as candidate predictors for the analysis of the meta-data. Logistic regression models using these candidate predictors were fitted to each imputed meta-data set. Note that only studies providing data on a particular predictor contribute to the estimation of the effect of that predictor. To account for these study differences as well as for varying pretest probabilities of CAD across the individual studies, study-specific intercepts were used for the logistic regression meta-models. Coefficients and their standard errors from the fits on each imputed meta-data set are combined using the methods of Rubin et al. [15, 16]. All

predictors that were statistically significant (at level ≤0.05) in the combined analysis were used in the chest pain rule I. Further stepwise exclusion until only six predictor remained resulted in a simpler chest pain rule.

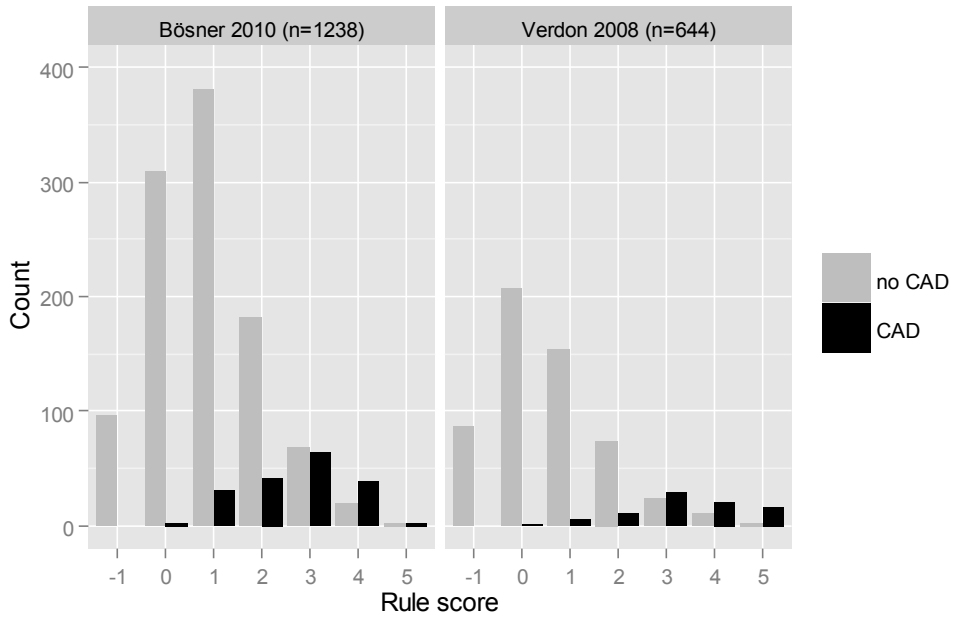


Figure 2 presents counts of patients with each rule score separately for patients with and without CAD using data of the third imputed data set of the Bösner 2010[11] and Verdon 2008[2] study, respectively. These studies were the only ones that collected data on all six of the parameters appearing in the final rule (chest pain rule III).
Note: In Verdon 2008 [2] the predictor “history of CAD” was not asked in a direct way, but study physicians were asked to report up to 3 main diagnoses. Therefore, the information on the predictor may be less reliable in this sample.

Table 1: Characteristics of studies and patients included in analysis.

	Sox 1990 [4]	Buntinx 1992 [9]	Nilsson 2003 [10]	Verdon 2008 [2]	Bösner 2010 [11]
Country	USA	Belgium	Sweden	Switzerland	Germany
Setting	1 Drop-in clinic with multiple PCPs	25 PCPs	3 Health care centres each served by 4 PCPs	58 PCPs in private practice	74 PCPs in private practice
N*	395	299	523	644	1238
Age (mean, sd)	41.5 (14.2)	47.1(17.3)	54.2 (14.4)	55.4 (19.0)	59.4 (13.9)
Female sex (%)	52.8	48.5	50.3	52.3	56.2
Reference standard	Delayed-type reference standard	Delayed-type reference standard	Delayed-type reference standard	Delayed-type reference standard	Delayed-type reference standard
Duration of follow-up	At least 1 year	2 weeks to 2 months	3 months	12 months	6 months
Reference diagnosis established by	2 internist-investigators independently assigned diagnosis.	Treating physicians	Treating physicians	Treating physicians/ diagnoses were reviewed by a group of independent clinicians	Independent expert panel (1GP, 1 cardiologist, 1 research fellow)
Prevalence of CAD as cause of chest pain (%)	7.4%	10.4%	11.9%	13.2%	14.5%

* Number of patients aged ≥18y with valid reference diagnosis

PCP: primary care physicians

Table 2: Results of the multivariate meta-analysis.

Predictors†	Number studies/ Number patients‡	Regression coefficient§ (Standard error)	Odds ratio for CAD diagnosis (95% CI)
Older Age¶	5/ 3099	1.43 (0.16)*	4.19 (3.06 to 5.7)*
Physician initially suspected a serious condition**	3/ 2181	1.30 (0.19)*	3.67 (2.53 to 5.3)*
CP that feels like pressure	4/ 2576	0.64 (0.18)*	1.90 (1.33 to 2.7)*
CP related to effort	4/ 2576	1.19 (0.17)*	3.29 (2.36 to 4.6)*
History of CAD	2/ 1633	1.73 (0.22)*	5.64 (3.66 to 8.7)*
Pain reproducible by palpation	4/ 2576	-1.54 (0.24)*	0.21 (0.13 to 0.3)*
Male sex	5/ 3099	0.28 (0.14)*	1.32 (1.01 to 1.7)*
Emergency visit	4/ 1861	-0.18 (0.19)	0.84 (0.58 to 1.2)
History of CP	3/ 1338	0.43 (0.25)	1.54 (0.94 to 2.5)
Patient assumed CP was related to heart	2/ 1761	1.13 (0.23)*	3.10 (1.97 to 4.9)*
Retrosternal CP	4/ 2576	0.25 (0.17)	1.28 (0.92 to 1.8)
Radiation to neck, jaw	4/ 2576	0.61 (0.29)*	1.84 (1.04 to 3.2)*
Stabbing CP	4/ 2576	-0.43 (0.21)*	0.65 (0.43 to 1.0)*
Nausea	3/ 1932	-0.09 (0.34)	0.91 (0.47 to 1.8)
Sputum	3/ 1338	-0.75 (1.13)	0.47 (0.05 to 4.3)
Abnormal findings pulmonary auscultation	3/ 1338	-0.45 (0.62)	0.64 (0.19 to 2.1)
Abnormal findings cardiac auscultation	2/ 1039	0.75 (1.09)	2.12 (0.25 to 17.9)
History of hypertension	2/ 1633	0.35 (0.21)	1.42 (0.94 to 2.1)
History of smoking	3/ 1932	0.63 (0.26)*	1.88 (1.13 to 3.1)*

* $p \leq 0.05$

† Predictors listed in the predictor candidate list and entered in the model.

‡ Number of studies refers to the number that routinely collected the item. Number of patients refers to number of patients who gave a response to the item.

§ The data are the result of regression analyses of five meta-data sets, each containing all patients in the five studies but differing in the values imputed to missing data in a study. Estimates of regression coefficients and standard errors gained from the five imputed datasets were combined according to the rules proposed by Rubin [16].

¶ Age is included in the model as a binary variable with gender-specific thresholds (male: ≥ 55 y, female ≥ 65 y).

CP: chest pain, CAD Coronary Artery Disease

** This assessment was based on a very first impression or gut feeling.

Regression coefficients below '0' and odds ratios below 1 indicate that the presence of the symptom or sign decreases the likelihood of CAD. Regression coefficients above '0' and odds ratios above 1 indicate that the presence of the symptom or sign increases the likelihood of CAD.

Table 3. Discriminatory power of three different chest pain rules.		
Predictors in the model. Each predictor was coded as “yes” or “no”.	Weight of the predictor if coded as “yes”.	AUC
Chest pain rule I		
Older age† Male sex Physician initially suspected a serious condition Patient assumed CP was related to heart Radiation to neck, jaw Stabbing CP Chest discomfort feels like “pressure” CP related to effort Pain reproducible by palpation History of smoking History of CAD	+1.49 +0.25 +1.32 +1.14 +0.63 - 0.46 +0.69 +1.23 - 1.59 +0.57 +1.81	0.87
Chest pain rule II		
Older age† Physician initially suspected a serious condition Chest discomfort feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD	+1.55 +1.35 +0.84 +1.25 - 1.70 +1.71	0.85
Chest pain rule III		
Older age† Physician initially suspected a serious condition Chest discomfort feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD	+1 +1 +1 +1 - 1 +1	0.84
CP: chest pain, CAD: coronary artery disease, AUC: Area under the ROC curve *Chest pain rule I:* All predictors that were significant (α≤0.05) were included and weighted according to the regression coefficients. *Chest pain rule II*: Rule I was simplified by excluding the least significant predictor stepwise until only six highly significant predictors (p<0.01) were included in the model. *Chest pain rule III*: Rule II was simplified by rounding the regression coefficients estimates.to unity. * Weights above ‘1’ indicate that the presence of the symptom or sign increases the likelihood of CAD. Weights values below 1 indicate that the presence of the symptom or sign decreases the likelihood of CAD. † Age is included in the model as a binary variable (male: ≥ 55 y, female ≥ 65 y).		

Table 4: Diagnostic accuracy of chest pain rule III in the two studies that routinely collected all of the predictors using a threshold of 2 points (CAD negative if score < 2; CAD positive if score ≥ 2).

