Clinical Assessment of Coronary Heart Disease

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About Us The cardiology department of the Heidelberg University Hospital is a tertiary referral center covering a population of 500,000 inhabitants with almost 12,000 hospitalized cases per year and more than annual 68,000 outpatient visits.

The Chest Pain Unit, part of the internal medicine Emergency Department, is visited by almost 9000 patients/year, with 1300 undergoing an evaluation for suspected acute coronary syndrome (ACS).

The department provides interventional and noninvasive services. The interventional spectrum includes more than 9000 coronary angiographies, >4000 PCI, >350 TAVI, 100 MitraClip, and >400 peripheral interventions of arteries and veins.

Noninvasive imaging includes cardiac MRI including stress MRI and contrast MR angiography, cardiac CT, and full spectrum of 2/3-D echocardiography and transoesophageal echocardiography.

Other services provided include implantations of pacemaker, ICD, CRT-P/D, complex EP studies, RF, and cryoablation procedures.

There are several active research groups with a focus on molecular genetics, epigenetics, and omics-based technologies, with a particular interest on genetic cardiomyopathies. Research activities are also on diagnosis and management of ACS, and cardiac imaging with MRI/CT.

Introduction

- The number of patients presenting with chest pain to emergency departments is increasing exponentially whereas numbers of patients with unstable angina or confirmed myocardial infarction (MI) remain stable or are even declining over the past two decades [1]. The rush to emergency departments of patients who present with chest pain leads to crowding and dissatisfaction of both medical staff and patients [2, 3].
- In order to provide an accurate diagnosis ensuring timely and appropriate treatment or discharge to avoid unnecessary hospitalization, clinical assessment to establish a working diagnosis is paramount.
- However, in patients presenting with suspected MI to the emergency department, the diagnostic performance of chest pain characteristics for MI is limited [4–7]. Atypical complaints are more often observed in the elderly, in women, and in patients with diabetes, chronic renal disease, or dementia. Atypical presentations include epigastric pain, indigestion-like symptoms, and isolated dyspnea.

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- For this reason the 2015 European Society of Cardiology (ESC) guidelines [8] recommend that in patients with suspected non ST-elevation-acute coronary syndromes (NSTE-ACS), diagnosis of ACS should be based on a combination of clinical history, symptoms, physical findings, ECG, and biomarkers, preferentially cardiac troponin I or T.
- Although diagnostic algorithms are based on biomarker measurements, ECG, and clinical assessment, guidelines can vary widely across continents and even within Europe.

Chest Pain Assessment

- The dilemma starts with the limited ability of chest pain characteristics alone to predict the presence of obstructive coronary artery disease (CAD). Therefore, classical prediction rules or more refined rules, such as the modified Diamond Forrest rule [9] recommended by the ESC [8], include age, gender, and other risk factors for assessment of pretest probability.
- The classification of angina into typical angina, atypical angina, or non-anginal chest pain is old and standardized to an insensitive reference for MI (World Health Organization—WHO—definition). At that time, chest pain duration of 20 min or more at rest was found to be associated with NSTEMI [10].
- Typical angina was diagnosed in the presence of substernal chest pain, occurring during exercise and relieved following rest. If only two criteria are applied the chest pain was labeled as atypical, and in the presence of one or none of the three criteria symptoms were classified as non-anginal chest pain.
- Historically, unstable angina was further subclassified using the Braunwald classification scheme that had been prospectively validated for short-term outcomes [11]. In the troponin era, atypical features do not exclude ACS [12].
- The relief of chest pain with nitroglycerin is not predictive of ACS [13]. Conversely the relief of chest pain by antacids, anticholinergic drugs, or lidocaine-containing agents does not predict the absence of ACS [14].
- Using cardiac troponins in the context of a Universal MI definition instead of the WHO definition of MI changed the spectrum of ACS with increasing numbers of NSTEMI while numbers of unstable angina declined [15].
- Using more sensitive and cardio-specific troponins improved detection of patients with atypical presentations.
- Women, elderly, younger patients, and patients with diabetes mellitus have been reported to present with atypical presentations. Chest pain is decreasing with increasing age and dyspnea becomes more prevalent in the elderly [16]. Dyspnea is associated with acute heart failure and indicates a higher mortality rate [17].
- More recent data suggest that at least five chest pain characteristics are very similar between men and women [18]. Rubini-Gimenez et al. [18] evaluated the predictive ability of 34 chest pain characteristics to predict the likelihood for an adjudicated diagnosis of MI in 2475 consecutive patients with suspected ACS. Interestingly, chest pain characteristics were not very helpful to predict final MI. In particular, there were only five chest pain characteristics that significantly decreased the likelihood of the diagnosis of AMI, with similar likelihood in women and men. These characteristics included stabbing pain; aggravation of the pain by breathing, movement, or palpation; pain located in the left side of the chest and infra-mammillary pain; pain without radiation; and pain duration of less than 2 min.
- An updated definition of angina and classification of chest pain established from findings of numerous trials is shown in Table 2.1.

