Supplemental data

Supplement A

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

Database/search engine	Search	Query	Items found
PubMed	#5	Search (#1) OR #2 Filters: Humans; Dutch; English; German	1376
	#4	Search (#1) OR #2 Filters: Humans	1535
	#3	Search (#1) OR #2	1599
	#2	Search ((((“Chest pain”[MeSH] OR chest pain*[tiab] OR angina pectoris[tiab] OR stable angina*[tiab] OR unstable angina*[tiab] OR preinfarction angina*[tiab] OR angina at rest[tiab] OR variant angina*[tiab] OR prinzmetal*[tiab]) AND (“Myocardial ischemia”[MeSH] OR “myocardial ischemia” OR “acute coronary syndrome” OR angina pectoris[tiab] OR coronary disease*[tiab] OR coronary heart disease*[tiab] OR coronary artery disease*[tiab] OR coronary arteriosclerosis[tiab] OR coronary atherosclerosis[tiab] OR myocardial infarct*[tiab] OR heart attack*[tiab])) AND ((“General practitioners”[MeSH] OR general practitioner*[tiab] OR general practice physician*[tiab]) OR (“General practice”[MeSH] OR general practice*[tiab] OR family practice*[tiab]) OR (“Primary health care”[MeSh] OR primary health care[tiab] OR primary healthcare[tiab] OR primary care[tiab]) OR (“Physicians, primary care”[MeSH] OR primary care physician*[tiab]) OR (“Physicians, family”[MeSH] OR family physician*[tiab]))))	1232
	#1	Search ((((“Chest pain”[MeSH] OR chest pain*[tiab] OR angina pectoris[tiab] OR stable angina*[tiab] OR unstable angina*[tiab] OR preinfarction angina*[tiab] OR angina at rest[tiab] OR variant angina*[tiab] OR prinzmetal*[tiab]) AND (“Myocardial ischemia”[MeSH] OR “myocardial ischemia” OR “acute coronary syndrome” OR angina pectoris[tiab] OR coronary disease*[tiab] OR coronary heart disease*[tiab] OR coronary artery disease*[tiab] OR coronary arteriosclerosis[tiab] OR coronary atherosclerosis[tiab] OR myocardial infarct*[tiab] OR heart attack*[tiab])) AND (“Decision Support Techniques”[MeSH] OR decision aid*[tiab] OR clinical prediction rule*[tiab] OR decision model*[tiab])))	405

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

Supplement B : QUADAS-2 results for included studies

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

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

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

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

Supplement C. Inclusion- and exclusion criteria of studies

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

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

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

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

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

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

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

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