Sample	Sensitivity % (95% CI)	Specificity % (95% CI)	+ LR (95% CI)	-LR (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Bösner 2010[11]	82.0 (75.1-87.3)	73.8 (70.9-76.4)	3.13 (2.74-3.57)	0.24 (0.17-0.34)	34.7 (30.2-39.5)	96.0 (94.3-97.2)
Verdon 2008[2]	88.2 (79.5-93.6)	82.2 (78.7-85.2)	4.95 (4.08-6.02)	0.14 (0.08-0.26)	43,0 (35.8-50.4)	97.9 (96.1-98.9)

Predictors and respective score values included in chest pain rule III:
age, physician initially suspected a serious condition, chest discomfort feels like “pressure,” chest pain related to effort, pain reproducible by chest wall palpation, history of CAD; variables were weighted as ‘1’ if regression coefficient > 0 and as ‘-1’ if coefficient < 0.
+LR: positive likelihood ratio; -LR: negative likelihood ratio (the likelihood ratio is the amount that the odds of CAD change if the score is above (LR-positive) or below (LR-negative) the threshold chest pain score); PPV: positive predictive value; NPV: negative predictive value.
Note: In Verdon 2008[2] the predictor “history of CAD” was not asked in a direct way, but study physicians were asked to report up to 3 main diagnoses. Therefore, the information on this predictor may be less reliable in this sample.

CONFLICT OF INTEREST/FINANCIAL DISCLOSURE:

The authors declare that they have no competing interests.

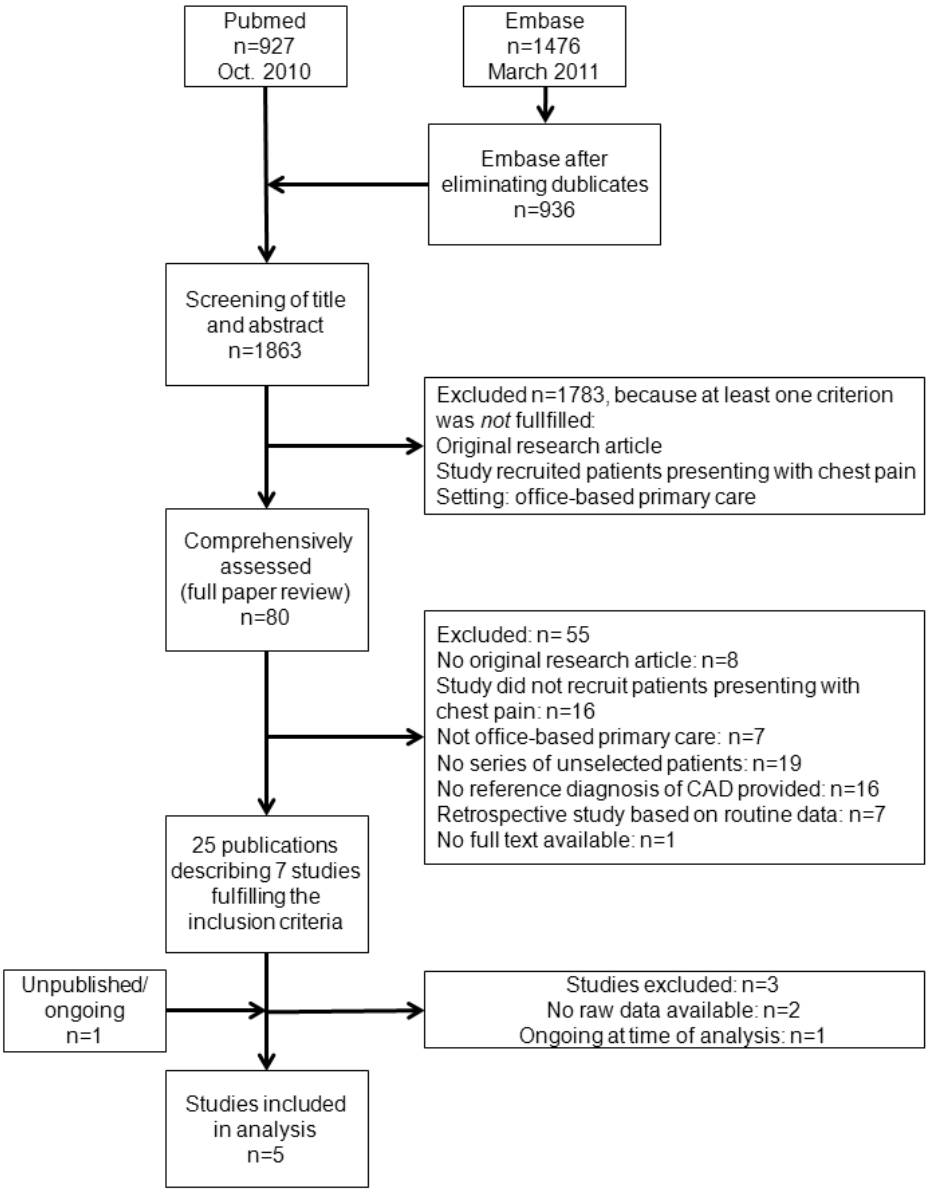
Supplement/ web only tables and figures

Table of contents:

Supplement 1: Search

We searched PubMed (October 2010) and EMBASE (March 2011). We used search terms "chest pain" and "primary care." Search strategies included subject headings (MeSH, Embtree) as well as free-text terms. Additionally, we searched the online published abstracts of the annual meetings of the North American Primary Care Research Group and the European General Practice Research Network.Two reviewers independently screened title and abstracts. They retrieved and screened full text articles of all potentially relevant studies. A third reviewer reassessed all selected full text articles for relevance. The three reviewers resolved disagreements by discussion.

Figure 1. Flow of search



Supplement 2: Predictors included in the analysis

Table 1a: Predictors and percentages of missing values

Predictor	Sox 1990	Buntinx 1992	Nilsson 2003	Verdon 2008	Bösner 2010	All
Age	0.25	0	0	0	0	0.03
Sex	0	0.33	0	0	0	0.03
Context of consultation						
Did the patient require a home visit?	-	0	-	0.16	0	0.05
Did the PCP know the patient?	0	-	-	0.62	0.32	0.35
Was the encounter an emergency/ an urgent visit?	0	0.67	0	0.31	-	0.21
Was chest pain the main complaint?	-	0	-	0.62	0.24	0.32
Was CP present during consultation?	-	-	-	2.48	1.7	1.97
Had the patient experienced CP before?	1.01	2.34	-	2.64	-	2.09
PCPs'/ Patients' concern						
Did the PCP initially (very first impression) suspected a serious condition?	-	0.33	-	4.81	3.23	3.30
Was the patient anxious?	5.57	0.67	-	0.47	2.5	2.25
Did the patient think the pain was related to the heart?	-	-	7.07	-	11.23	9.99
Pain characteristics - localization						
Retrosternal CP	0.76	0.67	-	0	0.08	0.23
Precordial CP	0.76	0.67	-	0	0.08	0.23
Left-sided CP	0.76	-	-	0	0.08	0.18
Right-sided CP	0.76	-	-	0	0.08	0.18
Pain characteristics – radiation						
Band-shaped radiation of pain	5.82	4.35	-	0	0.08	1.44
CP radiating to left shoulder/arm	5.82	4.35	-	0	0	1.40
CP radiating to right shoulder/arm	5.82	-	-	0	0	1.01
CP radiating to neck, jaw, bottom side of face	5.82	4.35	-	0	0	1.40
CP radiating to abdomen	5.82	4.35	-	0	0	1.40
Pain characteristics intensity						
Intensity of CP	1.77	-	-	1.09	-	1.35
Pain characteristics – quality/ word descriptors						
Stabbing pain	2.53	3.01	-	0	0.65	1.05
CP feels like "pressure"	2.53	3.01	-	0	0	0.74
Burning pain	2.53	3.01	-	0	0.65	1.05
Dull pain	2.53	-	-	0	0.65	0.79
Pain characteristics – duration and course						
Time since first occurrence of the pain	9.62	5.69	0.57	-	1.78	3.26
Continuous pain	0.76	0	-	9.94	0.57	2.87
Duration of a typical pain episode	16.96	-	-	9.94	1.29	6.46
Frequency of CP	19.75	-	-	-	18.01	18.43
Clinical Course of pain	3.54	-	-	3.42	-	3.46
Pain depend on/ provoked by / related to						
CP related to breathing	3.29	0	-	0	3.55	2.21
CP related to movement	3.29	0	-	0	3.55	2.21
CP related to swallow	3.29	0	-	0	-	0.97
CP related to ingestion	-	-	-	0	3.55	2.34
CP related to effort/ exercise	3.29	0	-	0	3.55	2.21
CP related to cough	3.29	0	-	0	-	0.97
CP related to body position	10.13	-	-	0	-	3.85
Relief after administration of NTG	91.14	78.60	-	-	-	85.73
Relief after administration of antacid	64.81	79.93	-	-	-	71.33

Additional complaints/ associated symptoms						
Fever	4.56	0	-	0	-	1.35
Cough	0.76	0	-	0	0	0.12
Dyspnea	1.77	0	-	0	0	0.27
Sweating	0	4.01	-	0	3.47	2.14
Paleness	-	2.68	-	0	3.23	2.20
Nausea	0	0	-	-	0	0
Signs of a cold/ respiratory infect	8.1	-	-	-	0	1.96
Sputum	71.14	0	-	0	-	21.00
Reduced state of consciousness	0	-	-	0	-	0
Physical examination						
Heart rate	-	22.41	-	0	17.61	13.07
Blood pressure	-	16.72	-	-	10,26	11.52
Arrhythmia	-	13.04	-	0	-	4.14
Pulmonary auscultation	77.97	0	-	0	-	23.02
Cardiac auscultation	77.97	-	-	0	-	29.64
Pain reproducible by palpation	2.78	4.68	-	0	27.3	14.09
Medical history – coronary risk factors, previous cardiac events						
History of dyslipidemia/ hyperlipidemia	0	-	-	-	9.05	6.86
History of diabetes (diabetes mellitus)	0	-	-	-	9.05	6.86
Family history of myocardial infarction	5.06	14.05	-	-	9.05	9.01
History of hypertension	0	-	-	-	9.05	6.86
Smoking	1.77	4.35	-	-	9.05	6.83
History of myocardial infarction	0	-	-	-	-	0
History of known CAD	0	-	-	-	9.05	6.86

PCP: primary care physician; CP: chest pain; NTG: nitro-glycerine; CAD: coronary artery disease

Table 1 b: Description of the predictors within the individual studies

	Age Available in all data sets as a continuous variable (years).
	Sex Available in all data sets as a dichotomous variable.
	Context of consultation
	Did the patient require a home visit? Buntinx 1992: dichotomous variable Verdon 2008: categorical variable (telephone, home visit, practice) Bösner 2010: dichotomous variable Nilsson 2003: na (All encounters took place in the primary health care centre). Sox 1990: na (All encounters took place in the primary health care centre).
	Did the PCP know the patient? Buntinx 1992: na Verdon 2008: dichotomous variable Bösner 2010: dichotomous variable Nilsson 2003: na Sox 1990: na
	Was the encounter an emergency/ an urgent visit? Buntinx 1992: dichotomous variable Verdon 2008: dichotomous variable Bösner 2010: na Nilsson 2003: dichotomous variable Sox 1990: na
	Was chest pain the main complaint? In general, all patients in all studies had had chest pain. But not in all patients chest pain was the main complaint.

