Review

Interventional Cardiology

Role and timing of coronary intervention in non-ST-elevation myocardial infarction

Karim D Mahmoud[1,2] & David R Holmes Jr*[,1]

[1]Division of Cardiovascular Diseases, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA

[2]Department of Cardiology, Thorax Center, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

*Author for correspondence:
Tel.: +1 507 255 2504
Fax: +1 507 255 2550
holmes.david@mayo.edu

Non-ST-elevation myocardial infarction (NSTEMI) has become the most common presentation of acute myocardial infarction. Its treatment is challenging and often less straightforward compared with ST-elevation myocardial infarction (STEMI). First, clinicians must decide whether an initial invasive or an initial conservative treatment is appropriate for their NSTEMI patient. If an invasive strategy is chosen, subsequent decisions on the optimal timing of coronary angiography and possible intervention have to be made. Both aggressive and conservative strategies have their own potential risks and benefits. Aggressive strategies may result in more procedural complications, which is especially unwanted in patients otherwise at low risk of events. By contrast, conservative strategies may be harmful in high-risk patients who benefit most from early reperfusion therapy. We aim to discuss the evidence base of this decision process where risk stratification is of paramount importance with the goal of obtaining the optimal outcome for the individual patient.

Keywords: acute coronary syndrome • angiography • coronary artery bypass grafting delay • coronary artery disease • myocardial infarction • percutaneous coronary intervention • risk stratification • strategy • timing

With an estimated incidence of 150–200 per 100,000 in the USA, non-ST-elevation myocardial infarction (NSTEMI) represents the most common presentation of acute myocardial infarction [1,2]. Its usual cause is atherosclerotic plaque rupture or erosion and formation of a nonocclusive thrombus in a coronary artery, although other conditions that cause a supply/demand imbalance to the myocardium may also cause NSTEMI (e.g., coronary spasm or dissection or severe anemia) [3,4]. With the introduction of troponin assays the last decade has seen an increase in the incidence of NSTEMI, while the incidence of ST-elevation myocardial infarction (STEMI) has simultaneously decreased [1,2]. That the improved sensitivity to diagnose NSTEMI does not necessarily result in additional identification of low-risk NSTEMI patients is reflected in a contemporary Swedish study. In this nationwide analysis no improvement in 1-year survival of NSTEMI patients was seen between 1990 and 2010, while STEMI patients did show improved survival [5]. In an analysis from the Global Registry of Acute Coronary Events (GRACE), 6-month outcome in NSTEMI patients did show a modest improvement between 1999 and 2005, but this was only after adjustment for the worsening baseline risk profile that was seen over time in NSTEMI patients but not in STEMI patients [6]. Thus, diagnosis, risk stratification and treatment of NSTEMI continues to be a major challenge in the upcoming decade and is often less straightforward than in STEMI. We aim to give an overview of the role and timing of coronary intervention as well as the importance of risk stratification in selecting an appropriate treatment strategy in patients with NSTEMI.

Future Medicine part of fsg

Risk stratification

Before estimating risk in a NSTEMI patient and deciding on if and when to take a patient to the cardiac catheterization laboratory, one needs to question what the possible scenarios in terms of presentation, angiographic findings and invasive management may be. First, it is important to note that approximately 4% of NSTEMI patients present with cardiogenic shock upon admission [7]. This is a population with an exceedingly high mortality rate (higher than in STEMI patients presenting with cardiogenic shock) and is unlikely to be represented in major clinical trials. In the 2005 GRACE registry, in-hospital invasive management in NSTEMI patients consisted of angiography in 62.6% of cases with 34.6% of patients undergoing subsequent percutaneous coronary intervention (PCI) and 5.1% of patients undergoing coronary artery bypass grafting (CABG) [6]. These rates were 76.2% for angiography, 43.6% for PCI and 11.5% for CABG in the 2009 results of the US National Cardiovascular Data Registry [8]. Upon coronary angiography, between 9 and 14% of patients with NSTEMI do not have a coronary stenosis ≥50% [9–11]. Typical findings in NSTEMI patients with significant coronary artery disease are single-vessel disease in 40–45%, two-vessel disease in 25–30%, three-vessel disease in 15–22% and left main disease in 6–13% [11,12]. Approximately 20% of NSTEMI patients with angiographically significant coronary artery disease are managed medically. These patients more often have a history of (extensive) coronary artery disease with prior interventions and have a poorer outcome [13].

