

ACUTE CORONARY SYNDROMES: DIAGNOSIS

Definitions

The term **acute coronary syndromes (ACS)** refer to acute myocardial ischaemia that is sufficiently severe and prolonged to cause myocardial damage, and results in the release of a biomarker of myocardial necrosis into the circulation. Depending on the extent of myocardial necrosis, ACS present **with or without ST-elevation or new LBBB** (Figure 1 and Table 1).^{1, 2}

The clinical definition of myocardial infarction denotes the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischaemia. According to the fifth universal definition of myocardial infarction (MI) from the Joint ESC/ACCF/AHA/WHF task force, acute myocardial injury is defined as a rise and/or fall in cardiac troponin with at least one value above the sex-specific 99th percentile URL.³ The 99th percentile URL is designated as the decision level for the presence of myocardial injury, and must be determined for each specific assay with quality control materials used at the URL to validate appropriate assay imprecision. Chronic myocardial injury is considered if two or more cardiac troponin I or T values are above the sex-specific 99th percentile URL when testing is performed in a stable clinical setting. It is confirmed when a cardiac or non-cardiac condition associated with cardiac remodeling is identified and is excluded when the elevation in cardiac troponin is explained by analytical interference or reduced clearance.³ The new definition of types of MI is presented in Figure 2, and the ICD classification in Table 2.

Unstable angina (UA) is a clinical term that denotes rest angina (usually lasting >20 minutes), new onset (within the past 2 months and at least Canadian Cardiovascular Society III in severity), and increasing angina (in severity and frequency). Its diagnostic hallmark was lack of enzyme rise but in the era of high-sensitivity assays the term is rather obsolete.⁴

Variant angina (Prinzmetal's angina, periodic angina) denotes angina that usually occurs spontaneously and is characterized by transient ST-segment elevation that spontaneously resolves or resolves with nitrates without progression to STEMI. **Secondary unstable angina** is due to additional conditions in the presence of coronary stenoses, such as tachycardia, fever, thyrotoxicosis, anemia, aortic stenosis, hypertension or hypotension and hyperviscosity states.

Presentation and Evaluation of Acute Chest Pain

Typical symptoms are **chest pain, indigestion or “heartburn”, nausea and/or vomiting, persistent shortness of breath, or dizziness and/or loss of consciousness**, although diabetics

and the elderly may have vague symptoms or no symptoms at all.⁵ Definitions and differential diagnosis of **chest pain** are presented in Table 3 and Figure 3.

Approximately 80% of women and men with ACS present with chest pain or pressure. Other symptoms, like diaphoresis, indigestion/epigastric pain, shortness of breath, and shoulder/arm pain occur commonly in both men and, more often, women with ACS.² Physical exercise or emotional stress are common triggers of anginal symptoms, and occurrence at rest or with minimal exertion associated with anginal symptoms usually indicates ACS (Figure 4). Positional chest pain is usually nonischemic (e.g., musculoskeletal). Relief with nitroglycerin is not necessarily diagnostic of myocardial ischemia and should not be used as a diagnostic criterion.⁶ Women who present with chest pain are at risk for underdiagnosis, and potential cardiac causes should always be considered.⁶ Age should be taken into account; nonagenarians have substantially higher rates of death with or without preceding rehospitalization after NSTEMI, and twice the adjusted mortality than those aged 65-79 years.⁷ In patients >75 years of age, ACS should be considered with accompanying symptoms such as shortness of breath, syncope, or acute delirium, or an unexplained fall. Cocaine and methamphetamine use should also be considered in patients presenting with acute chest pain.⁶

In patients with **ST-elevation MI**, prodromal symptoms of chest discomfort may be absent and retrosternal compressing or heaviness-like pain that lasts more than 30 min is typical. Described with a clenched fist against the sternum (Levine sign). The pain may radiate to both sites of the chest with a predilection for the left side, the jaw or the arms and wrists. It may be epigastric misdiagnosed as indigestion. Diaphoresis, nausea and vomiting may appear. Diabetics, the elderly and heart transplant recipients may suffer myocardial infarction without symptoms. Silent MIs accounted for 25% of all MIs in the Framingham study, and approximately 17% of diabetics have pathological Q waves.⁸ In patients with acute chest pain the prevalence of acute MI is 80% in the presence of ≥ 1 mm of new ST-segment elevation and 20% with new ST-segment depression or T-wave inversion. In the absence of electrocardiographic changes consistent with the presence of ischemia, the risk of acute myocardial infarction is 4% among patients with acute chest pain and a history of coronary artery disease and 2% among patients with no such history.⁹ Female sex, no radiating chest pain, and low troponin levels (baseline hs-TnI ≤ 40.8 ng/L) suggest secondary MI.¹⁰