	Buntinx 1992: open-ended question, free text Verdon 2008: dichotomous variable Bösner 2010: dichotomous variable Nilsson 2003: na Sox 1990:na
	Was CP present during consultation? Buntinx 1992: na Verdon 2008: dichotomous variable Bösner 2010: dichotomous variable Nilsson 2003: na Sox 1990: na
	Had the patient experienced CP before? Buntinx 1992: dichotomous variable Verdon 2008: dichotomous variable Bösner 2010: na Nilsson 2003: na Sox 1990: dichotomous variable
	GPs'/ Patients' concern
	Did the PCP initially (very first impression) suspected a serious condition? Buntinx 1992: dichotomous variable Verdon 2008: combination of two dichotomous variables both describing impressions of the GP Bösner 2010: dichotomous variable Nilsson 2003: na Sox 1990: na
	Was the patient anxious? Buntinx 1992: categorical variable describing the impression of the GP Verdon 2008: combination of two categorical variables describing the impression of the GP and the expression of the patient Bösner 2010: categorical variable, definitions of categories provided Nilsson 2003: na Sox 1990: na
	Did the patient think the pain was related to the heart? Buntinx 1992: na Verdon 2008: na Bösner 2010: dichotomous variable Nilsson 2003: dichotomous variable Sox 1990: na
	Pain characteristics - localization The four variables that are related to localisation of the pain are not exclusive. That means that the pain for example could be localized in the retrosternal area of the chest *and* in the left or right side.
	Retrosternal CP Buntinx 1992: categorical variable describing the localisation of the pain (retrosternal, precordial, others) Verdon 2008: derived from a graphical presentation of the pain area in the questionnaire Bösner 2010: derived from a graphical presentation of the pain area in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the localisation of the pain
	Precordial CP Buntinx 1992: categorical variable describing the localisation of the pain (retrosternal, precordial, others) Verdon 2008: derived from a graphical presentation of the pain area in the questionnaire Bösner 2010: derived from a graphical presentation of the pain area in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the localisation of the pain
	Left-sided CP Buntinx 1992: na Verdon 2008: derived from a graphical presentation of the pain area in the questionnaire Bösner 2010: derived from a graphical presentation of the pain area in the questionnaire Nilsson 2003: na USA: categorical variable describing the localisation of the pain
	Right-sided CP Buntinx 1992: na Verdon 2008: derived from a graphical presentation of the pain area in the questionnaire Bösner 2010: derived from a graphical presentation of the pain area in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the localisation of the pain
	Pain characteristics – radiation The four variables that are related to radiation of the pain are not exclusive.
	Band-shaped radiation of pain Buntinx 1992: categorical variable describing the radiation of the pain Verdon 2008: derived from a graphical presentation of the pain radiation in the questionnaire

	Bösner 2010: derived from a graphical presentation of the pain radiation in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the radiation of the pain
	CP radiating to left shoulder/arm Buntinx 1992: categorical variable describing the radiation of the pain Verdon 2008: derived from a graphical presentation of the pain radiation in the questionnaire Bösner 2010: derived from a graphical presentation of the pain radiation in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the radiation of the pain
	CP radiating to right shoulder/arm Buntinx 1992: na Verdon 2008: derived from a graphical presentation of the pain radiation in the questionnaire Bösner 2010: derived from a graphical presentation of the pain radiation in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the radiation of the pain
	CP radiating to neck, jaw, bottom side of face Buntinx 1992: categorical variable describing the radiation of the pain Verdon 2008: derived from a graphical presentation of the pain radiation in the questionnaire Bösner 2010: derived from a graphical presentation of the pain radiation in the questionnaire Nilsson 2003: na USA: categorical variable describing the radiation of the pain
	CP radiating to abdomen Buntinx 1992: categorical variable describing the radiation of the pain Verdon 2008: derived from a graphical presentation of the pain radiation in the questionnaire Bösner 2010: derived from a graphical presentation of the pain radiation in the questionnaire Nilsson 2003: na Sox 1990: categorical variable describing the radiation of the pain
	Pain characteristics - intensity
	Intensity of CP Buntinx 1992: na Verdon 2008: ordinal variable Bösner 2010: na Nilsson 2003: na Sox 1990: ordinal variable
	Pain characteristics – quality/ word descriptors The variables related to the quality of pain are not exclusive, i.e. it could be that a patient described his pain as oppressive and burning.
	Stabbing pain Buntinx 1992: categorical (5) variable describing quality of pain Verdon 2008: categorical (6) variable describing quality of pain Bösner 2010: categorical (4) variable describing quality of pain Nilsson 2003: na Sox 1990: categorical (10) variable describing quality of pain
	Pressure Buntinx 1992: categorical (5) variable describing quality of pain Verdon 2008: categorical (6) variable describing quality of pain Bösner 2010: categorical (4) variable describing quality of pain Nilsson 2003: na Sox 1990: categorical (10) variable describing quality of pain
	Burning pain Buntinx 1992: categorical (5) variable describing quality of pain Verdon 2008: categorical (6) variable describing quality of pain Bösner 2010: categorical (4) variable describing quality of pain Nilsson 2003: na Sox 1990: categorical (10) variable describing quality of pain
	Dull pain Buntinx 1992: na Verdon 2008: categorical (6) variable describing quality of pain Bösner 2010: categorical (4) variable describing quality of pain Nilsson 2003: na Sox 1990: categorical (10) variable describing quality of pain
	Pain characteristics – duration and course
	Time since first occurrence of the pain Buntinx 1992: ordinal variable (<1hour, <1day, >1day) Verdon 2008: na Bösner 2010: ordinal variable (<1hour, <1day, >1day) Nilsson 2003: ordinal variable (> 1 week, 1 day – 1 week, < 1 day) Sox 1990: open-ended question, input in days.

	Continuous pain Buntinx 1992: categorical variable describing the course of the pain (continuously, changing, only if palpated) Verdon 2008: ordinal (6) variable describing the duration of a pain episode Bösner 2010: ordinal (6) variable describing the duration of a pain episode Nilsson 2003: na Sox 1990: categorical (3) variable (constant, intermittent, steady with variation)
	Duration of a typical pain episode Buntinx 1992: na Verdon 2008: categorical (6) variable describing the duration of a pain episode Bösner 2010: categorical (6) variable describing the duration of a pain episode Nilsson 2003: na Sox 1990: open-ended question, input in minutes
	Frequency of CP Buntinx 1992: na Verdon 2008: na Bösner 2010: categorical (3) question Nilsson 2003: na Sox 1990: open-ended question, input number per day
	Clinical Course of pain Buntinx 1992: na Verdon 2008: categorical (5) variable Bösner 2010: na Nilsson 2003: na Sox 1990: categorical (5) variable
	Pain characteristics - classification
	Pain depend on/ provoked by / related to The variables related to the "pain depend on" are not exclusive, i.e. it could be that a patient described his pain as being related to e.g. effort and breathing.
	CP related to breathing Buntinx 1992: categorical variable (5) describing factors/ activities that cause the pain Verdon 2008: categorical variable (5) describing factors/ activities that cause in the pain Bösner 2010: categorical variable (4) describing factors/ activities that cause in the pain Nilsson 2003:na Sox 1990: categorical variable (9) describing factors/ activities that cause in the pain
	CP related to movement Buntinx 1992: categorical variable (5) describing factors/ activities that cause the pain Verdon 2008: categorical variable (5) describing factors/ activities that cause in the pain Bösner 2010: categorical variable (4) describing factors/ activities that cause in the pain Nilsson 2003:na Sox 1990: categorical variable (9) describing factors/ activities that cause in the pain
	CP related to swallow Buntinx 1992: categorical variable (5) describing factors/ activities that cause the pain Verdon 2008: categorical variable (5) describing factors/ activities that cause in the pain Bösner 2010: na Nilsson 2003:na Sox 1990: categorical variable (9) describing factors/ activities that cause in the pain
	CP related to ingestion Buntinx 1992: na Verdon 2008: categorical variable (5) describing factors/ activities that cause in the pain Bösner 2010: categorical variable (4) describing factors/ activities that cause in the pain Nilsson 2003:na Sox 1990: na
	CP related to effort/ exercise Buntinx 1992: categorical variable (5) describing factors/ activities that cause the pain Verdon 2008: categorical variable (5) describing factors/ activities that cause the pain Bösner 2010: categorical variable (4) describing factors/ activities that cause the pain G2: na Nilsson 2003:na Sox 1990: categorical variable (9) describing factors/ activities that cause the pain
	CP related to cough Buntinx 1992: categorical variable (5) describing factors/ activities that cause the pain Verdon 2008: categorical variable (5) describing factors/ activities that cause in the pain Bösner 2010: na Nilsson 2003:na Sox 1990: categorical variable (9) describing factors/ activities that cause in the pain
	CP related to body position Buntinx 1992: na