In addition to clinical judgment, several validated multivariable risk models are available to estimate the risk of adverse outcome in NSTEMI patients. This risk estimation is of great importance since it will guide the subsequent treatment strategy, as is discussed later. American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend the use of the GRACE, Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) or Thrombolysis In Myocardial Infarction (TIMI) risk models in patients with suspected acute coronary syndrome (Class IIaB) [14]. The European Society of Cardiology (ESC) guidelines mainly refer to the GRACE score to estimate prognosis and the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) risk score to estimate bleeding risk (Class IB) [15]. Clinical characteristics considered by these risk scores are summarized in Table 1. The GRACE score was developed from a large ongoing intercontinental registry of patients with acute coronary syndromes. Risk models are available that predict in-hospital or 6-month death, or death or myocardial infarction [16–18]. The 6-month risk estimates can be calculated both upon admission and at discharge. The commonly used GRACE risk model that estimates the 6-month risk of death or myocardial infarction upon admission was developed among 21,688 GRACE patients and had a c-statistic of 0.73 in the initial validation cohort (the c-statistic for 6-month mortality alone was 0.81) [18]. Due to its complexity, the GRACE score requires digital calculation. Nonetheless, it is widely used and has been validated extensively [19,20]. The GRACE score is accessible online [21]. The PURSUIT risk score was developed among 9461 participants of the PURSUIT trial testing eptifibatide (Integrilin) versus placebo in patients with acute coronary syndrome without persistent ST-elevation [22]. The PURSUIT risk score predicts 30-day death (initial c-statistic: 0.80) and death or myocardial infarction (initial c-statistic: 0.66) by using a scoring scheme and has been subjected to external validation [23]. The TIMI risk score estimates 14-day risk of mortality, new or recurrent myocardial infarction, or severe recurrent ischemia requiring urgent revascularization and is an easy to memorize risk score where 1 point is awarded for each characteristic [24]. It was developed in 1957 patients with unstable angina or NSTEMI receiving unfractionated heparin in the TIMI 11B trial (testing enoxaparin vs unfractionated heparin) and has subsequently been validated by the TIMI investigators (c-statistic of 0.59–0.65) and others [20,24–25]. The TIMI risk score is available online [26]. Studies comparing the GRACE, PURSUIT and TIMI risk scores have concluded that the GRACE score yields the best predictive power [20,27]. The CRUSADE bleeding score can be calculated to estimate in-hospital major bleeding risk in patients with NSTEMI, which may have consequences in selecting anticoagulant and antiplatelet therapy [28]. The CRUSADE score was developed in 71,277 patients enrolled in the US CRUSADE quality improvement initiative and has been validated both within the CRUSADE registry (c-statistic: 0.70) and externally [28,29]. It works with a scoring chart that is hard to memorize but can be calculated at [30]. With regard to risk stratification, the importance of age must be stressed. In the PURSUIT risk score, age ≥70 years is awarded more risk points than any other characteristic including heart failure and abnormalities on the admission ECG [22]. Similarly, age ≥65 years was associated with the highest odds ratio for adverse outcome in the development cohort of the TIMI risk score [24] and age

Table 1. Characteristics considered by commonly used risk models.

Characteristics	GRACE (prognosis)	PURSUIT (prognosis)	TIMI (prognosis)	CRUSADE (bleeding)
Age	X	X	X	
Gender (higher risk in male/female)		Male		Female
Cardiovascular risk factors			X[†]	
Prior coronary artery disease (>50% stenosis)			X	
Prior aspirin use (in past 7 days)			X	
Angina severity		X	X	
Heart rate	X	X		X
Systolic blood pressure	X	X		X
Signs of heart failure	X	X		X
Cardiac arrest	X			
ST-segment deviation	X	X	X	
Creatinine (serum/clearance)	Serum			Clearance
Hematocrit				X
Elevated cardiac enzymes/markers	X		X	

CRUSADE: Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines; GRACE: Global Registry of Acute Coronary Events; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; TIMI: Thrombolysis In Myocardial Infarction.

(per decade increase) and cardiac arrest represented the highest hazard ratio for death at 6 months in the GRACE risk model beyond ST-deviation and cardiac biomarker elevation [18]. Age is not included in the CRUSADE bleeding score, but may already be accounted for in the Cockcroft–Gault creatinine clearance calculation [28].

The usage of risk models greatly enhances the ability to differentiate between low- and high-risk patients and their use should be part of the daily clinical routine. Although there is no question about the importance of clinical judgment in individual cases, it has recently been shown that the GRACE score outperforms physician-perceived risk in terms of prognostic accuracy in aggregate analysis [31]. Nonetheless, it is important to be aware of the limitations of risk models. With c-statistic values typically reported approximately 0.60–0.85 [20], the aforementioned risk models show moderate to excellent – but not perfect – discriminatory capacity in terms of separating patients with and without adverse outcome. Efforts to further improve risk scores by adding biomarkers have been successfully attempted, such as addition of NT-proBNP to the TIMI risk score [32] and addition of NT-proBNP or growth differentiation factor-15 to the GRACE risk score [33]. However, these strategies are associated with additional costs for biomarker assessment and have not (yet) been adopted into broad clinical practice. Finally, new risk scores incorporating clinical, laboratory and angiographic characteristics have been developed in the light of the increasing use of early angiography and PCI in patients with acute coronary syndromes [34,35]. These later risk scores that include angiographic characteristics may better predict in-hospital and long-term outcome after PCI. They are however limited and not suitable to determine the optimal initial treatment strategy upon admission.