Painful left bundle branch block is a rarely diagnosed chest pain syndrome caused by intermittent LBBB in the absence of myocardial ischemia. Painful LBBB ECG morphology within seconds/minutes of its onset is consistent with the new LBBB pattern with a very low (<1.8) precordial S/T wave ratio and inferior QRS axis. It can coexist with coronary artery disease, complicating the assessment of chest pain in the setting of LBBB.¹¹

Physical Examination

With non-ST-elevation ACS or uncomplicated STEMI, physical examination may be unremarkable (Table 4). Tachycardia and elevated respiratory rate may be present. In STEMI without in-time recanalization, a S_4 is invariably present, and fever may appear between 4 to 48h and resolves by the 4th day post MI. Pericardial friction rubs are common within the first 2-3 days following a transmural infarct.

Initial Assessment

Initial assessment is presented in Tables 5 and 6, and Figure 4.

ECG Changes

Immediate 12-lead ECG, and then serial ECGs in 15-30 min intervals if the initial ECG is non-diagnostic, are taken. In patients with minor myocardial injury the ECG may be unremarkable. Artificial intelligence is becoming of increased importance for diagnosis of acute STEMI.¹² Electrocardiographic findings of myocardial ischaemia or infarction are presented in Table 7.

Non-ST elevation ACS

Symptoms associated with ***ST segment depression, T wave inversion or non-specific ST-T abnormalities*** suggest NSTEMI-ACS (Figure 5). These findings are present in 30-50% of patients with an ACS. However apart from assisting diagnosis they also carry adverse prognostic significance when present as new findings. New ST-segment deviation, even of only 0.05 mV, is an important and specific measure of ischemia and prognosis. T-wave inversion is sensitive for ischemia but is less specific, unless it is marked (≥ 0.3 mV).¹³ The possible effect of cardiac memory should be considered in patients with pacing or following episodes of arrhythmias.¹⁴ Comparison with previous ECGs is valuable for the assessment of ST changes. Supplemental electrocardiographic leads, such as V7 to V9 are useful to rule out posterior MI.

ST-elevation MI

ECG changes may not be present depending on the extent and location of myocardial injury, and the presence of preexisting abnormalities (conduction defects, hypertension and ventricular hypertrophy, electrolyte disturbances, and drugs). The typical ECG patterns of MI seen in leads that face the area of damage are appearance of ***Q waves*** (> 0.03 s, loss of forces directed towards the electrode), ***ST-segment elevation*** (upward convexity), and ***T-wave inversion*** (after 4 hours) (Figure 6 and Table 8). New ST elevation at the J-point in at least two contiguous leads: ≥ 2.5 mm in men < 40 years, ≥ 2 mm in men ≥ 40 years, or ≥ 1.5 mm in women regardless of age in leads V2–V3 and/or ≥ 1 mm in the other leads (in the absence of

left ventricular hypertrophy or left bundle branch block).² ST-T changes are not specific; healthy young men may have concave ST-segment elevation of 1 to 3 mm in one or more precordial leads.¹⁵ Other conditions associated with ST elevation are shown in Table 9. Limb leads misplacement may mimic an inferior MI (Figure 7). ST elevation and symptoms of MI are indications for reperfusion therapy, and the number of leads demonstrating ST elevation has been a useful risk marker in MI. In patients with Wolff-Parkinson-White syndrome secondary ST-T changes may be seen and are discordant, that is, in a direction opposite to the delta wave. Concordant changes or the presence of reciprocal changes is abnormal and suggests myocardial ischemia. The direction of the ischemic T-waves points away from the area of ischemia. The presence of Q waves does not reliably distinguish between transmural or subendocardial MI. Q-wave regression, however, indicates improved LVEF.¹⁶