	Verdon 2008: categorical variable (5) describing factors/ activities that cause in the pain Bösner 2010: na Nilsson 2003:na Sox 1990: categorical variable (9) describing factors/ activities that cause in the pain
	Relief after administration of NTG Buntinx 1992: categorical variable (relief, no relief, not tried) Verdon 2008: na Bösner 2010: na Nilsson 2003: na Sox 1990: categorical variable (relief, no relief, not tried)
	Relief after administration of antacid Buntinx 1992: categorical variable (relief, no relief, not tried) Verdon 2008: na Bösner 2010: na Nilsson 2003: na Sox 1990: categorical variable (relief, no relief, not tried)
	Additional complaints/ associated symptoms The following variables described if one or more of several additional complaints occurred. They are not exclusive, that means that 2 or more additional symptoms could occur in the same patient.
	Fever Buntinx 1992: categorical (6) variable describing additional symptoms Verdon 2008: combination of two variables (reported by patient [no threshold provided], result of physical examination [>37.8°C]) Bösner 2010: na Nilsson 2003:na Sox 1990: combination of two variables (reported by patient [≥100°F], result of physical examination [≥100°F])
	Cough Buntinx 1992: categorical (6) variable describing additional symptoms Verdon 2008: combination of two variables (reported by patient, result of physical examination) Bösner 2010: categorical (5) variable describing additional symptoms Nilsson 2003: na Sox 1990: Combination of two variables (additional symptoms, other complaints caused patient to come in)
	Dyspnea Buntinx 1992: categorical (6) variable describing additional symptoms (dyspnoea at rest) Verdon 2008: combination of two variables: reported by patient (difficulty breathing) and result of physical examination (tachypnea) Bösner 2010: categorical (5) variable describing additional symptoms (dyspnoea) Nilsson 2003: na Sox 1990: combination of two variables: reported by patient (difficulty breathing) and result of physical examination (tachypnea)
	Sweating Buntinx 1992: dichotomous variable describing GP's impression during consultation Verdon 2008: categorical variable describing the results of the physical examination Bösner 2010: categorical (5) variable describing GP's impressions during consultation Nilsson 2003: na Sox 1990: categorical variable describing symptoms the patients experienced during the chest episode
	Paleness Buntinx 1992: dichotomous variable describing GP's impression during consultation Verdon 2008: categorical variable describing the results of the physical examination Bösner 2010: dichotomous variable describing GP's impression during consultation Nilsson 2003: na Sox 1990: na
	Nausea Buntinx 1992: na Verdon 2008:na Bösner 2010: categorical (5) variable describing additional symptoms Nilsson 2003:na Sox 1990: categorical variable describing symptoms the patients experienced during the chest episode
	Signs of a cold/ respiratory infect Buntinx 1992: na Verdon 2008: na Bösner 2010: categorical (5) variable describing additional symptoms Nilsson 2003: na Sox 1990: categorical (3) variable describing symptoms beginning at time of first chest pain
	Reduced state of consciousness Buntinx 1992: na Verdon 2008: categorical variable describing additional symptoms

	Bösner 2010: na Nilsson 2003: na Sox 1990: categorical variable describing cough if present.
	Physical examination
	Heart rate (Heart rate ordinal: bradycardia, tachycardia, normal) Buntinx 1992: derived from continuous variable (b/m), (bradycardia<60b/m, tachycardia>100b/m) Verdon 2008: variable describing results of the physical examination, no threshold provided Bösner 2010: derived from continuous variable (b/m), (bradycardia<60b/m, tachycardia>100b/m) Nilsson 2003: na Sox 1990: na
	Blood pressure (ordinal variable high, normal, low) Buntinx 1992: derived from continuous variable (High blood pressure if sys> 150 or dia >90, low blood pressure if sys<100 or dia < 60) Verdon 2008: na Bösner 2010: derived from continuous variable High blood pressure if sys> 150 or dia >90, low blood pressure if sys<100 or dia < 60) Nilsson 2003: na Sox 1990: na
	Arrhythmia Buntinx 1992: ordinal (3) variable Verdon 2008: variable describing results of the physical examination Bösner 2010: na Nilsson 2003: na Sox 1990: na
	Pulmonary auscultation Buntinx 1992: dichotomous variable Verdon 2008: variable describing results of the physical examination Bösner 2010: na Nilsson 2003: na Sox 1990: variable describing results of the physical examination
	Cardiac auscultation Buntinx 1992: na Verdon 2008: variable describing results of the physical examination Bösner 2010: na Nilsson 2003: na Sox 1990: variable describing results of the physical examination
	Pain reproducible by palpation Buntinx 1992: ordinal variable (4) Verdon 2008: variable describing results of the physical examination Bösner 2010: dichotomous variable Nilsson 2003: na Sox 1990: variable describing results of the physical examination
	Medical history – coronary risk factors, previous cardiac events ***The following variable are related to information regarding the presence of cardiovascular risk factors or a history of previous cardiac events***
	History of dyslipidemia/ hyperlipidemia Buntinx 1992: na Verdon 2008: na Bösner 2010: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by GP Nilsson 2003: na Sox 1990: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by patient
	History of diabetes (diabetes mellitus) Buntinx 1992: na Verdon 2008: na Bösner 2010: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by GP Nilsson 2003: na Sox 1990: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by patient
	Family history of myocardial infarction Buntinx 1992: categorical (4) variable describing family history Verdon 2008: na Bösner 2010: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by GP Nilsson 2003: na Sox 1990: categorical variable describing the absence/ presence of risk factors, no definition provided,

	reported by patient
	History of hypertension Buntinx 1992: na Verdon 2008: na Bösner 2010: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by GP Nilsson 2003: na Sox 1990: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by patient
	Smoking Buntinx 1992: dichotomous variable, no definition provided Verdon 2008:na Bösner 2010: categorical variable describing the absence/ presence of risk factors, no definition provided, reported by GP Nilsson 2003: na Sox 1990: dichotomous variable, no definition provided
	History of myocardial infarction Buntinx 1992: na Verdon 2008: free text field asking for known conditions Bösner 2010: na Nilsson 2003: na Sox 1990: categorical variable describing the known conditions, no definition provided, reported by patient
	History of known CAD Buntinx 1992: na Verdon 2008: free text field asking for up to 3 known conditions Bösner 2010: categorical variable describing the known conditions, no definition provided, reported by GP Nilsson 2003: na Sox 1990: categorical variable describing the known conditions, no definition provided, reported by patient

Supplement 3: Equation for logistic regression using study-specific intercept and study-specific indicators.

The logistic regression model with study-specific intercepts and study-specific indicators is defined as:

$$Logit(P(Y_{ij}=1)) = \beta_{0i} + \sum_{k=1}^{P} \beta_k X_{kij} * \mathrm{I}_{\mathrm{ki}} \quad i=1,2,...,5;\ j=1,2,...,n_{i,} \qquad (1)$$

where Y_{ij} is the outcome variable for patient j in study i (0 indicates that CAD is absent; 1 that CAD is present in that individual), X_{kij} represents the kth covariate for patient j in study i, β_{0i} (i=1,2,…,5) is the study-specific intercept for the ith study, $\beta_k$is the coefficient for the covariate/predictor X_k, I_{ki} is the study indicator for the kth covariate (1 if the variable is available in individual study i, or 0 if the variable is not available in individual study i), P is the total number of all candidate predictors across studies, and n_i is the number of patients in study i. As we have only five studies, we used a fixed effects model rather than a random effects model, for which 10 studies or more would be typically needed.

We combined all predictors that were statistically significant ($\alpha \leq 0.05$) into one linear score to be used for classifying patients for CAD

$$\text{Score} = \sum_{k=1}^{P} {}_k X_k * I_{\mathrm{k}} \qquad (2)$$

where X_k represents the kth predictor-value for the patient, I_k is the data availability-indicator for the kth predictor (1 if the predictor is available, or 0 if the predictor is not available), $\hat{\beta}_k$ is the estimated coefficient for the predictor X_k,, P is the number of predictors.

Supplement 4: Results of the cross validation

In order to do an internal validation, we used a 3-fold cross-validation approach. The whole sample was randomly partitioned in three sets (1, 2 and 3). Then we iterated three times the following procedure:

1. Take one of the sets as test sample, the other two as learning sample
2. Using the learning sample, refit the full model, and simplify it gradually to a simplified model with the 6 most important predictors, and associated further simplified clinical tool (with all coefficients rounded to 1 or -1).
3. For each of the simplified models (with original and rounded coefficients), measure sensitivity, specificity etc. using the test sample. So the model built with the learning sample is then tested with another test sample.

Supplement Table 2: Regression coefficients and standard errors obtained from the IPD meta-analysis for each cross-validation.

Note that the results of the cross-validation showed that the respective models had similar predictors and the predictors had similar coefficients.