Table 2.1 Definition of angina and classification of chest pain [4]

Finding	Definition
Typical angina	Substernal discomfort Precipitated by exertion Improved with rest or nitroglycerin (or both) in less than 10 min (many patients also report radiation to shoulders, jaw, or inner arm)
Atypical angina	Substernal discomfort with atypical features Nitroglycerin not always effective Inconsistent precipitating factors Relieved after 15–20 min of rest
Non-anginal chest pain	Pain unrelated to activity Unrelieved by nitroglycerin Otherwise not suggestive of angina

Differential Diagnoses of Chest Pain

- Assessment and interpretation of clinical symptoms require clinical expertise as some differential diagnoses of chest pain may be life threatening.
- The "Big Five" include:
  - Acute myocardial infarction (AMI)
  - Aortic dissection
  - Pulmonary embolism
  - Tension pneumothorax
  - Boerhaave syndrome (mediastinitis following esophageal rupture)
- A multitude of benign differential diagnoses have to be considered as well. These differential diagnoses include:
  - Cardiac
  - Vascular
  - Gastrointestinal
  - Orthopedic causes [8]
- In some cases the clinical picture may be straightforward but sometimes symptoms and clinical signs are equivocal or absent. Therefore, cardiac imaging and testing for noncardiac acute conditions have been recommended for the workup and differential diagnoses of chest pain patients (see Table 2.2).
- These imaging modalities include:
  - Cardiac computed tomography (CT)
  - Echocardiography
  - X-ray
  - Cardiac magnetic resonance (CMR)
  - Various stress imaging tests
  - Laboratory testing [8, 19, 20]
- In order to differentiate an acute from a chronic troponin elevation, serial troponin measurements are mandatory, with few exceptions, to disclose a rise and/or fall of troponin.
- In addition, the diagnosis of MI according to the 3rd version of the Universal MI definition [21] requires the presence of myocardial ischemia as the reason of myocardial necrosis. Therefore, interpretation of troponin values cannot be made in isolations, and elevated troponin in the absence of a significant obstruction should not be labeled false positive but should be interpreted in the appropriate clinical context.
- Differential diagnoses with regard to elevated troponin include an almost endless list of cardiac, noncoronary but also extra-cardiac disorders [22].
- Reasons for acute troponin elevations should also include:
  - Acute myocarditis
  - Aortic dissection
  - Acute pulmonary embolism
  - Stress cardiomyopathy (Tako Tsubo)
  - Heart failure
  - Structural heart disease, e.g., aortic stenosis
  - Hypertensive emergencies and atrial tachyarrhythmias [22]

Table 2.2 Overview of selected guideline recommendations

Variable	NICE 2014 [19]	ACC/AHA 2014 [20]	ESC 2015 [8]
ECG	12-lead immediately	12-lead immediately	12-lead immediately
Preferred biomarker Baseline measurement	Cardiac troponin At presentation	Cardiac troponin At presentation	Cardiac troponin At presentation
Standard protocol for repeat measurement	10–12 h after onset of symptoms	3–6 h after symptom onset	3 h after admission if hsTn available
Serial change criteria	At least one value above the 99th percentile	If cTn below or close to 99th percentile: Change ≥3 standard deviations If cTn >99th percentile: increase or decrease ≥20%	If hsTn <99th percentile: increase by >50% of ULN (e.g., 7 ng/L for hsTnT) If cTn >99th percentile: increase or decrease ≥20%
Early rule-out protocols:	Recommended	Not recommended	Recommended (except in patients presenting very early, i.e., within 1 h from chest pain onset, then second cardiac troponin level should be obtained at 3 h
Option A	Presentation and 3 h if hsTnT or hsTnI (Abbott architect) available	hsTn not available	1-h rule-out if hsTnT or hsTnI (Abbott Architect) available
Option B	—	—	2 h ADP together with TIMI score and ECG
Option C	—	—	Instant if normal cTn (<99th percentile but >limit of detection) and copeptin <95% percentile
Specific recommendations with hsTn cutoff: hsTnT	99th percentile cutoff, i.e., 14 ng/L	99th percentile cutoff	99th percentile cutoff, for 1-h rule-out <12 ng/L and delta <3 ng/L
hsTnI (Abbott Architect)	99th percentile 26.2 ng/L Sex-specific cutoff: 34.2 ng/L for men and 15.6 ng/L for women		99th percentile, for 1-h rule-out <5 ng/L and delta 0–1 h <2 ng/L
Clinical risk score recommendation	***General:*** Prediction of 6-month mortality such as GRACE score	***Undifferentiated chest pain (including discomfort, pressure, and squeezing):*** TIMI risk score PURSUIT score GRACE score NCDR-ACTION ***Chest pain:*** Sanchis score Vancouver rule HEART score $HEARTS_3$ score Hess prediction rule	***General:*** GRACE score, preferentially over TIMI risk score