ECG criteria for identification of the infarct-related artery in anterior and inferior MI are shown in Table 9.^{15, 17} Right precordial ST elevation combined with inferior ST depression are signs of **proximal LAD occlusion**, whereas a 1- to 3-mm upsloping ST-segment depression at the J point in leads V₁ to V₆ with tall, positive symmetrical T waves, and a 1- to 2-mm ST-elevation in lead aVR may rarely be seen.¹⁸ According to the fifth universal definition of myocardial infarction, ST-segment elevation myocardial infarction typically requires ST-segment elevation in at least 2 contiguous leads. However, isolated ST-segment elevation in a single lead may also indicate coronary artery occlusion (Figure 8).¹⁹ This is because the precordial leads V₁ to V₃ not only reflect electrical activity in the horizontal plane but also possess frontal plane components and exhibit electrical continuity with the limb leads aVR, aVL, and aVF.²⁰ ST segment elevation greater in lead II than lead III, and ST depression in anteroseptal leads indicate **circumflex occlusion**.^{17, 21} Supplemental electrocardiographic leads V₇ to V₉ are useful to rule out **posterior MI**.²² The appearance of a tall and broad R wave in lead V₁, in the absence of conditions with modified QRS shape, such as right ventricular hypertrophy, complete right bundle-branch block, or WPW syndrome, is associated with a **lateral**, than a posterior, MI.²³ Narrow QRS complexes with tall R waves in the anterior chest leads may be seen in **posterolateral** myocardial infarction, but also in ventricular preexcitation, RV or septal hypertrophy, RBBB, dextroposition, misplaced precordial leads, and left septal fascicular block.²⁴ ST-segment elevation in leads I, aVL, and V₂-V₆, but prominent R wave without ST-segment elevation in V₁, and ST-segment depression in inferior leads, usually in the context of RBBB and LAH, is seen in **left main stem occlusion** (Figure 9).²⁵ A subtle, noncontiguous pattern of ST-segment elevation in I, aVL, and V₂, with ST-segment depression in III, is considered to be a reliable sign of acute occlusion of the **first diagonal** branch of the LAD.²⁶ Coronary **vasospasm** may be indistinguishable from ischemic myocardial infarction. However self-resolving ST-T changes, increase in R wave height, decrease in height or disappearance of S waves, and peaking or

pseudonormalization of T waves resembling a QRS-T monophasic curve at the peak of the attack, may be seen (Figure 10).^{27, 28} T wave inversion in the precordial leads indicate imminent LAD occlusion (**Wellens syndrome**). The diagnostic criteria of Wellens syndrome are either symmetrical and deeply inverted T waves in V2 and V3 (type B) or biphasic T waves in V2 and V3 (type A) along with isoelectric or minimally elevated ST segment, no precordial Q waves, history of angina, pattern present in pain-free state, and normal or slightly elevated cardiac serum markers (Figure 11).²⁹ Bizarre morphologies of ST-segments and T waves that typically spares one of the limb leads are due to electromechanical association artifact. They are due to arterial pulsations or precordial pulsations at the site where the limb leads or chest leads are placed, and can mimic acute coronary syndromes and MI (Figure 12).³⁰

MI in the presence of LBBB. The BARCELONA algorithm is specific and highly sensitive for diagnosis of MI (Table 10, and Figure 13).³¹

MI in dextrocardia. Global negativity in lead I (negative P wave, T wave, and QRS), inverted P wave in lead II, and poor precordial R-wave progression are important clues of dextrocardia on ECG. With inferior STEMI, the inferior leads show ST elevation per usual. In anterior STEMI, precordial ST elevation is limited to V1 (Figure 14).³²

RV infarction. RV infarction results from proximal RCA occlusion, occurs in approximately 50% of patients with inferior MI, and is associated with increased in-hospital morbidity and mortality due to shock and arrhythmias.³³ Suspected when ST elevation in V1 or V1 and V2 but no other precordial leads, and inferior leads with ST elevation in lead III > ST elevation in lead II. The most sensitive electrocardiographic sign of right ventricular infarction is ST-segment elevation of more than 1 mm with an upright T wave in lead V4R, but this sign is rarely present more than 12 hours after the infarction.

Atrial infarction. PR elevation, the hallmark of diagnosis, is seen in 10% of MI. Occlusion of the circumflex coronary artery proximal to the origin of the LA branch causes atrial infarction.³⁴ Although isolated atrial infarction is seen in 3.5% of autopsies of patients with STEMI, it often occurs in conjunction with ventricular infarction and can cause atrial arrhythmias or even rupture of the atrial wall.^{35, 36}