Parameter		Cross-validation I	Cross-validation II	Cross-validation III
Intercept	Sox 1990	-4.857 (1.057)**	-4.882 (1.381)**	-4.723 (1.034)**
	Buntinx 1993	-3.972 (0.727)**	-3.960 (0.808)**	-4.319 (0.782)**
	Nilsson 2003	-3.900 (0.415)**	-3.561 (0.377)**	-3.547 (0.361)**
	Verdon 2008	-4.049 (0.411)**	-3.918 (0.392)**	-4.169 (0.402)**
	Bösner 2010	-5.269 (0.466)**	-4.991 (0.416)**	-5.227 (0.442)**
Age		1.401 (0.195)**	1.507 (0.193)**	1.431 (0.190)**
Male sex		0.226 (0.177)	0.179 (0.172)	0.460 (0.173)**
Emergency visit		-0.024 (0.234)	-0.268 (0.247)	-0.276 (0.239)
History of CP		0.503 (0.306)	0.663 (0.303)**	0.146 (0.316)
PCP initially suspected a serious condition		1.300 (0.232)**	1.141 (0.226)**	1.520 (0.232)**
Patient assumed CP was related to heart		1.407 (0.324)**	1.002 (0.280)**	1.045 (0.279)**
Retrosternal CP		0.480 (0.215)**	0.034 (0.207)	0.237 (0.212)
Radiation to neck, jaw		0.733 (0.338)**	0.410 (0.366)	0.710 (0.363)*
Stabbing CP		-0.577 (0.259)**	-0.266 (0.252)	-0.445 (0.261)*
CP feels like “pressure”		0.289 (0.216)	0.878 (0.211)**	0.747 (0.221)**
CP related to effort		1.390 (0.205)**	1.174 (0.204)**	1.081 (0.206)**
Nausea		-0.579 (0.412)	0.125 (0.396)	0.162 (0.383)
Sputum		-0.696 (1.136)	-1.096 (1.366)	-0.524 (1.125)
Abnormal findings (pulmonary auscultation)		-0.668 (0.661)	-0.513 (0.806)	-0.178 (0.612)
Abnormal findings (cardiac auscultation)		0.897 (0.938)	0.763 (1.492)	0.639 (1.181)
Pain reproducible by palpation		-1.330 (0.284)**	-1.827 (0.303)**	-1.474 (0.299)**
History of hypertension		0.401 (0.280)	0.335 (0.248)	0.333 (0.255)
History of smoking		0.765 (0.306)**	0.800 (0.330)**	0.316 (0.313)
History of CAD		1.578 (0.274)**	1.822 (0.261)**	1.863 (0.270)**

CP: chest pain, PCP: primary care physician, CAD: coronary artery disease.
** The variable was significant predictor at 5% level of significance (p-value < 0.05) within the model of the respective cross-validation

Supplement Table 3: Discriminatory power for chest pain rules and each cross validation. Note, that all 3 cross validation procedures resulted in the same simplified diagnostic model (model II) with comparable discriminative power.

Chest pain rule		Cross-validation I	Cross-validation II	Cross-validation III
I	Predictors	Age PCP initially suspected a serious condition Patient assumed CP was related to heart Retrosternal CP Radiation to neck, jaw Stabbing CP CP related to effort Pain reproducible by palpation History of smoking History of CAD	Age History of CP PCP initially suspected a serious condition Patient assumed CP was related to heart CP feels like “pressure” CP related to effort Pain reproducible by palpation History of smoking History of CAD	Age Male sex PCP initially suspected a serious condition Patient assumed CP was related to heart CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD
	AUC	0.87	0.89	0.87
II	Predictors	Age PCP initially suspected a serious condition CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD	Age PCP initially suspected a serious condition CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD	Age PCP initially suspected a serious condition CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD
	AUC	0.85	0.86	0.85
III	Predictors	Age PCP initially suspected a serious condition CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD	Age PCP initially suspected a serious condition CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD	Age PCP initially suspected a serious condition CP feels like “pressure” CP related to effort Pain reproducible by palpation History of CAD
	AUC	0.83	0.85	0.84

CP: chest pain, PCP: primary care physician, CAD: coronary artery disease, AUC: area under the curve.

Chest pain rule I included all predictors which were significant at α level =0.05. Predictors were weighted according to the coefficient estimates.

Chest pain rule II: Rule I was simplified by stepwise exclusion of the least significant predictor unless only six predictors remained.

Chest pain rule: Variables were the same like in rule II, but predictors were equally weighted (1 if $\hat{\beta}_k$ > 0 and -1 if $\hat{\beta}_k$ < 0)

Supplement Table 4: Parameter estimates for a simplified chest pain rule (rule II) with only 6 predictors for each cross validation.
Note, that parameter estimates for the regression coefficients were similar across cross-validation procedures.

		Cross-validation 1	Cross-validation 2	Cross-validation 3
Intercept	Sox 1990	-3.869 (0.324)**	-3.971 (0.329)**	-3.991 (0.326)**
	Buntinx 1993	-3.906 (0.351)**	-3.881 (0.345)**	-4.090 (0.370) **
	Nilsson 2003	-2.729 (0.205)**	-2.955 (0.218)**	-2.755 (0.204) **
	Verdon 2008	-3.645 (0.285)**	-3.694 (0.278)**	-3.929 (0.296) **
	Bösner 2010	-3.858 (0.251)**	-4.042 (0.257)**	-4.080 (0.268) **
Age		1.519 (0.181)**	1.591 (0.183)**	1.550 (0.181)**
PCP initially suspected a serious condition		1.371 (0.217)**	1.155 (0.216)**	1.547 (0.221)**
CP feels like “pressure”		0.635 (0.191)**	1.003 (0.194)**	0.892 (0.201)**
CP related to effort		1.399 (0.188)**	1.253 (0.197)**	1.102 (0.193)**
Pain reproducible by palpation		-1.560 (0.258)**	-1.904 (0.276)**	-1.629 (0.274)**
History of CAD		1.466 (0.254)**	1.799 (0.245)**	1.882 (0.249)**
CP: chest pain, PCP: primary care physician, CAD: coronary artery disease. ** p-value < 0.001				

Supplement 5: Results of the sensitivity analysis testing the rule in patients with acute and non-acute pain.

Supplement Table 5: Likelihood ratios for individual predictors of the CPR separately in patients with acute and non-acute pain.
The definition of acute pain was based on the time since the initial onset of pain (onset of chest pain≤24h versus onset of chest pain>24h). This variable was available in 4 studies (Sox 1990, Buntinx 1992, Nilsson 2003, and Bösner 2010) In Verdon 2008 this variable was not available and the determination of 'acute' was based on whether the visit was considered to be an emergency.

Variable 'Higher age' was derived from patient age and gender. A patient who was male and less than 55 years old or was a female who was less than 65 years old was classified as younger; otherwise the patient was classified as older. The defining data were collected in all studies. An older patient adds +1 to the rule score.
Variable 'PCP initially suspected a serious condition' was collected in studies Verdon 2008, Buntinx 1992 and Bösner 2010. A positive response adds +1 to the rule score.
Variable 'CP feels like "pressure"' was collected in studies 1, 2, 4 and 5. A positive response adds +1 to the rule score.
Variable 'CP related to effort' was collected in studies Verdon 2008, Buntinx 1992, Sox 1990 and Bösner 2010. A positive response adds +1 to the rule score.
Variable 'Pain reproducible by palpation' was collected in studies 1, 2, 4 and 5. A positive response reduces the rule score by -1.
Variable 'History of CAD' was collected in studies Sox 1990 and Bösner 2010. A positive response adds +1 to the rule score.

Predictor	Acute pain		Non-acute pain	
	N	LR+(95% CI)	N	LR+(95% CI)
Higher age*	716	2.23 (1.89 to 2.65)	2372	2.34 (2.15 to 2.54)
PCP initially suspected a serious condition	440	2.50 (1.99 to 3.14)	1691	3.84 (3.10 to 4.76)
CP feels like "pressure"	577	1.63 (1.38 to 1.92)	1972	1.75 (1.60 to 1.92)
CP related to effort	573	2.12 (1.53 to 2.93)	1957	2.42 (2.07 to 2.83)
Pain reproducible by palpation	549	0.27 (0.15 to 0.50)	1775	0.21 (0.14 to 0.31)
History of CAD	289	2.80 (1.93 to 4.07)	1285	6.09 (4.67 to 7.94)

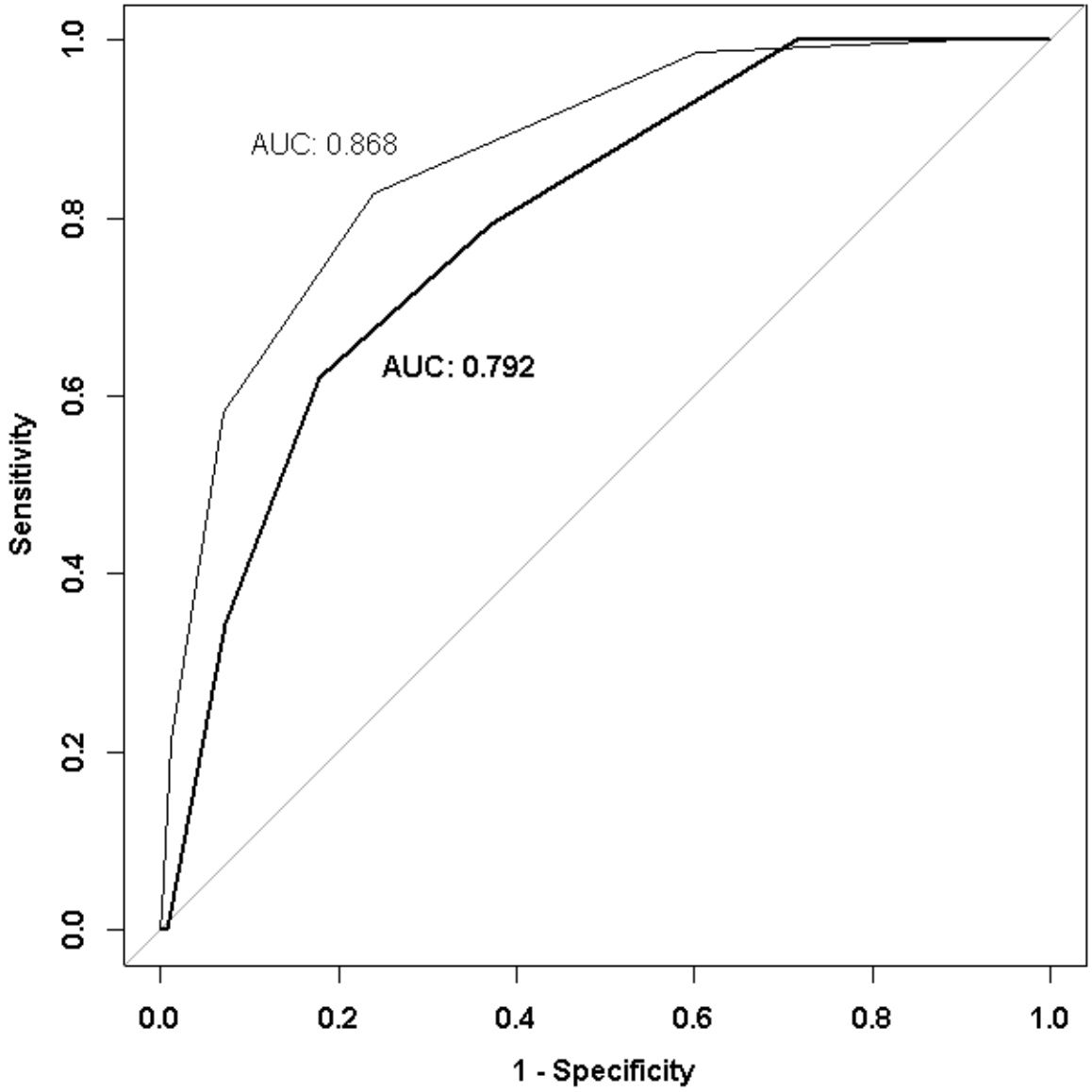
*: male ≥ 55, female ≥65.
LR+: Likelihood ratio, if symptom or sign is present.
CP= chest pain
CAD=coronary artery disease