Table 2.2 (continued)

Variable	NICE 2014 [19]	ACC/AHA 2014 [20]	ESC 2015 [8]
Management Invasive:	***General:*** Offer coronary angiography (with follow-on PCI if indicated) within 96 h of first admission to hospital to patients who have an intermediate or higher risk of adverse cardiovascular events (predicted 6-month mortality above 3.0%)	***Stabilized high-risk patient:*** Early invasive strategy within 24 h of admission (preferred) or delayed invasive strategy within 25–72 h Not high/intermediate risk: delayed invasive approach is reasonable	***General:*** Immediate invasive strategy (<2 h): Paralleling the STEMI pathway, this strategy should be undertaken for patients with ongoing ischemia, characterized by at least one very-high-risk criterion Early invasive strategy (<24 h): patients qualify if they have at least one high-risk criterion Invasive strategy (<72 h): maximal delay for coronary angiography in patients without recurrence of symptoms but with at least one intermediate-risk criterion
Conservative:	Offer conservative management without early coronary angiography to patients with a low risk of adverse cardiovascular events (predicted 6-month mortality 3.0% or less)	Extensive comorbidities Acute chest pain and a low likelihood of ACS who are troponin negative, especially women	In low-risk patients, a noninvasive stress test (preferably with imaging) for inducible ischemia is recommended before deciding on an invasive strategy
Selective:	Offer coronary angiography (with follow-on PCI if indicated) to patients initially assessed to be at low risk of adverse cardiovascular events (predicted 6-month mortality 3.0% or less) if ischemia is subsequently experienced or is demonstrated by ischemia testing	Ischemia-guided strategy may be considered for patients with NSTE-ACS (without serious comorbidities or contraindications to this approach) who have an elevated risk for clinical events	Patients with no recurrence of chest pain, no signs of heart failure, no abnormalities in the initial or subsequent ECG, and no increase in (preferably high-sensitivity) cardiac troponin level are at low risk of subsequent CV events In this setting, a noninvasive stress test (preferably with imaging) for inducible ischemia is recommended before deciding on an invasive strategy
Discharge recommendations	***Non-high risk:*** To detect and quantify inducible ischemia, consider ischemia testing before discharge for patients whose condition has been managed conservatively and who have not had coronary angiography	***Possible ACS who have normal serial ECGs and cardiac troponins:*** Treadmill ECG, stress myocardial perfusion imaging, or stress echocardiography before discharge or within 72 h after discharge	***Unstable angina:*** Regular ward or discharge, no rhythm monitoring

(continued)

Table 2.2 (continued)

Variable	NICE 2014 [19]	ACC/AHA 2014 [20]	ESC 2015 [8]
Cardiac imaging	Echocardiography and coronary CT	***Possible ACS and a normal ECG, normal cardiac troponins, and no history of CAD:*** *Coronary CT angiography to assess coronary artery anatomy, or rest myocardial perfusion imaging with technetium-99m to assess coronary artery anatomy, or to exclude myocardial ischemia*	Echocardiography, X-ray, CT, CMR Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy

Key: *cTn* cardiac troponin, *hsTn* high-sensitivity troponin, *hsTnT* high-sensitivity troponin T, *hsTnI* high-sensitivity troponin I, *ULN* upper limit of normal, *ADP* adenosine diphosphate, *TIMI* thrombolysis in myocardial infarction, *ACS* acute coronary syndrome, *CT* computed tomography, *ECG* electrocardiogram, *NSTE* non-ST elevation, *CV* cardiovascular, *CMR* cardiac magnetic resonance, *CAD* coronary artery disease