Enzymic Assays

A **cardiac-specific troponin (cTn)** should be measured as soon as possible in all patients with acute chest pain and suspected ACS, and if negative within 6 h of the onset of symptoms. Troponin is a regulatory protein complex located on the thin filament of striated muscles. It consists of three subunits, encoded by different genes. C that binds to Ca, I bonds to actin, and T binds to tropomyosin. **Troponin I (TnI)** appears to be more sensitive to short durations

of ischemia than **troponin T (TnT)**,^{37, 38} and also appears more specific for the detection of myocardial injury than TnT in patients with skeletal myopathy.³⁹ Usually troponins rise after 3 h, peak at 24h and return to normal in 5-10 days (Figure 15). In ST-elevation myocardial infarction troponins may increase 20-50 times above the upper limit of the reference range. The release of biomarkers following cardiac injury depends on blood flow. If coronary blood flow is absent, as may happen with ST-segment elevation MI where the incidence of total occlusion is high, it will take longer for cTn to be released.⁴⁰ Other causes of troponin elevations are presented in Table 11.

High-sensitivity troponin assays (**hs-TnT and hs-TnI**) offer a higher negative predictive value for the exclusion of myocardial injury, and the degree of elevation is associated with mortality in ACS.⁴¹ hs-TnI seems to be superior in early presenters, while hs-TnT seems to be superior in late presenters (>3h).⁴² There is rapid release of cTn, a molecule of low molecular weight (particularly TnI), and increased concentrations can be detected 30 seconds after ischemia,³⁷ provided that coronary blood flow is not absent due to total vessel occlusion, as happens in 30% of NSTEMI.⁴⁰ However, result reporting may be complicated by the threshold used, and variability in precision of hs-cTn assays that depend on the analytical platform and the sample matrix.⁴⁰ Comparison of commercially available hs-cTn assays in patients with suspected ACS found up to 2-fold differences in results that could influence the proportion of patients referred for further observation or investigation,⁴³ and cut-off values should be set by each laboratory depending on the assay used. The **co-efficient of variation (CV)** is a measure of the assay's reproducibility (or precision) and is measured as the ratio of the standard deviation over the mean value for repeated testing of the same sample. The **limit of the blank (LoB)** is the measurement of noise in the system. It is the lowest value that can be distinguished from zero, and is measured as the upper 95 percentile of observed values from repeated blank sample measurements. However, there is a high degree of assay imprecision at LoB concentrations.⁴⁰ The **limit of detection (LoD)** is the lowest observable value as one gradually dilutes a cardiac troponin (cTn) sample. The detection limit has been used as a criterion in a number of studies to rule out myocardial infarction but it does not guarantee high precision.⁴⁰ Thus, the FDA has restricted the reporting to the **limit of quantitation (LoQ)** which is the concentration at which the CV for the assay is < 20%. The more sensitive and accurate an analysis is, the lower the quantitation limit will be. The **99th-percentile upper reference limit (URL)** represents the upper limit of a healthy reference population, that is known as the normally distributed 99 percentiles, which is about three standard deviations from the mean value. Therefore, 1% of normal subjects can have a value above the URL of 99 percentiles. Although assay- and population- and sex-dependent, the 99th-percentile is used to determine cut-off values for hs-TnT and hs-TnI.⁴¹ The new hs-

cTnT-gen6 may overcome some of the limitations of the currently used hs-cTnT-gen5 assay.⁴⁴

Due to their higher sensitivity and diagnostic accuracy for the detection of MI at presentation, the time interval to the second cTn assessment can be shortened with the use of hs-cTn assays. The ESC commends to use the 0 h/1 h algorithm as the best option or the 0 h/2 h as the second option (Figure 16).² The 0h/1 h algorithm has been found safe in triaging patients with suspected ACS.^{45, 46} However, during long-term follow-up (12 months) in the RAPID-TnT RCT, a 0/1- hour hs-cTnT protocol (reported to <5 ng/L) versus standard practice masked hs-cTnT testing (reported to ≤ 29 ng/L) assessed at 0/3 hours, resulted in an increase in all-cause death or myocardial infarction among those with low-level troponin elevations.⁴⁷ For patients remaining in the observe-zone according to the 0h/1 algorithm, a combination of a 3h-hs-cTnT concentration (<15 ng/L) and a 0/3h absolute change (<4 ng/L) is necessary to safely rule out NSTEMI.⁴⁸