Supplement Table 6: Area under the curve (AUC) and respective 95% confidence interval (95% CI) for the five imputed data sets derived from Bösner et al. 2010.[6]

Imputation	Acute pain			Non-acute pain			P*
	n	AUC	95% CI	n	AUC	95% CI	
1	169	.792	0.711 - 0.873	1069	.861	0.833 - 0.890	0.116
2	171	.786	0.706 - 0.867	1067	.867	0.838 - 0.896	0.067
3	**169**	**.792**	**0.712 - 0.873**	**1069**	**.868**	**0.841 - 0.868**	**0.081**
4	168	.795	0.715 - 0.875	1070	.871	0.844 - 0.899	0.078
5	170	.799	0.724 - 0.8734	1068	.867	0.838 - 0.896	0.097
* DeLong's test that two ROC curves differ.							

Supplement Figure 2: ROC graph for the third imputed data set (denoted by bold-faced type in table 6) derived from the study Bösner et al. 2010.[6]

This study collected data on all six of the parameters appearing in the final rule. The third data set is the one with the median p value (see table 7). The study population included 169 patients with acute pain and 1069 with non-acute pain. The bold face curve indicates patients with acute pain.



Supplement 6: Sensitivity analysis to measure effect of deleting the variable "physician is concerned that chest pain is serious"

The variable "physician is concerned that chest pain is serious" was one predictor in the final rule. Three studies gathered data on this variable. In the German study, the wording was "I do not like the picture of the patient." Of course, it is a metaphor. It means that the initial, more general impression of the patient hints towards a serious underlying condition. In the Belgian and the Swiss study, study physicians were ask for their initial total, general impression ("serious" or "not serious").

A reviewer expressed concern about the use of the predictor 'GP concern' in the rules, so we explored the importance of that predictor to the final rule by comparing the sensitivity, specificity, and AUC for chest pain rules that differed only by the deletion of the variable "GP concern." Table 3 of the article lists the coefficients for the 3 rules as well as the AUC for each rule.

We used the primary data file that had all 5 within-study imputations for the 5 studies (the same one as was used for Table 3) and calculated chest-pain scores for each person in each data set using the coefficients for each of the rules as defined in Table 3. Using a statistical package in R (pROC*) we derived AUCs for each rule to test their agreement with those in Table 3. If the agreement was reasonably close, we would repeat the process using a rule which does not use 'GP concern' and calculate the sensitivity, specificity of the rule with several cut-points and its AUC. We selected imputation 3 as the data to use in this first analysis. For each chest pain rule, we used data from the study groups that had routinely collected all the predictors of the rule.

Study ID	Country	Author year	N
1	CH	Verdon 2008	644
2	Belgium	Buntinx 1992	299
3	Sweden	Nilsson 2003	523
4	USA	Sox 1990	395
5	Germany	Bösner 2010	1238

In the description of the results, "cases" are participants with a CAD final diagnosis and "controls" are participants with a non-CAD final diagnosis. The following 3 sets of results compare the AUCs for the 3 chest pain rules as calculated for Table 3 of the article with their counterparts using the pROC package.

Chest pain rule I using data from Study ID 5
cases = 180, controls = 1058
Area under the curve (by pROC): 0.879; 95% CI: 0.8537-0.9038 (DeLong)
AUC from Table 3: 0.87, which is within the 95% CI by pROC

Chest pain rule II using data from Study IDs 1&5
cases = 265, controls = 1617
Area under the curve (by pROC): 0.880; 95% CI: 0.8579-0.9011 (DeLong)
AUC from Table 3: 0.85, which is within the 95% CI by pROC

Chest pain rule III using data from Study IDs 1&5
cases = 265, controls = 1617
Area under the curve (by pROC): 0.877; 95% CI: 0.856-0.8977 (DeLong)
AUC from Table 3: 0.85, which is <u>not</u> within the 95% CI by pROC

Since the AUCs calculated by pROC and by the method used for Table 3 were similar, we used pROC to measure the effect of eliminating the predictor 'GPs concern' from rule III, using each of the 5 imputations and 3 different thresholds for the calculation of sensitivity and specificity. The results from the 5 imputations were quite similar (tables at the end of this note), so we used imputation 3 for the next table, which summarizes results from pROC runs on 4 rules looking only at imputation 3 and threshold <2. The replacement predictors "rad_neck" (pain radiates to the neck) and "chest pain is 'stabbing'" were the next best predictors available in Study IDs 1&5.

Supplement Table 7: accuracy of several variants on Rule III

Chest pain rule III	AUC	Sensitivity	Specificity	Likelihood Ratio	
				Positive	Negative
Rule includes 'GP concern'	0.877	0.84	0.77	3.67	0.21
Rule does not include 'GP concern'	0.867	0.76	0.82	4.19	0.29
Replace 'GP concern' with 'rad_neck' (with coefficient = +1)	0.866	0.77	0.81	4.04	0.28
Replace 'GP concern' with' stabbing' (with coefficient = -1)	0.855	0.92	0.58	2.20	0.14

Interpretation: Dropping 'GP concern' has little or no effect on discrimination (AUC or Area Under the Curve) but lowers the sensitivity and increases the specificity of the rule.

*Xavier Robin, Natacha Turck, Alexandre Hainard, Natalia Tiberti, Frédérique Lisacek, Jean-Charles Sanchez and Markus Müller (2011). "pROC: an open-source package for R and S+ to analyze and compare ROC curves". BMC Bioinformatics, 12, p. 77. DOI: 10.1186/1471-2105-12-77

Discussion:

Whether to keep or drop the variable "Physician initially suspected a serious condition" presents an interesting problem that decision theory can help to answer.

Keeping the variable "Physician initially suspected a serious condition" results in a higher sensitivity of the rule (using a prediction score cut-point of <2) but the specificity is lower. From decision theory, one should operate on the flat part of the receiver operating characteristic curve (ROC curve) when disease prevalence is high, which means high sensitivity at the cost of lower specificity. Therefore, one should keep the variable "Physician initially suspected a serious condition" in a population with a relatively high prevalence of CAD.

When the population has a low prevalence of CAD, decision theory says that one should operate on the steep part of the receiver operating characteristic curve (close to the origin on the ROC curve), which means high specificity at the cost of low sensitivity. Therefore, one should drop the variable when the prevalence of CAD in the clinical population is relatively low.

Of course, other factors may enter in to the decision, such as the experience of the clinicians evaluating the patient, placing more reliance on the variable when experienced clinicians are caring for the patient.

The following tables use data from Study IDs 1&5; cases = 265, controls = 1617

Supplement Table 8: Accuracy of Rule iii with and without the variable "GP concern" as tested in each imputed data set

Imputation 1 - Chest pain rule III

	With 'GPs concern'				Without 'GPs concern'			
	AUC=0.873				AUC=0.862			
	95% CI=0.851 - 0.894				95% CI=0.840 - 0.884			
			Likelihood Ratio				Likelihood Ratio	
Threshold	Sensitivity	Specificity	Positive	Negative	Sensitivity	Specificity	Positive	Negative
<1	0.98	0.44	1.75	0.04	0.97	0.47	1.84	0.06
<2	0.83	0.77	3.54	0.23	0.74	0.82	4.09	0.31
<3	0.60	0.93	8.02	0.43	0.42	0.95	8.57	0.61

Imputation 2 - Chest pain rule III

	With 'GPs concern'				Without 'GPs concern'			
	AUC=0.876				AUC=0.864			
	95% CI=0.855 - 0.897				95% CI=0.843 - 0.886			
			Likelihood Ratio				Likelihood Ratio	
Threshold	Sensitivity	Specificity	Positive	Negative	Sensitivity	Specificity	Positive	Negative
<1	0.98	0.44	1.74	0.05	0.97	0.47	1.83	0.07
<2	0.84	0.76	3.58	0.21	0.76	0.82	4.10	0.30
<3	0.61	0.93	8.19	0.42	0.43	0.95	8.73	0.60

Imputation 3 Chest pain rule III

	With 'GPs concern'				Without 'GPs concern'			
	AUC=0.877				AUC=0.867			
	95% CI=0.856 - 0.898				95% CI=0.846 - 0.888			
			Likelihood Ratio				Likelihood Ratio	
Threshold	Sensitivity	Specificity	Positive	Negative	Sensitivity	Specificity	Positive	Negative

<1	0.98	0.44	1.74	0.04	0.97	0.47	1.85	0.06
<2	0.84	0.77	3.67	0.21	0.76	0.82	4.19	0.29
<3	0.60	0.93	8.38	0.43	0.42	0.95	9.19	0.61