Role of coronary intervention

General concept

Coronary revascularization strategies in NSTEMI are summarized in Box 1. The initial conservative strategy consists of observation and stabilization by institution of at least a β-blocker, an anticoagulant and dual antiplatelet therapy. If medical therapy succeeds, the patient usually undergoes a noninvasive stress test before discharge. The patient will proceed

Box 1. Coronary revascularization strategies.

- Initial conservative strategy (selective invasive) – angiography is only performed in case of:
  - Hemodynamic or electrical instability
  - Refractory or recurrent angina despite optimal medical therapy
  - Dynamic ECG changes
  - High-risk stress test results
- Initial invasive strategy (routine invasive) – routine angiography within 72 h of presentation:
  - Urgent – within 2 h of presentation
  - Early (nonurgent) – after 2 h but within 24 h of presentation
  - Delayed – after 24 h but within 72 h of presentation

to coronary angiography if medical therapy fails (i.e., if the patient develops refractory or recurrent angina) or in case of a high-risk stress test result. A potential advantage of this strategy is that initial stabilization and pretreatment with anticoagulant and antiplatelet agents may result in lower periprocedural complications in patients that do proceed to angiography compared with the initial invasive strategy (Figure 1). Furthermore, it may reduce the use of angiography with its associated costs and risks in low-risk patients and allows for a more thorough clinical assessment and recognition of (latent) comorbid conditions.

In the initial invasive strategy, patients routinely undergo coronary angiography within 72 h. Its potential benefit is evident in patients that are considered to be at high risk of adverse outcome upon admission. In these patients, timely angiography and intervention may prevent ischemic events otherwise occurring during the 'observation and stabilization' period in the conservative strategy (Figure 1). However, even in stabilized intermediate-risk patients, the initial invasive strategy can be seen as an effective method of risk stratification since it provides clarity with regard to coronary anatomy. It can identify patients with a high-risk coronary anatomy in an early phase regardless of adequate classification by risk models, such as patients with three-vessel or left main disease amenable for CABG and patients with a proximal left anterior descending artery (LAD) lesion suitable for PCI. Finally, it may reduce length of hospitalization and occurrence of rehospitalization regardless of angiographic findings [14,15].

Conservative versus invasive strategy

The first randomized trial comparing an invasive and conservative strategy was conducted in the early 90s [36], but current guidelines and contemporary meta-analyses have mainly focused on trials conducted in the stent era (Table 2). This will also be the focus of our overview (in chronologic order). Notably, most trials were conducted in patients with non-ST-elevation acute coronary syndromes (NSTE-ACS) and therefore also included patients with unstable angina. Key baseline and procedural characteristics differed substantially between the trials (Table 2).

The Scandinavian multicenter FRISC-II trial randomized 2457 patients with NSTE-ACS to an initial invasive strategy versus an initial conservative strategy [9]. In the invasive group 98% of patients underwent coronary angiography after a median of 4 days, versus 47% after a median of 17 days in the conservative group. Subsequent treatment is listed in Table 2. After an initial hazard for the invasive group in the first 2 weeks, the primary end point of the trial – a composite of death and myocardial infarction at 6 months – was reached in 9.4% in the invasive group versus 12.1% in the conservative group ($p = 0.031$). This was mainly driven by a difference in myocardial infarction rather than death (Table 2). Furthermore, at 6 months patients in the invasive group had lower rehospitalization rates and were less likely to report angina. However, the invasive strategy resulted in a higher occurrence of in-hospital serious adverse events (3.8 vs 1.6%) including major bleeding (1.6 vs 0.7%) and of periprocedural myocardial infarction in the first 6 months (5.4 vs 2.1%; $p < 0.001$) [9,37].

In the TACTICS-TIMI 18 trial, 2220 NSTE-ACS patients were randomized to an initial invasive strategy versus and initial conservative strategy [38]. A major difference with the FRISC-II trial was the substantially higher use of glycoprotein IIb/IIIa inhibitors in patients undergoing PCI. Patients in the TACTICS-TIMI 18 trial underwent invasive procedures earlier during index hospitalization with 97% of patients in the invasive group undergoing angiography after a median of 22 h compared with 51% in the conservative group after a median of 3 days. The primary end point of the trial was a composite of death, myocardial infarction or rehospitalization for an acute coronary syndrome at 6 months, and occurred in 15.9% of patients assigned to the invasive strategy versus 19.4% assigned to the conservative strategy ($p = 0.025$). Also in this trial, there were no differences in death: the composite end point was mainly driven by differences in the occurrence of myocardial infarction and rehospitalization (Table 2). Of note, the invasive strategy

was at the expense of a higher overall bleeding rate (5.5 vs 3.3%; p < 0.01) although TIMI major bleeding was similar (1.9 vs 1.3%; p = 0.24). Hospitalization was 1 day shorter in the invasive group.