Clinical Scores

Acute Coronary Syndrome

- A number of risk-scoring systems have been developed to predict short- and medium-term outcome in patients with acute coronary syndromes [23–25]. Many of these risk-scoring systems were derived from clinical trial populations, which generally excluded the highest risk patients.
- Other risk scores were derived from large patient databases in an attempt to model a more representative ACS population with a broader spectrum of risk.
- Most of the risk scores include ECG signs of myocardial ischemia and cardiac biomarkers of necrosis, as well as other clinical features at presentation.
- In NSTE-ACS, quantitative assessment of ischemic risk by means of scores is superior to the clinical assessment. There are numerous clinical scores that have been established in different populations. Endpoints and duration of follow-up as well as performance of the scores vary widely.
- The GRACE risk score [26] provides the most accurate stratification of risk both on admission and at discharge, and has been validated in prospective registries on patients with acute coronary syndrome [8, 27].
- The TIMI risk score is simple to use and has also been validated in several clinical trials [28, 29]. Its discriminative accuracy is inferior to that of the GRACE risk score and the GRACE 2.0 risk calculation [8].
- More recently the HEART score has been established and validated prospectively [30, 31]. An overview on the different multivariable clinical scores is given in Table 2.2.
- The usefulness of clinical scores is to estimate increased individual risk and accordingly guide need and timing of coronary angiography and coronary intervention [27], or as a tool to identify a low-risk patient who might be safely discharged after rule-out of MI [24].

Prediction of Cardiovascular Disease Risk in Individuals Without Known CVD

- In all individuals without known cardiovascular disease (CVD), several risk scores have been developed to estimate the risk of CVD including the Framingham score(s), the PROCAM score, and more recently the ESC-score [32–41].
- There are several review articles providing a critical overview of an incomplete number of available risk scores with advantages and limitations [32, 33].

- Briefly, the Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual [34]. The Framingham Risk Score was first developed based on the data obtained from the Framingham Heart Study, to estimate the 10-year risk of developing coronary heart disease.
- The ESC-SCORE is a cardiovascular disease risk assessment and management tool developed by the European Society of Cardiology, using data from 12 European cohort studies (N = 205,178) covering a wide geographic spread of countries at different levels of cardiovascular risks [35]. The score includes gender, age, smoking, systolic blood pressure, and total cholesterol as risk factors, and estimates fatal cardiovascular disease events over a 10-year period.
- The SCORE data contains some three million person-years of observation and 7934 fatal cardiovascular events. Three different formats have been developed including:
  - A Web-based version, offering graphical display of absolute CVD risk, including relative risk for younger patients, patient data history, and progress monitoring
  - A downloadable PC version since 2008
  - A quick calculator
- In the USA, the American Heart Association (AHA) and the American College of Cardiology (ACC) introduced a new atherosclerotic cardiovascular disease (ASCVD) risk score in the year 2013 to guide ASCVD risk-reducing therapy [36].
- The ideal target populations to estimate the 10-year risk of ASCVD events are non-Hispanic African-American and non-Hispanic white men and women from 40 to 79 years of age.
- 10-year risk was defined as the risk of developing a first ASCVD event, defined as nonfatal myocardial infarction or coronary heart disease (CHD) death or fatal or nonfatal stroke. The recommendation to calculate 30-year or lifetime risk for ASCVD events is weak [36].
- The Joint British Societies rather recommend use of the JBS3 score as a risk calculator provided conveniently on an smartphone "app" that intends to help healthcare practitioners to better illustrate the risk of CVD and the gains that can be made from interventions such as reducing blood pressure, or stopping smoking [37].
- In contrast to other scores, the JBS3 score extends estimation of CVD risk over a lifetime and considers death from competing diseases such as cancer.
- This risk calculator is based on the concept that early lifestyle interventions and drug treatment can decrease or slow down CVD and thereby the risk of future CVD events. Therefore, it is recommended to estimate both 10-year risk and lifetime risk of CVD in all individuals, except for those with existing CVD or certain high-risk diseases, i.e., diabetes age >40 years, patients with chronic kidney disease (CKD) stages 3–5, or familial hypercholesterolemia.
- Although this score is still relatively new for the medical community, particularly outside the UK, it has been applied by the insurance industry for many years to determine appropriate levels of insurance premium risk over a lifetime to help inform prevention strategies with lifestyle changes (interventions) and, where necessary, drug therapy.
- JBS3 includes estimation of the widely used 10-year risk estimation, as previously recommended in JBS2, but now extends this to include CVD risk over a lifetime.
- Another risk score for estimation of CVD that is recommended in the UK by the National Institute for Health and Care Excellence (NICE) guidelines instead of the Framingham Risk Score [38] is the QRISK2 [39].
- The most recent version of QRISK is a prediction algorithm for cardiovascular disease (CVD) that—in analogy to the Framingham Risk Score—includes traditional risk factors (age, systolic blood pressure, smoking status, and ratio of total serum cholesterol to high-density lipoprotein cholesterol).
- However, the QRISK also includes body mass index, family history of cardiovascular disease, chronic kidney failure, rheumatoid