Imputation 4 Chest pain rule III

	With 'GPs concern'				Without 'GPs concern'			
	AUC=0.879				AUC=0.869			
	95% CI=0.858 - 0.899				95% CI=0.848 - 0.890			
			Likelihood Ratio				Likelihood Ratio	
Threshold	Sensitivity	Specificity	Positive	Negative	Sensitivity	Specificity	Positive	Negative
<1	0.98	0.45	1.77	0.04	0.97	0.48	1.86	0.06
<2	0.85	0.77	3.63	0.20	0.76	0.82	4.16	0.29
<3	0.60	0.93	8.02	0.43	0.43	0.95	8.95	0.60

Imputation 5 Chest pain rule III

	With 'GPs concern'				Without 'GPs concern'			
	AUC=0.877				AUC=0.866			
	95% CI=0.855 - 0.898				95% CI=0.844 - 0.887			
			Likelihood Ratio				Likelihood Ratio	
Threshold	Sensitivity	Specificity	Positive	Negative	Sensitivity	Specificity	Positive	Negative
<1	0.98	0.44	1.74	0.05	0.97	0.48	1.84	0.07
<2	0.85	0.76	3.60	0.20	0.76	0.82	4.20	0.29
<3	0.60	0.93	8.53	0.43	0.41	0.96	9.24	0.62

Supplement Table 9: Log of reasons for exclusion (studies being excluded after assessing full texts)

Publication	Reason for exclusion
Abdul-Ghaffar 2010 [7]	Not office-based primary care (patients were recruited in hospital), retrospective study based on routine data
Adelman 1998 [8]	Not office-based primary care
Allen 2010 [9]	Study did not recruit patients presenting with chest pain (study recruited physicians not patients), conference paper
Barker 1987 [10]	No original research article, narrative review
Beltrame 2009 [11]	Study did not recruit patients presenting with chest pain, series of selected patients
Blacklay 1968 [12]	Retrospective study based on routine data , series of selected patients (patients who received an ECG)
Blacklock 1977 [13]	Retrospective study based on routine data
Braun 1988 [14]	Series of selected patients (patients with unspecific chest pain were included), no reference diagnosis of CAD reported (only the initial, clinical diagnosis established by the GP was provide), retrospective study based on routine data
Bruyninckx 2008 [15]	Series of selected patients , no reference diagnosis of CAD reported (reference diagnosis of CAD was only reported in a selected sub sample (referrals))
Bruyninckx 2009 [16]	Series of selected patients , no reference diagnosis of CAD reported (reference diagnosis of CAD was only reported in a selected sub sample (referrals))
Bruyninckx 2010 [17]	Prognostic study, no reference diagnosis of CAD reported
Buescher 2001 [18]	Not office-based primary care, selective series of patients
Cabane 1996 [19]	Study did not recruit patients presenting with chest pain, no reference diagnosis of CAD reported, series of selected patients (RCT to compare lysine acetylsalicylate and paracetamol in patients presenting with pain)
Cheng 1997	No original research article, narrative review
Croft 2003 [20]	Study did not recruit patients presenting with chest pain, retrospective study based on routine data, series of selected patients
Dodani 1998 [21]	No original research article, narrative review
Favero 2003 [22]	Series of selected patients (only patients in whom the GP assumed a cardiac origin were included)
Fink 2010 [23]	Study did not recruit patients presenting with chest pain, no

	reference diagnosis of CAD reported
Fry 1988 [24]	No original research article, narrative review
Gill 1999 [25]	Study did not recruit patients presenting with chest pain, retrospective study using routine data, series of selected patients (patients with angina and suspected angina were recruited)
Gold 1982 [26]	Retrospective study using routine data, no reference diagnosis of CAD reported (the study investigated the occurrence and management of six different symptoms)
Grijseels 1996 [27]	Series of selected patients (patients referred to hospital)
Hobkirk 1985 [28]	Series of selected patients (patients were recruited based on the diagnosis of angina pectoris)
Jelinek 2009 [29]	No original research article, narrative review
Katerndahl 1997 [30]	No reference diagnosis of CAD reported
Klinkman 1994 [31]	No raw data available (primary investigator was approached several times without success)
Lindbloom 1998 [32]	Not office-based primary care , Study did not recruit patients presenting with chest pain, series of selected patients (referred for stress echocardiography testing)
Major 1957 [33]	Full text not available
Malla 1987 [34]	No reference diagnosis of CAD reported (study investigated the prevalence of alcoholism in patients presenting with different symptoms in primary care)
Mantani 2002 [35]	No reference diagnosis of CAD reported, (study investigated reasons for consultation, chief symptoms, and referrals to specialized departments). Full text only in Japanese available, assessment was based on abstract.
Martina 1997 [36]	Not office-based primary care (patients were recruited in ED of the hospital, 20% were patients referred by GPs), no reference diagnosis of CAD reported
Molinari 2002 [37]	Series of selected patients (patients with symptoms suggestive of coronary events), no reference diagnosis of CAD provided
Moll van Charante 2006 [38]	Not office-based primary care
Morris 1992 [39]	Study did not recruit patients presenting with chest pain (study investigated the prevalence of different symptoms (e.g. chest pain by exertion using the Rose questionnaire) in a general population)
Mueller 2010 [40]	Study did not recruit patients presenting with chest pain, no reference diagnosis of CAD reported (study investigated the

	prevalence of health problems uncovered by a standardized assessment for elderly patients)
Murtagh 1995 [41]	No original research article, narrative review
Pacy 1982 [42]	Series of selected patients (only patients assessed as emergency cases were recruited)
Poole 1980 [43]	Chest pain not reason for encounter (patients recruited physicians, not patients)
Research Committee, Royal College of General Practitioners 1982 [44]	Study did not recruit patients presenting with chest pain (patients were recruited based on the diagnosis of angina pectoris)
Richards 2000 [45]	Chest pain not reason for encounter, not office-based primary care (population-based study, reference diagnosis based on the Rose angina questionnaire
Rosser 1990 [46]	No raw data available according to primary investigator
Rosser 1991 [47]	No raw data available according to primary investigator
Rowe 1985 [48]	No original research article, narrative review
Ruigomez 2006 [49]	Retrospective study based on routine data, series of selected patients (only patients with chest pain of unspecified type or origin were recruited)
Sakurai 1998 [50]	Series of selected patients (patients who were diagnosed as having myocardial infarction (MI), angina pectoris (AP), asymptomatic IHD, or acute cardiac death were enrolled)
Schmidt 1984 [51]	No reference diagnosis of CAD reported (only the GP's initial clinical diagnosis during consultation)
Shiels 2004 [52]	Study did not recruit patients presenting with chest pain, no reference diagnosis of CAD reported
Smith 2003[53]	Study did not recruit patients presenting with chest pain
Stewart 2003 [54]	Series of selected patients (patients with angina pectoris), routine data
Sulke 1991 [55]	Study did not recruit patients presenting with chest pain, no reference diagnosis of CAD reported (study investigated the use and interpretation of exercise electrocardiography)
Svavarsdottir 1996 [56]	Retrospective study based on routine data
Tafalla 2010 [57]	Study did not recruit patients presenting with chest pain, series of selected patients
Taylor 2010 [58]	No original research article, narrative review
Torbal 2004 [59]	Series of selected patients (patients with chest pain suggestive of acute coronary syndrome who were referred to hospital)
Van der Does 1980 [60]	No reference diagnosis of CAD reported (diagnostic outcome

	was myocardial infarction), no raw data available according to primary investigator
Wannamethee 2000 [61]	Chest pain not reason for encounter, not office-based primary care (population-based study)
Wingard 1989 [62]	Not office-based primary care, study did not recruit patients presenting with chest pain (patients were not recruited according to a presenting symptom)
Yelland 2001 [63]	Chest pain was not the only reason for encounter, selective series of patients (referrals)

1. Rubin DB. Multiple imputations in sample surveys – a phenomenological Bayesian approach to nonresponse. In: U.S. Department of Commerce, editor. Imputation and Editing of Faulty or Missing Survey Data Washington, DC: U.S. Department of Commerce; 1978. p. 1-23.
2. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*. 2010 2010;**1**(2):97-111.
3. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons; 1987.
4. Schafer JL. Analysis of incomplete multivariate data. 1. ed., 1. CRC Press reprint ed. Boca Raton: Chapman & Hall/CRC; 2000.
5. Breiman L. Random Forests. *Machine Learning*. 2001;**45**:5-32.
6. Bösner S, Becker A, Abu Hani M, et al. Accuracy of symptoms and signs for coronary heart disease assessed in primary care. *Br J Gen Pract*. 2010 Jun;**60**(575):246-57.
7. Abdul-Ghaffar N, Matthews T, Roseingrave J, Trower J, Jo E, Sharpe N. The wairarapa heart health quality improvement programme. *Heart Lung and Circulation*. [Conference Abstract]. 2010;**19**:S2.
8. Adelman A. Evaluation of chest pain using cardiac troponins T and I. *J Fam Pract*. 1998 Mar;**46**(3):200-1.
9. Allen A, Lee T, Sequist T. Physician risk attitudes and the evaluation of acute chest pain. *Journal of General Internal Medicine*. [Conference Abstract]. 2010;**25**:S352.
10. Barker B, Murtagh J. Angina. *Aust Fam Physician*. 1987 Jul;**16**(7):957.
11. Beltrame JF, Weekes AJ, Morgan C, Tavella R, Spertus JA. The prevalence of weekly angina among patients with chronic stable angina in primary care practices: The Coronary Artery Disease in General Practice (CADENCE) Study. *Arch Intern Med*. 2009 Sep 14;**169**(16):1491-9.
12. Blacklay FW. The electrocardiograph in the diagnosis of chest pain in general practice. *Practitioner*. 1968 Apr;**200**(198):577-81.
13. Blacklock SM. The symptom of chest pain in family practice. *J Fam Pract*. 1977 Mar;**4**(3):429-33.
14. Braun RN. The contribution of intuitive diagnostics to the patient with cardic pain. [German] Was Leistet Die Intuitive Diagnostik Beim Herzschmerz? *Wiener Klinische Wochenschrift*. 1988;**100**(3):83-6.
15. Bruyninckx R, Van den Bruel A, Aertgeerts B, Van Casteren V, Buntinx F. Half of the patients with chest pain that are urgently referred are transported in unsafe conditions. *Eur J Emerg Med*. 2008 Dec;**15**(6):330-3.