With 131 patients, the Czech VINO study was a considerably smaller trial comparing an invasive versus a conservative strategy in a high-risk population of only NSTEMI patients [39]. The VINO trial was successful with regard to its ambition to offer early procedures in the invasive group; the mean time to angiography was 6.2 h versus 61 days in the conservative group and the mean time to PCI was 8.6 h versus 55 days, respectively. The occurrence of the primary end point – death or myocardial infarction at 6 months – was 6.3% in the invasive group and 22.4% in the conservative group (p < 0.001). In this trial a 6-month mortality benefit in favor of the invasive group was found (3.1 vs 13.4%; p = 0.030). This finding may be explained by the high risk profile of the included patients.

RITA-3 was a British multicenter trial that randomized 1810 NSTE-ACS patients to an initial invasive versus an initial conservative strategy [40]. In contrast to the other studies, the presence of elevated cardiac biomarkers was not an inclusion criterion. Indeed, patients with CK or CK-MB elevations higher than twice the upper limit of normal were even excluded, resulting in a relatively low-risk study population (Table 2). Patients in the invasive group underwent angiography during the initial hospitalization after a median of 2 days compared with an in-hospital angiography rate of 16% in the conservative group. The co-primary end points of the trial were a composite of death, myocardial infarction or refractory angina warranting re-admission at 4 months and death or myocardial infarction at 1 year. At 4 months, the primary end point occurred in 9.6% of patients in the invasive group versus 14.5% of patients in the conservative group (p = 0.001). However, this difference was entirely driven by a 50% reduction in refractory angina in the invasive group and no significant differences were seen in death or myocardial infarction at 4-months or 1-year follow-up (Table 2). In-hospital bleeding occurred in 8% in the invasive group and 4% in the conservative group. In the invasive group, patients used fewer antianginal agents at 1-year follow-up. It has been argued that the lack of reduction in myocardial infarction with invasive management seen in RITA-3 compared with the FRISC-II and TACTICS-TIMI 18 trials may at least be partially explained by their different definitions of myocardial infarction [40]. FRISC-II and TACTICS-TIMI 18 both used different definitions for spontaneous and periprocedural myocardial infarction of which the definition of spontaneous myocardial infarction was more sensitive. As a consequence, a greater proportion

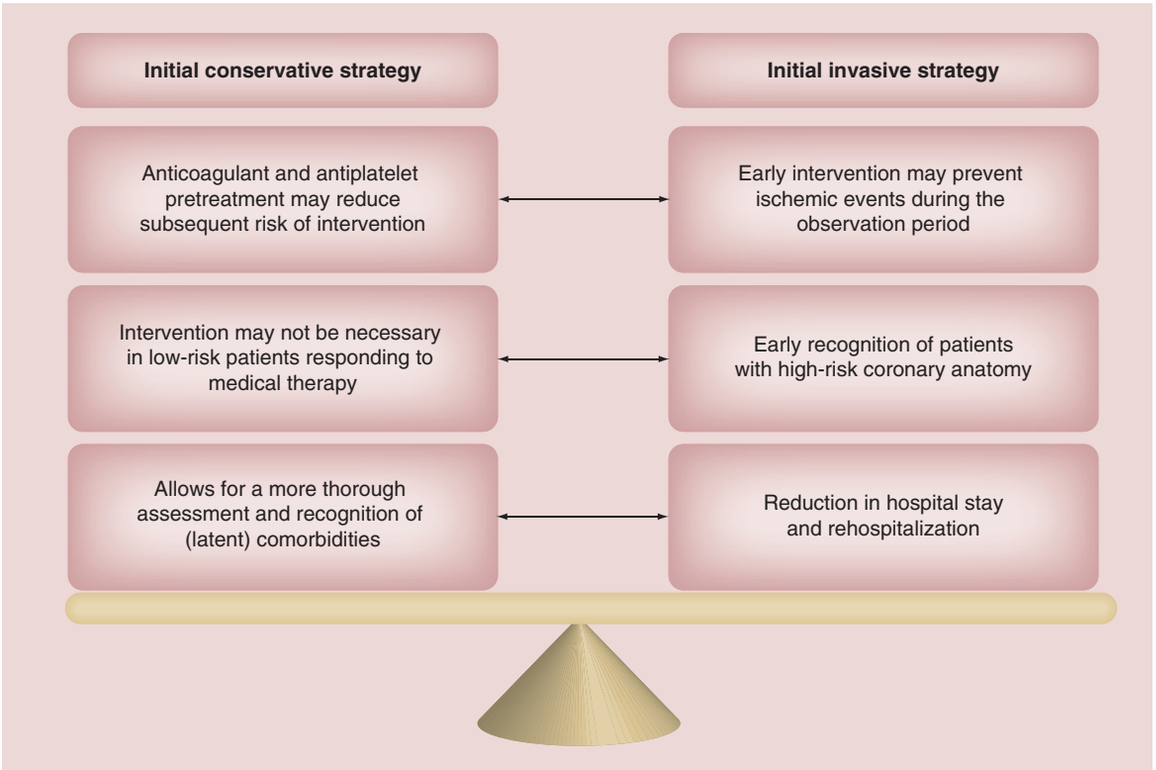

Figure 1. Weighing the benefits of an initial conservative strategy versus an initial invasive strategy.