arthritis, atrial fibrillation, social deprivation (Townsend score), and use of antihypertensive treatment.
- QRISK excludes patients with a preexisting diagnosis of diabetes and does not include electrocardiogram assessment of left ventricular hypertrophy. The second version also accounts for statin use and a method to adjust for missing data. The algorithm has been validated using an external dataset [40, 41].
- QRISK has also been developed further to estimate individualized lifetime risk of cardiovascular disease [42].

High-Sensitivity Troponins

- Several years ago manufacturers started to develop novel high-sensitivity generations of cardiac troponin (cTn) assays in order to comply with the precision criteria of the 2000 ESC/ACC consensus document on the redefinition of myocardial infarction [43].
- It has been proposed that a cTn assay should be designated as a "high-sensitivity" assay if cTn can be measured in at least 50% of healthy individuals, in order to ensure a high clinical sensitivity [44].
- These high-sensitivity assays are characterized by a substantially higher analytical sensitivity than conventional sensitive assays, allowing the measurement of cTn in ng/L, rather than microgram/L [45].
- The more sensitive high-sensitivity troponin (hsTn) assays differ regarding their analytical characteristics. In direct comparison, 19 cTn assays were found to show very heterogenous analytical characteristics regarding the 99th percentile value and their analytical sensitivity, as reflected by the proportion of detectable cTn concentrations in a healthy reference population [46].
- Whether the clinical performance of the different hsTn assays is similar is unsettled as yet only a few studies have directly compared hscTn assays head to head for the detection of reversible ischemia, diagnosis, and prognosis.
- The key differentiating feature of hsTn assays, when compared to the conventional sensitive cTn assays, is not apparent at higher values but is restricted to the area around the 99th percentile cutoff.
- The clinical interpretation of hsTn concentrations in this range is challenging, but important, as most of the increased sensitivity for the detection of myocardial injury is at the low concentration level.
- In clinical routine, there is substantial evidence that the use of more sensitive cTn assays enables more accurate and earlier detection of myocardial infarction (MI) [47–50]. Numerous trials [49, 50] and a recent meta-analysis [51] now provide substantial evidence that high-sensitivity assays, using the 99th percentile as the threshold for positivity, can achieve sensitivity at presentation of 90% or more.
- A higher analytical sensitivity changes the spectrum of ACS, as hsTn assays used at lower thresholds increase the incidence of non-ST-segment elevation myocardial infarction (NSTEMI), particularly small MI, that would have been mislabeled as unstable angina (UA) [52, 53].
- Maximizing early sensitivity results in some loss of clinical specificity [22]. Thus, lowering the diagnostic cutoff increases the number of patients with analytically true cTn elevations that are related to myocardial injury, but not to MI.
- Compared to conventional sensitive assays, the prevalence of detectable and elevated cTn values increases with the use of hsTn assays in various study populations, including patients with acute [54] or chronic heart failure [55–57], and stable CAD [58], and in general populations of middle-aged individuals [59–61], and patients with structural heart disease are identified at earlier clinical stages [55, 62].
- Not uncommonly, patients with suspected ACS may present with symptoms other than typical chest pain. Therefore, the diagnosis may be uncertain in many patients who require strategies to overcome the loss of clinical specificity. Such strategies to increase the clinical specificity without a loss of sensitivity

include a strict adherence to the Universal MI definition, use of recommended cutoffs, and relevant concentration change in serial testing.