The increased sensitivity of these new assays makes it possible to detect low levels of Tn even in healthy subjects. In a meta-analysis, cut-off values of hs-TnT 3 ng/L or 5 ng/L measured at varying times and not always after the recommended 3 hours from presentation, detected MI with a sensitivity of 97%, and a specificity of 42%.⁴⁹ The HiSTORIC Trial has found safe and effective an early rule-out pathway that rules out myocardial infarction at presentation in patients with cardiac troponin concentrations below a risk stratification threshold of 5 ng/L, unless they presented within 2 hours of symptom onset where testing is repeated 3 hours from presentation. Patients with cardiac troponin concentrations ≥ 5 ng/L at presentation are retested at 3 hours after presentation, and myocardial infarction is ruled out if concentrations are unchanged (delta <3 ng/L) and remain below the 99th centile diagnostic threshold.⁵⁰ In the High-STEACS trial, in patients presenting ≤ 3 h, a threshold of 2 ng/L had greater sensitivity and negative predictive value [99.4% (95% confidence interval 99.2%–99.5%) and 99.7% (99.6%–99.8%)] compared with 5 ng/L. The sensitivity of the 99th centile was low in both early and late presenters.⁵¹ The elimination half-lives of cTn I and T in patients with an ongoing myocardial infarct are 2 to 4 hours, with a clearance of cTnI and cTnT of 40 to 77 mL/min.⁵²

Thus, troponin assays should always be interpreted within the context of clinical situation and repeated in 2-3 hours to confirm myonecrosis by consistent elevation.⁵³ Single-sample rule out using very low concentrations of high-sensitivity cTn on presentation to exclude myocardial injury has been found useful in triaging low risk patients.⁵⁴⁻⁵⁷ A low HEART (history, electrocardiogram, age, risk factors, and initial troponin) score may help as well.⁵⁸ However, the use of a single blood test is currently recommended only in patients who present at least 2h,⁴⁰ or 3h,⁴¹ after symptom onset.

Troponin levels (together with an ECG) should also be considered in **pregnant women** with chest pain,⁵⁹ and in patients with **renal** impairment.⁶⁰ The 99th percentile for cardiac troponin is lower for **females** than males, and the prevalence of persistently elevated cardiac troponin values increases with **age**.³ Age alters the diagnostic performance of cardiac troponin, with reduced specificity and positive predictive value in older patients (>75 years) in whom absolute changes in concentration rather than absolute values should be considered.⁶¹ Concentrations in healthy very young vs. 'healthy' very old individuals differ by up to 300%.² Many older adults have persistent elevations attributable to myocardial fibrosis and CKD.⁵ High-sensitivity cardiac troponin (hs-cTn) may be found above the upper limit of normal in >50% of patients with active **chronic skeletal muscle disorder** and significantly higher versus controls. This is not observed for cTnI and may be explained in part by re-expression of cTnT in skeletal muscle.⁶² cTn transiently increases (9-90%>URL hs-cTnI) after the performance of **endurance exercise** with peak values typically 2 to 6 hours after exercise. Few studies have investigated the predictive value of exercise-induced cTn for cardiovascular events, but older long-distance walkers with a postexercise cTn concentration >URL experienced increased cardiovascular events.⁶³

Procedure-related myocardial infarction is considered when acute myocardial ischaemia and injury occur due to a complication of any cardiac procedure (percutaneous or surgical) within 30 days. Immediately following a procedure, the diagnosis is likely with higher cardiac biomarker levels that have increased from preprocedural levels and continue to rise at 6 h (e.g. >5 times URL for intervention) and 24 h (e.g. >35 times URL for surgery).³ Myocardial injury after noncardiac surgery is defined by elevated postoperative cardiac troponin concentrations that exceed the 99th percentile of the upper reference limit of the assay (troponin fourth generation ≥ 30 ng/L or hsTnT ≥ 20 –<65 ng/L with an absolute change of ≥ 5 ng/L or any elevation ≥ 65 ng/L or any absolute change ≥ 14 ng/L).⁶⁴

Cardiac myosin-binding protein C (cMyC) is a cardiac-restricted protein that is more abundant than cardiac troponins, and in early presenters (<3h of chest pain) provides discriminatory power comparable to hs-TnT and hs-TnI.⁶⁵ **Creatine kinase** (starts rising within 4-8 h and returns to normal within 2-3 days) and **myoglobin** (starts raising 1-4 h, peaks at 6 h and returns to normal at 24 h) are not specific for myocardial injury. Of the **creatine kinase isoenzymes** (MM in skeletal and heart muscle, BB in brain and kidney), the muscle and brain (CKMB) isoenzyme are of clinical use by means of immunoassays with anti-MB monoclonal antibodies. It is also present in other tissue (small intestine, tongue, diaphragm, uterus, prostate) and raising after physical exercise. CKMB is now considered obsolete for the initial diagnosis of MI.⁶⁶