Table 2. Randomized trials on initial invasive versus initial conservative revascularization strategies.

Characteristic	FRISC-II (1999) [9]		TACTICS-TIMI 18 (2001) [37]		VINO (2002) [38]		RITA-3 (2002) [39]		ICTUS (2005) [40]	
	Invasive (n = 1222)	Cons. (n = 1235)	Invasive (n = 1114)	Cons. (n = 1106)	Invasive (n = 64)	Cons. (n = 67)	Invasive (n = 895)	Cons. (n = 915)	Invasive (n = 604)	Cons. (n = 596)
Baseline										
Age (years)	66 (median)	65 (median)	62 (mean)	62 (mean)	66 (mean)	66 (mean)	63 (mean)	62 (mean)	62 (median)	62 (median)
Male (%)	71	68	65	67	64	58	61	64	74	73
Diabetes (%)	13	12	28	27	30	21	15	12	14	13
Prior myocardial infarction (%)	23	22	39	39	22	30	30	26	25	21
ST-depression (%)	45	46	39†	38†	47	46	36	37	47†	49†
Positive cardiac biomarkers (%)	57	58	56	52	100	100	19	17	100	100
Procedures at 6 months										
Angiography (%)	98	47	98	61	100	55	97‡	48‡	99‡	67‡
PCI (%)	43	18	42	29	52	13	36‡	16‡	61‡	40‡
GPi use (%)	10	10	94	59	0	0	25	25	93	69
Stent use (%)	61	70	83	86	44	50	88	90	88	88
CABG (%)	35	19	22	16	35	30	22‡	12‡	18‡	14‡
Dual antiplatelet therapy (%)	w/stent	w/stent	0	0	w/stent	w/stent	w/stent	w/stent	61	49
Outcomes										
Time to outcome	6 (months)	6 (months)	6 (months)	6 (months)	6 (months)	6 (months)	1 (years)	1 (years)	1 (years)	1 (years)
Death/myocardial infarction (%)	9.4§	12.1§	7.3§	9.5§	6.3§	22.4§	7.6	8.3	NA	NA
Death (%)	1.9	2.9	3.3	3.5	3.1§	13.4§	4.6	3.9	2.5	2.5
Myocardial infarction (%)	7.8§	10.1§	4.8§	6.9§	3.1§	14.9§	3.8	4.8	15.0§	10.0§
Rehospitalization (%)	31§	49§	11.0	13.7	9.4	17.5	6.5§	11.6§	7.4§	10.9§

†ST-deviation.
‡Rate at 1 year.
§$p < 0.05$ between invasive and conservative group. W/stent indicates dual antiplatelet therapy in stented patients only, usually ≤1 month. In the ICTUS trial dual antiplatelet therapy was also prescribed more routinely.
CABG: Coronary artery bypass grafting; Cons.: Conservative; GPi: Glycoprotein IIb/IIIa inhibitor; NA: Not available; PCI: Percutaneous coronary intervention.

of the patients in the conservative group was exposed to a more sensitive definition of myocardial infarction. By contrast, the same definition for spontaneous and periprocedural myocardial infarction was used in RITA-3.

The final trial in this field was the multicenter Dutch ICTUS trial [41]. In this trial, a relatively high-risk population of 1200 NSTEMI patients with elevated troponin T levels were randomized to an initial invasive strategy versus an initial conservative strategy. The median time to PCI was 23 h in the invasive group and 11.8 days in the conservative group. There was a high use of glycoprotein IIb/IIIa inhibitors, although more frequently so in the invasive group (Table 2). The primary end point of the trial consisted of 1-year death, myocardial infarction or hospitalization for angina. This occurred in 22.7% of patients in the invasive group and 21.2% of patients in the conservative group (p = 0.33). The (remarkably low) rate of death was the same in both groups (2.5%), and while rehospitalization rates were significantly lower in the invasive group, an unexpected excess in myocardial infarction was seen (Table 2). The later was solely the consequence of a more than twofold higher rate of PCI and CABG related myocardial infarction in the invasive group (11.3 vs 5.4%; p = 0.001). The rate of in-hospital major bleeding was 3.1% in the invasive group and 1.7% in the conservative group. The findings of the ICTUS trial may be explained by routine monitoring of cardiac biomarkers after each PCI procedure (resulting in a higher rate of periprocedural myocardial infarction in the invasive group) on the background of a more advanced pharmacological treatment strategy including high-dose statins and dual antiplatelet therapy with clopidogrel (limiting the event rate in the conservative group). Additionally, the ICTUS investigators have shown that actual in-hospital revascularization was associated improved outcome [42]. This may well explain the lack of benefit for the invasive strategy in the intention-to-treat analyses, since the rate of in-hospital revascularization was relatively high in the conservative group (40%) compared with the invasive group (76%).