- A working group of the ESC [45] recommends, by consensus, an increase of >50% of the 99th percentile value if the baseline value lies below the 99th percentile and the second value exceeds the 99th percentile.
- In cases where the initial cTn value is already above the 99th percentile value, an increase of only 20% on the second sample is necessary to diagnose NSTEMI [45].
- The most recent achievement with biomarker testing is the implementation of hsTn assays, instead of the conventional, less sensitive troponin assays, in patients with suspected ACS [8].
- The higher analytical sensitivity and precision of the more sensitive assays have facilitated an earlier and more accurate detection of NSTEMI [47–50]. Accordingly, recent ESC guidelines [8] recommend the use of hsTn assays with a second sample after 3 h, or optionally after 6 h, in order to rule out NSTEMI earlier than with standard cardiac troponin (cTn) assays.
- As an alternative, a 1-h diagnostic protocol can be used if validated hsTn assays are available, a 2-h accelerated diagnostic protocol with cTn, or an instant rule-out using a single hsTn with a cutoff at the limit of detection (LoD), or a combination of a normal cTn or hsTn together with a normal copeptin.
- An overview on differences regarding diagnosis, risk estimation, and management of ACS without ST-segment elevation across guidelines, i.e., NICE 2014 [19] versus ACC/AHA 2014 [20] versus ESC 2015 [8], is provided in Table 2.2.

References

1. Goodacre S, Cross E, Arnold J, Angelini K, Capewell S, Nicholl J. The health care burden of acute chest pain. Heart. 2005;91:229–30.
2. Guttmann A, Schull MJ, Vermeulen MJ, Stukel TA. Association between waiting times and short term mortality and hospital admission after departure from emergency department: population based cohort study from Ontario, Canada. BMJ. 2011;342:d2983.
3. Diercks DB, Roe MT, Chen AY, Peacock WF, Kirk JD, Pollack CV Jr, Gibler WB, Smith SC Jr, Ohman M, Peterson ED. Prolonged emergency department stays of non-ST-segment-elevation myocardial infarction patients are associated with worse adherence to the American College of Cardiology/American Heart Association guidelines for management and increased adverse events. Ann Emerg Med. 2007;50:489–96.
4. Chun AA, McGee SR. Bedside diagnosis of coronary artery disease: a systematic review. Am J Med. 2004;117:334–43.
5. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, Montalescot G. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the global registry of acute coronary events. Chest. 2004;126:461–9.
6. Canto JG, Shlipak MG, Rogers WJ, Malmgren JA, Frederick PD, Lambrew CT, Ornato JP, Barron HV, Kiefe CI. Prevalence, clinical characteristics, and mortality among patients with myocardial infarction presenting without chest pain. JAMA. 2000;283:3223–9.
7. Body R, Carley S, Wibberley C, McDowell G, Ferguson J, Mackway-Jones K. The value of symptoms and signs in the emergent diagnosis of acute coronary syndromes. Resuscitation. 2010;81:281–6.
8. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Agewall S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cuisset T, Erol Ç, Fitzsimons D, Halle M, Hamm C, Hildick-Smith D, Huber K, Iliodromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosemann T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology. Eur Heart J. 2016;37:267–315.
9. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. N Engl J Med. 1979;300:1350–8.
10. Braunwald E. Unstable angina. A classification. Circulation. 1989;80:410–4.
11. Hamm CW, Braunwald E. A classification of unstable angina revisited. Circulation. 2000;102:118–22.
12. Lee TH, Cook EF, Weisberg M, Sargent RK, Wilson C, Goldman L. Acute chest pain in the emergency