16. Bruyninckx R, Van den BA, Aertgeerts B, Van CV, Buntinx F. Why does the general practitioner refer patients with chest pain not-urgently to the specialist or urgently to the emergency department? Influence of the certainty of the initial diagnosis. *Acta Cardiol*. 2009;**64**(2):259-65.
17. Bruyninckx R, Van den Bruel A, Buntinx F, Van Casteren V, Aertgeerts B. Excess of mortality in patients with chest pain peaks in the first 3 days period after the incident and normalizes after 1 month. *Fam Pract*. 2010 Jul 16.
18. Buescher JJ, Kane KY. Can a bedside blood test predict death or myocardial infarction (MI) in patients with chest pain? *J Fam Pract*. 2001 Sep;**50**(9):800.
19. Cabane J, Festino C, Lablache Combier B. [Comparative trial of lysine acetylsalicylate and paracetamol on pain in daily medical practice]. *Presse Med*. 1996 Oct 12;**25**(30):1367-71.
20. Croft P, Lewis M, Hannaford P. Is all chronic pain the same? A 25-year follow-up study. *Pain*. 2003 Sep;**105**(1-2):309-17.
21. Dodani S. Evaluation of chest pain in general practice. *J Pak Med Assoc*. 1998 Aug;**48**(8):254-6.
22. Favero G, Moro A, Cavasin F, et al. Acute chest pain: Dealing with the symptom. [Italian] Il dolore toracico acuto: Gestione di un sintomo. *Ricerca e Pratica*. 2003 Mar;**19**(2):51-7.
23. Fink P, Schroder A. One single diagnosis, bodily distress syndrome, succeeded to capture 10 diagnostic categories of functional somatic syndromes and somatoform disorders. *J Psychosom Res*. 2010 May;**68**(5):415-26.
24. Fry J. Angina in general practice. *Lancet*. 1988 May 28;**1**(8596):1225.
25. Gill D, Mayou R, Dawes M, Mant D. Presentation, management and course of angina and suspected angina in primary care. *J Psychosom Res*. 1999 Apr;**46**(4):349-58.
26. Gold M, Azevedo D. The content of adult primary care episodes. *Public Health Rep*. 1982 Jan-Feb;**97**(1):48-57.
27. Grijseels EW, Deckers JW, Hoes AW, et al. Implementation of a pre-hospital decision rule in general practice. Triage of patients with suspected myocardial infarction. *EurHeart J*. 1996;**17**(1):89-95.
28. Hobkirk DW. Follow up study of angina in patients aged 30 to 59 in general practice. *Br Med J (Clin Res Ed)*. 1985 May 18;**290**(6480):1477-9.
29. Jelinek M, Barraclough K. Diagnosis in General Practice . Chest pain. *BMJ*. 2009;**339**:b4117.
30. Katerndahl DA, Trammell C. Prevalence and recognition of panic states in STARNET patients presenting with chest pain. *J Fam Pract*. 1997 Jul;**45**(1):54-63.
31. Klinkman MS, Stevens D, Gorenflo DW. Episodes of care for chest pain: a preliminary report from MIRNET. Michigan Research Network. *JFamPract*. 1994;**38**(4):345-52.
32. Lindbloom EJ, Stevermer JJ. Identifying cardiac risk in patients with atypical chest pain. *J Fam Pract*. 1998 Jun;**46**(6):458-9.
33. Major RC. Chest pain and dyspnea in general practice. *J Med Assoc Ga*. 1957 Oct;**46**(10):481.
34. Malla A, Merskey H. Screening for alcoholism in family practice. *Fam Pract Res J*. 1987 Spring;**6**(3):138-47.
35. Mantani N, Tomizawa T, Hoshino A, et al. Backgrounds of patients initially consulting the Department of General Medicine. [Japanese]. *Kitakanto Medical Journal*. 2002 Nov;**52**(6):453-7.

36. Martina B, Bucheli B, Stotz M, Battegay E, Gyr N. First clinical judgment by primary care physicians distinguishes well between nonorganic and organic causes of abdominal or chest pain. *J Gen Intern Med*. 1997 Aug;**12**(8):459-65.
37. Molinari G, Reboa G, Frascio M, et al. The role of telecardiology in supporting the decision-making process of general practitioners during the management of patients with suspected cardiac events. *J Telemed Telecare*. 2002;**8**(2):97-101.
38. Moll van Charante EP, ter Riet G, Drost S, van der Linden L, Klazinga NS, Bindels PJ. Nurse telephone triage in out-of-hours GP practice: determinants of independent advice and return consultation. *BMC Fam Pract*. 2006;**7**:74.
39. Morris JK, Cook DG, Walker M, Shaper AG. Non-consulters and high consulters in general practice: cardio-respiratory health and risk factors. *J Public Health Med*. 1992 Jun;**14**(2):131-7.
40. Mueller CA, Klaassen-Mielke R, Penner E, Junius-Walker U, Hummers-Pradier E, Theile G. Disclosure of new health problems and intervention planning using a geriatric assessment in a primary care setting. *Croatian Medical Journal*. 2010 December;**51**(6):493-500.
41. Acute chest pain. *Aust Fam Physician*. 1995 Mar;**24**(3):440-1; 5-8; quiz 52-3.
42. Pacy H, Chancellor A, Bridges-Wegg C, Mant A. Chest pain as an emergency in general practice. *Aust Fam Physician*. 1982 Nov;**11**(11):861-5.
43. Poole NW, Wilson FW, Barber JH. The general practice management of angina pectoris. *Practitioner*. 1980 Sep;**224**(1347):935-8.
44. Study of angina in patients aged 30 to 59 in general practice. Research Committee, Northern Region Faculty, Royal College of General Practitioners. *Br Med J (Clin Res Ed)*. 1982 Nov 6;**285**(6351):1319-21.
45. Richards H, McConnachie A, Morrison C, Murray K, Watt G. Social and gender variation in the prevalence, presentation and general practitioner provisional diagnosis of chest pain. *J Epidemiol Community Health*. 2000 Sep;**54**(9):714-8.
46. Rosser W, Henderson R, Wood M, Green L. An exploratory report of chest pain in primary care. A report from ASPN. *JAmBoard FamPract*. 1990;**3**(3):143-50.
47. Rosser WW. From idea to publication: the study of chest pain in the development of the Ambulatory Sentinel Practice Network. *Fam Med*. 1991 Sep-Oct;**23**(7):492-5.
48. Rowe WS. Chest pain and the diagnosis of angina. *Aust Fam Physician*. 1985 Apr;**14**(4):321, 5-6, 8.
49. Ruigomez A, Rodriguez LA, Wallander MA, Johansson S, Jones R. Chest pain in general practice: incidence, comorbidity and mortality. *Fam Pract*. 2006 Apr;**23**(2):167-74.
50. Sakurai A, Oka S, Sekine J, et al. Changes of ischemic heart disease in Utsunomiya, Japan, over 10 years: a survey of primary care physicians. *Jpn Circ J*. 1998 Sep;**62**(9):675-9.
51. Schmidt H, Hansen JG, Bitsch N, Steinmetz E. [Chest pain in general practice]. *Ugeskr Laeger*. 1984 Jul 2;**146**(27):2008-11.
52. Shiels C, Gabbay M, Dowrick C, Hulbert C. Depression in men attending a rural general practice: factors associated with prevalence of depressive symptoms and diagnosis. *Br J Psychiatry*. 2004 Sep;**185**:239-44.
53. Smith BH, Elliott AM, Hannaford PC. Pain and subsequent mortality and cancer among women in the Royal College of General Practitioners Oral Contraception Study. *Br J Gen Pract*. 2003 Jan;**53**(486):45-6.
54. Stewart S, Murphy NF, Walker A, McGuire A, McMurray JJ. The current cost of angina pectoris to the National Health Service in the UK. *Heart*. 2003 Aug;**89**(8):848-53.

55. Sulke AN, Paul VE, Taylor CJ, Roberts RH, Norris ADC. Open access exercise electrocardiography: A service to improve management of ischaemic heart disease by general practitioners. *Journal of the Royal Society of Medicine*. 1991;**84**(10):590-4.
56. Svavarsdottir AE, Jonasson MR, Gudmundsson GH, Fjeldsted K. Chest pain in family practice. Diagnosis and long-term outcome in a community setting. *CanFamPhysician*. 1996;**42**:1122-8.
57. Tafalla M, Nuevo J, Zapardiel J, Gisbert JP. [Study of the clinical profile and management of patients with gastroesophageal reflux disease in primary care in Spain]. *Gastroenterol Hepatol*. 2010 Aug-Sep;**33**(7):490-7.
58. Taylor CJ, McManus RJ. Standard medical care does not offer sufficient relief of non-specific chest pain leading to additional diagnostic testing of no clinical benefit. *Evidence-Based Medicine*. [Note]. 2010 June;**15**(3):86-7.
59. de Torbal A, Kors JA, van Herpen G, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. *Cardiology*. 2004;**101**(4):199-207.
60. van der Does E, Lubsen J, Pool J. Acute myocardial infarction: an easy diagnosis in general practice? *J R Coll Gen Pract*. 1980 Jul;**30**(216):405-9.
61. Wannamethee SG, Shaper AG, Walker M. Physical activity and mortality in older men with diagnosed coronary heart disease. *Circulation*. 2000 Sep 19;**102**(12):1358-63.
62. Wingard DL, Cohn BA, Kaplan GA, Cirillo PM, Cohen RD. Sex differentials in morbidity and mortality risks examined by age and cause in the same cohort. *Am J Epidemiol*. 1989 Sep;**130**(3):601-10.
63. Yelland MJ. Back, chest and abdominal pain. How good are spinal signs at identifying musculoskeletal causes of back, chest or abdominal pain? *Aust Fam Physician*. 2001 Sep;**30**(9):908-12.