Several meta-analyses have been published on the topic of invasive versus conservative treatment strategies in NSTE-ACS. One particularly meticulous meta-analysis was conducted by Hoenig *et al.* [43]. This study-level meta-analysis also considered additional follow-up from the FRISC-II [37,44–45], RITA-3 [46] and ICTUS trials [47]. No additional follow-up was available in TACTICS-TIMI 18 and VINO. Its principal findings were that the invasive strategy was not associated with a mortality benefit at any time point (in-hospital – relative risk: 1.53, 95% CI: 0.98–2.39; 4–5 years – relative risk: 0.90, 95% CI: 0.76–1.08) compared with the conservative strategy and was associated with an increased risk of periprocedural myocardial infarction and bleeding. The invasive strategy did, however, reduce the incidence of myocardial infarction during intermediate- and long-term follow-up (3–5 years – relative risk: 0.78; 95% CI: 0.67–0.92). Furthermore, the invasive strategy reduced the early and intermediate occurrence of refractory angina and early and intermediate but not late rehospitalization rates. In summary, the invasive strategy seems to reduce the long-term occurrence of myocardial infarction at the expense of a higher rate of early complications in NSTE-ACS patients. Still, one revascularization strategy does not confer a survival benefit over the other in a trial population. Observational studies have shown that an invasive strategy may safely be performed in a more general population [48–50], although a recent report emphasized that intraprocedural complications are common in the invasive strategy and adversely affect prognosis [51]. Therefore, risk stratification and consideration of specific subgroups is needed to effectively balance the early procedure related hazard of an invasive strategy against the risk of ischemic events in the conservative strategy.

Risk stratification & treatment selection

A systematic approach to risk stratification should be used upon admission to increase awareness of the guideline recommendations and help guide treatment selection while avoiding some common pitfalls. First, NSTE-ACS patients with refractory angina or hemodynamic or electrical instability should be selected for an invasive strategy whenever possible, since these patients are at very high risk of ischemic events. This is also reflected in international guideline recommendations (ACC/AHA Class IB; ESC Class IC) [14,15]. Second, a well-validated multivariable clinical risk score should be calculated and patients with a high baseline risk should be considered for an invasive strategy (ACC/AHA and ESC Class IA) [14,15]. The hypothesis of a baseline risk-dependent benefit from an invasive strategy was elegantly tested in a collaborative meta-analysis [52] that included patient-level data and 5-year follow-up from the FRISC-II [45], RITA-3 [46] and ICTUS trials [53]. In this analysis, the authors demonstrated that high-risk patients benefit most of an invasive strategy in terms of reduction of cardiovascular death or myocardial infarction (Figure 2). A prespecified subgroup analysis of the TACTICS-TIMI 18 trial also favored an invasive strategy in patients with an intermediate and high TIMI risk score, although the interaction was nonsignificant [38]. Further analy-

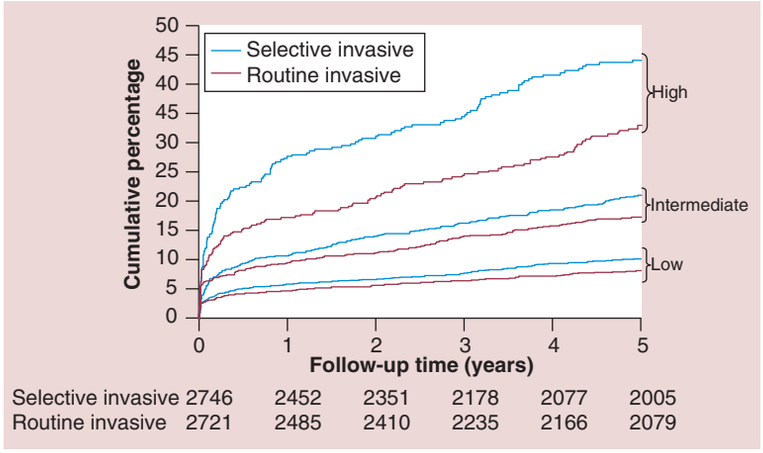

Figure 2. Five-year cumulative incidence of cardiovascular death or myocardial infarction by interventional strategy in a patient-level meta-analysis of the FRISC-II, ICTUS and RITA-3 trials. The figure clearly shows that high-risk patients gained most benefit from a routine invasive (initial invasive) strategy (n = 709; risk difference: -11.1%; 95% CI: -18.4 to -3.8%) compared with intermediate-risk (n = 1832; risk difference: -3.8%; 95% CI: -7.4 to -0.1%) and low-risk patients (n = 2926; risk difference: -2.0%; 95% CI: -4.1 to 0.1%; interaction p < 0.0001). A study specific risk score was calculated for this analysis which considered age, diabetes, prior myocardial infarction, ST-depression, hypertension and BMI <25 or ≥35 to be high-risk features.
Reprinted with permission from Elsevier [52].