room. Identification and examination of low-risk patients. Arch Intern Med. 1985;145:65–9.
13. Henrikson CA, Howell EE, Bush DE, Miles JS, Meininger GR, Friedlander T, Bushnell AC, Chandra-Strobos N. Chest pain relief by nitroglycerin does not predict active coronary artery disease. Ann Intern Med. 2003;139:979–86.
14. Swap CJ, Nagurney JT. Value and limitations of chest pain history in the evaluation of patients with suspected acute coronary syndromes. JAMA. 2005;294:2623–9.
15. Braunwald E, Morrow DA. Unstable angina: is it time for a requiem? Circulation. 2013;127:2452–7.
16. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, Van de Werf F, White HD, Weaver WD, Naylor MD, Gore JM, Krumholz HM, Ohman EM, American Heart Association Council on Clinical Cardiology; Society of Geriatric Cardiology. Acute coronary care in the elderly, part I: Non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology. Circulation. 2007;115:2549–69.
17. Mockel M, Searle J, Muller R, Slagman A, Storchmann H, Oestereich P, Wyrwich W, Ale-Abaei A, Vollert JO, Koch M, Somasundaram R. Chief complaints in medical emergencies: do they relate to underlying disease and outcome? The Charité Emergency Medicine Study (CHARITEM). Eur J Emerg Med. 2013;20:103–8.
18. Rubini Gimenez M, Reiter M, Twerenbold R, Reichlin T, Wildi K, Haaf P, Wicki K, Zellweger C, Hoeller R, Moehring B, Sou SM, Mueller M, Denhaerynck K, Meller B, Stallone F, Henseler S, Bassetti S, Geigy N, Osswald S, Mueller C. Sex-specific chest pain characteristics in the early diagnosis of acute myocardial infarction. JAMA Intern Med. 2014;174:241–9.
19. National Institute for Health and Clinical Excellence: Guidance. Unstable Angina and NSTEMI: The Early Management of Unstable Angina and Non-ST-Segment-Elevation Myocardial infarction. National Clinical Guideline Centre (UK). London: Royal College of Physicians (UK); 2010 niceorguk/guidance/cg94, last update November 2013, online access November 16 2016.
20. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ, Members AATF. 2014 aha/acc guideline for the management of patients with non-stelevation acute coronary syndromes: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:2354–94.
21. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, Katus HA, Lindahl B, Morrow DA, Clemmensen PM, Johanson P, Hod H, Underwood R, Bax JJ, Bonow RO, Pinto F, Gibbons RJ, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasché P, Ravkilde J, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S Collaborators: Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Ž, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S. Third universal definition of myocardial infarction. Circulation. 2012;126:2020–35.
22. Giannitsis E, Katus HA. Cardiac troponin level elevations not related to acute coronary syndromes. Nat Rev Cardiol. 2013;10:623–34.
23. Backus BE, Six AJ, Kelder JH, Gibler WB, Moll FL, Doevendans PA. Risk scores for patients with chest pain: evaluation in the emergency department. Curr Cardiol Rev. 2011;7:2–8.
24. Carlton EW, Khattab A, Greaves K. Identifying patients suitable for discharge after a single-presentation high-sensitivity troponin result: a comparison of five established risk scores and two high-sensitivity assays. Ann Emerg Med. 2015;66:635–45.
25. D'Ascenzo F, Biondi-Zoccai G, Moretti C, Bollati M, Omedè P, Sciuto F, Presutti DG, Modena MG, Gasparini M, Reed MJ, Sheiban I, Gaita F. TIMI, GRACE and alternative risk scores in acute coronary syndromes: a meta-analysis of 40 derivation studies on 216,552 patients and of 42 validation studies on 31,625 patients. Contemp Clin Trials. 2012;33:507–14.
26. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA, Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163:2345–53.
27. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the 6 months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ. 2006;333:1091–4.
28. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA. 2000;284:835–42.
29. Pollack CV Jr, Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non-ST elevation acute coronary syndrome to an unselected emergency depart-