Other Investigations

Elevation of **WBC** occurs within the first 2 hours, reaches a peak 2 to 4 days after infarction ($12\text{--}15 \times 10^3/\text{ml}$), and returns to normal in 1 week. The **ESR** rises after the second day and remains elevated for several weeks. **Hemoglobin** powerfully predicts cardiovascular events with mortality increasing progressively as values fall below 14 mg/dl or increase above 17 mg/dl. Iatrogenic bleeding is associated with a 5-fold increase in mortality. Approximately 48 h after ST-elevation MI, there is fall of **HDL cholesterol**. Thus a lipid profile should be obtained before that time or 8 weeks after the MI. **The oral glucose tolerance test** identifies the largest number of patients with previously undiagnosed diabetes compared to fasting plasma glucose and glycated haemoglobin (HbA1c).⁶⁷

Serial ECGs may be needed if the initial one is normal in the setting of clinical suspicion of an ACS.

Chest radiography Prominent pulmonary vascular markings reflect raised LVEDP. However, up to 12 h can elapse before pulmonary edema accumulates after the LVEDP has been raised (pulmonary wedge pressure > 18 mm Hg), and it takes 48 hours to resorb when LV filling pressures become normal. Signs of cardiomegaly may be seen with previous infarcts and LV dysfunction.

Echocardiography Areas of abnormal regional wall motion are seen almost universally in patients with large MIs at 2-D echocardiography. Apical thrombus and flaps of suspect aortic dissection may be seen and Doppler imaging may reveal MR, TR or VSD. Small pericardial effusion may be due to myocardial haemorrhage due to anticoagulants, pericarditis, or heart failure. Moderate effusion early after MI should raise the suspicion of free wall rupture.⁶⁸

Exercise testing In patients of low risk and uncertain diagnosis of MI, tests for ischemia can be undertaken within 6 to 12 h after admission or even immediately.⁶⁹

In patients with acute chest pain, **CT coronary angiography(CTA)** in an experienced center is faster to obtain than a stress test and improves diagnostic ability albeit at an increased radiation exposure (Tables 12 and 13).^{70, 71}

Cardiac magnetic resonance (CMR) has high sensitivity for detecting small amounts of myonecrosis, and may detect MI unrecognized by ECG in older individuals, and this is associated by increased mortality risk (Figure 17).^{72, 73} Resting myocardial perfusion imaging (MPI) in patients with ongoing chest discomfort and nondiagnostic ECG or biomarker results will also identify active ischemia. However, MPI cannot distinguish between recent and older infarcts; thus, abnormal MPI is not specific for ACS.⁷⁴ The recent availability of multiparametric mapping cardiovascular magnetic resonance imaging has provided new insights into the pathophysiology underlying myocardial oedema, microvascular obstruction, intramyocardial hemorrhage, and changes in the remote myocardial interstitial space after

STEMI. However, there are ongoing controversies surrounding the use of CMR to delineate the area at risk and the dynamic changes in myocardial oedema in the first few days after primary PCI.⁷⁵ Chest CT and CMR are also useful for excluding aortic dissection.

Triple-rule-out CT angiography allows simultaneous CT coronary angiography, pulmonary angiography for the exclusion of pulmonary embolism, and ascending aorta angiogram for the exclusion of dissection.⁷⁶

Invasive coronary angiography is indicated in patients with non-diagnostic tests in the context of significant ischemia and in patients with known CAD for assessment of deterioration of symptoms or invasive assessment of coronary lesions.

Indications and contraindications for specific tests in the differential diagnosis and management of patients with acute chest pain are presented in Tables 12-17 and Figures 16-21. Recommendations on the management of chest pain in pregnant women are presented in Figure 21.⁵⁹

Risk Stratification

Risk stratification models have been developed for suspected or established ACS. Clinical risk scores, such as EDACS, ADAPT, NOTR, and HEART are used to determine the probability of ACS or risk of 30-day major adverse cardiovascular events in patients presenting with **chest pain and ACS is suspected**.^{6, 41, 77} Patients who are deemed low-risk can be discharge home without admission or urgent cardiac testing (Tables 18 and 19). The Thrombolysis In Myocardial Infarction (TIMI),⁷⁸ GRACE (Global Registry of Acute Coronary Event) (Table 18),⁷⁹ PURSUIT, and FRISC are useful for subsequent decision making in **established ACS**. Clinical features, ECG and laboratory findings have been incorporated into these clinical risk scores that stratify patients into risk categories. The simplest but less accurate is the TIMI.

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