sis by the British NICE showed that these trial results are obtained in a population that does not include the patients at highest risk in clinical practice [54]. Thus, the actual benefit from an invasive strategy in high-risk patients among the general population may even be greater. Selection of an invasive strategy in low-risk patients is discouraged by current guidelines (ACC/AHA Class IIIC; ESC Class IIIA) [14,15].

A key issue in the context of risk stratification and revascularization strategy selection is the so called treatment–risk paradox. This refers to the observation that invasive management is more common in lower-risk patients and often denied in high-risk patients in clinical practice; a pattern that opposes guideline recommendations and the evidence-based clinical benefit patients are expected to derive from such interventions [55,56]. This observation seems to reflect an unwanted risk-averse strategy to coronary intervention, as it cannot be fully explained by confounding factors such as comorbidities. Another pitfall in risk estimation and treatment selection concerns cardiac biomarkers. Current guidelines mention that an invasive approach should be considered in patients with elevated cardiac biomarkers (mostly troponin) [14,15]. Indeed, an elevated troponin level is a high-risk feature (Table 1) and the idea of a single high-risk marker is attractive. However, the prognostic value of an elevated troponin level as a single variable is low and inferior to a multivariable risk score [57,58]. This is underscored by the results of the ICTUS trial, where all patients had elevated troponin levels but no benefit for an invasive strategy could be demonstrated [41].

Subgroups & treatment selection

Although treatment selection should principally be based on multivariable baseline risk, the findings in a number of specific subgroups are worth mentioning. Several studies have assessed elderly patients. In the Italian Elderly ACS trial 313 NSTE-ACS patients aged ≥75 years were randomized to an invasive versus a conservative strategy [59]. The primary end point, a composite of death, myocardial infarction, disabling stroke, and rehospitalization for bleeding or cardiovascular causes at 1 year, occurred in 27.9% of patients assigned to the invasive versus 34.6% of patients in the conservative group (p = 0.26). However, an invasive strategy was beneficial to patients with elevated troponin (hazard ratio: 0.43, 95% CI: 0.23–0.80, p-interaction = 0.03). As can be expected from their higher baseline risk, several large observational studies [60,61] and a recent meta-analysis of clinical trials [62] have also suggested benefit from an invasive strategy in elderly NSTE-ACS patients. Unfortunately, age seems to be particularly susceptible to the treatment–risk paradox resulting in underutilization of invasive management of these patients [60]. Clearly, comorbidities and patient preference for a conservative strategy should be considered [14,15], but in their absence advanced age alone should not be an argument for selection of a conservative treatment strategy [63]. Benefit from an invasive over a conservative strategy in elderly patients with comorbidities is subject of a small ongoing clinical trial (NCT01645943) [64].

Women typically represented one-quarter to one-third of the trial population (Table 2). In a randomized substudy of the OASIS-5 trial 92 women with NSTE-ACS were assigned to an invasive strategy and 92 women were assigned to a conservative strategy [65]. The primary end point, death, myocardial infarction or stroke at 2 years, showed a nonsignificant difference between the invasive (21%) and conservative (15.4%) strategy. However, major bleeding was more frequent in the invasive group and there was a trend towards higher 2-year mortality (8.8 vs 2.2%; hazard ratio: 4.65; 95% CI: 0.97–22.20). The investigators also combined their findings with the sex-specific results of previous trials in a meta-analysis yielding 2692 women [65]. They observed significant sex-specific heterogeneity with no apparent benefit from the invasive strategy in terms of 6- to 12-month death or myocardial infarction (odds ratio: 1.18; 95% CI: 0.92–1.53) or death (odds ratio: 1.51; 95% CI: 1.00–2.29) in women, while this benefit was seen in

men. However, these results should be interpreted with caution in the absence of a large clinical trial in women.

Benefit from an invasive strategy in diabetics was assessed in a study-level meta-analysis of clinical trials that included 9904 patients (18% diabetics) [66]. The authors found that the risk of 1-year death, myocardial infarction and rehospitalization for an acute coronary syndrome showed a nonsignificant trend favoring the invasive strategy with similar results in diabetic and nondiabetic patients. An invasive strategy did appear to result in fewer nonfatal myocardial infarctions at 1-year follow-up in diabetic patients (relative risk: 0.71; 95% CI: 0.55–0.92) but not in nondiabetic patients (relative risk: 0.98; 95% CI: 0.74–1.29). The study included both prestent-era and stent-era studies but the authors noted that their results would have been similar if they had only included stent-era trials. Given these findings, it is reasonable to state that an invasive strategy should be more accessible to diabetic patients.