ment chest pain population. Acad Emerg Med. 2006;13:13–8.
30. Six AJ, Backus BE, Kelder JC. Chest pain in the emergency room: value of the heart score. Neth Heart J. 2008;16:191–6.
31. Backus BE, Six AJ, Kelder JC, Bosschaert MA, Mast EG, Mosterd A, Veldkamp RF, Wardeh AJ, Tio R, Braam R, Monnink SH, van Tooren R, Mast TP, van den Akker F, Cramer MJ, Poldervaart JM, Hoes AW, Doevendans PA. A prospective validation of the heart score for chest pain patients at the emergency department. Int J Cardiol. 2013;168:2153–8.
32. Erbel R, Budoff M. Improvement of cardiovascular risk prediction using coronary imaging: subclinical atherosclerosis: the memory of lifetime risk factor exposure. Eur Heart J. 2012;33:1201–13.
33. Mureddu GF, Brandimarte F, Faggiano P, Rigo F, Nixdorff U. Between risk charts and imaging: how should we stratify cardiovascular risk in clinical practice? Eur Heart J Cardiovasc Imaging. 2013;14:401–16.
34. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837–47.
35. Conroy RM, Pyörälä K, Fitzgerald AE, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njølstad I. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003.
36. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr, Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129(Suppl. 2):S49–73.
37. JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014 Apr;100(Suppl 2):ii1–ii67. https://doi.org/10.1136/heartjnl-2014-305693.
38. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121:293–8.
39. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Brindle P. Performance of the QRISK cardiovascular risk prediction algorithm in an independent UK sample of patients from general practice: a validation study. Heart. 2008;94:34–9.
40. Collins GS, Altman DG. An independent external validation and evaluation of QRISK cardiovascular risk prediction: a prospective open cohort study. BMJ. 2009;339:b2584.
41. Collins GS, Altman DG. An independent and external validation of QRISK2 cardiovascular disease risk score: a prospective open cohort study. BMJ. 2010;340:c2442.
42. Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. BMJ. 2010;341:c6624.
43. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol. 2000;36:959–69.
44. Apple FS, Ler R, Murakami MM. Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population. Clin Chem. 2012;58:1574–81.
45. Thygesen K, Mair J, Giannitsis E, Mueller C, Lindahl B, Blankenberg S, Huber K, Plebani M, Biasucci LM, Tubaro M, Collinson P, Venge P, Hasin Y, Galvani M, Koenig W, Hamm C, Alpert JS, Katus H, Jaffe AS, Study Group on Biomarkers in Cardiology of ESC Working Group on Acute Cardiac Care. How to use high-sensitivity cardiac troponins in acute cardiac care. Eur Heart J. 2012;33:2252–7.
46. Apple FS. A new season for cardiac troponin assays: it's time to keep a scorecard. Clin Chem. 2009;55:1303–6.
47. Melanson SE, Morrow DA, Jarolim P. Earlier detection of myocardial injury in a preliminary evaluation using a new troponin I assay with improved sensitivity. Am J Clin Pathol. 2007;128:282–6.
48. Giannitsis E, Kurz K, Hallermayer K, Jarausch J, Jaffe AS, Katus HA. Analytical validation of a high sensitivity cardiac troponin T assay. Clin Chem. 2010;56:254–61.
49. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Fröhlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, Lackner KJ, Münzel TF, Blankenberg S. Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med. 2009;361:868–77.
50. Reichlin T, Hochholzer W, Bassetti S, Steuer S, Stelzig C, Hartwiger S, Biedert S, Schaub N, Buerge C, Potocki M, Noveanu M, Breidthardt T, Twerenbold R, Winkler K, Bingisser R, Mueller C. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. N Engl J Med. 2009;361:858–67.
51. Goodacre S, Thokala P, Carroll C, Stevens JW, Leaviss J, Al Khalaf M, Collinson P, Morris F, Evans P, Wang J. Systematic review, meta-analysis and economic modelling of diagnostic strategies for suspected acute coronary syndrome. Health Technol Assess. 2013;17:v–vi, 1–188
52. Kontos MC, Fritz LM, Anderson FP, Tatum JL, Ornato JP, Jesse RL. Impact of the troponin standard

on the prevalence of acute myocardial infarction. Am Heart J. 2003;146:446–52.
53. Kavsak PA, MacRae AR, Lustig V, Bhargava R, Vandersluis R, Palomaki GE, et al. The impact of the ESC/ACC redefinition of myocardial infarction and new sensitive troponin assays on the frequency of acute myocardial infarction. Am Heart J. 2006;152:118–25.
54. Pascual-Figal DA, Casas T, Ordonez-Llanos J, Manzano-Fernández S, Bonaque JC, Boronat M, Muñoz-Esparza C, Valdés M, Januzzi JL. Highly sensitive troponin T for risk stratification of acutely destabilized heart failure. Am Heart J. 2012;163:1002–10.
55. Latini R, Masson S, Anand I, Missov E, Carlson M, Vago T, et al. for the Val-HeFT Investigators. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation. 2007;116:1242–9.
56. Barlera S, Tavazzi L, Franzosi MG, Marchioli R, Raimondi E, Masson S, Urso R, Lucci D, Nicolosi GL, Maggioni AP, Tognoni G, Investigators GISSI-HF. Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a Nomogram. Circ Heart Fail. 2013;6:31–9.
57. Nagarajan V, Hernandez AV, Tang WH. Prognostic value of cardiac troponin in chronic stable heart failure: a systematic review. Heart. 2012;98:1778–86.
58. Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E, Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) Trial Investigators. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med. 2009;361:2538–47.
59. de Lemos JA, Drazner MH, Omland T, Ayers CR, Khera A, Rohatgi A, et al. Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA. 2010;304:2503–12.
60. deFilippi CR, de Lemos JA, Christenson RH, Gottdiener JS, Kop WJ, Zhan M, Seliger SL. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. JAMA. 2010;304:2494–502.
61. Saunders JT, Nambi V, de Lemos JA, Chambless LE, Virani SS, Boerwinkle E, Hoogeveen RC, Liu X, Astor BC, Mosley TH, Folsom AR, Heiss G, Coresh J, Ballantyne CM. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the atherosclerosis risk in communities study. Circulation. 2011;123:1367–76.
62. Filusch A, Giannitsis E, Katus HA, Meyer FJ. Highsensitive troponin T: a novel biomarker for prognosis and disease severity in patients with pulmonary arterial hypertension. Clin Sci (Lond). 2010;119:207–13.