Another subgroup that should be considered for an initial invasive strategy is patients exhibiting a characteristic ECG pattern with precordial T-wave inversion, also known as Wellens' syndrome. These patients often have a critical proximal LAD stenosis and may be at risk of a large anterior myocardial infarction if managed conservatively [67,68]. Similarly, echocardiographic assessment of left ventricular function and mitral regurgitation may help to select patients for an invasive strategy, since compromised left ventricular function (<40%) suggests possible presence of left main or three-vessel disease amenable for CABG [14,69] and presence of grade 2–4 mitral regurgitation may be associated with adverse outcome if invasive management is delayed [70]. Furthermore, guidelines recommend to consider an invasive strategy in patients with overt heart failure, recent PCI or prior CABG [14,15]. These patients were largely excluded in the revascularization strategy trials.

Timing of coronary intervention

Delay to reperfusion in NSTEMI

In the interval between symptom onset and reperfusion therapy several factors can be identified in patients with NSTEMI that are especially complicating compared with STEMI patients. First, NSTEMI patients tend to have a longer prehospital delay [71], and are less likely to use emergency medical services [72]. Certainly, a short time to first medical contact is desirable to facilitate expeditious diagnosis and early pharmacological therapy and to treat possible life-threatening complications such as arrhythmia or cardiogenic shock. Second, while 12-lead ECG-based prehospital triage has shown to contribute to early diagnosis and treatment in STEMI patients [73,74], this is not the case in NSTEMI patients who also require (in-hospital) cardiac biomarker assessment for diagnosis [75]. Finally, whereas delay to reperfusion should be as short as possible to optimize outcome in STEMI patients [76], the relation between delay to reperfusion and outcome in NSTEMI is more complex. In the last decade, several trials have assessed the optimal timing of coronary intervention in NSTE-ACS patients. It is useful to subdivide these into trials comparing early versus delayed intervention [77–82] and trials comparing urgent versus early intervention (Box 1) [83–85].

Early versus delayed invasive management

The international TIMACS trial is by far the largest trial that has addressed the timing of angiography in NSTE-ACS patients selected for an invasive strategy [77]. It assigned patients to early angiography within 24 h (n = 1593; median delay: 14 h) versus delayed angiography after 36 h (n = 1438; median delay: 50 h). In the early group, PCI was performed in 59.6% and CABG in 14.8% of patients. These rates were 55.1% for PCI and 13.6% for CABG in the delayed group. The primary end point of the trial was a composite of 6-month death, myocardial infarction or stroke and occurred in 9.6% in the early group and 11.3% in the delayed group (p = 0.15). However, in a prespecified analysis there was a significant interaction between the primary end point and patient baseline risk, suggesting significant benefit from early intervention in high-risk patients with a GRACE score >140 (hazard ratio: 0.65; 95% CI: 0.48–0.89) compared with patients with a GRACE score ≤140 (HR: 1.12; 95% CI: 0.81–1.56; p-interaction = 0.01). Furthermore, early intervention was associated with a lower rate of refractory ischemia at 30 days and 6 months (1.0 vs 3.3% at 6 months; p < 0.001). Bleeding rates were similar in both groups. The findings of the TIMACS trial have mainly driven the current guideline recommendations, stating that an invasive strategy should be instituted within 12 to 24 h (ACC/AHA Class IIaB) or 24 h (ESC Class IA) of admission in stable high-risk patients [14,15].

The oldest study that has addressed the timing of angiography in NSTE-ACS patients is the ELISA trial [78]. In this pilot trial 220 patients were randomized to early angiography (n = 109; median delay: 6 h) versus late angiography (n = 111; median delay: 50 h). Only patients in the late angiography group were pretreated with a glycoprotein IIb/IIIa inhibitor. Revascularization rates in the early and late group were 61 versus 58% for PCI and 14 versus 19% for CABG. The primary end point of the trial, enzymatic infarct size,

was in favor of the late group (lactate dehydrogenase area under the curve 629 vs 432 U/l; p = 0.02). However, it is uncertain which part of this benefit may be attributed to timing of intervention since glycoprotein IIb/IIIa inhibitor use also differed between the trial arms. No differences in clinical events were seen in this single-center pilot trial (30-day death or myocardial infarction 9.2 vs 9.0%; p = 0.97).

The multicenter German ISAR-COOL trial aimed to compare early angiography (n = 203; median delay: 2.4 h) with a prolonged cooling-off period of at least 3 days before angiography (n = 207; median delay: 86 h) in NSTE-ACS patients [79]. Subsequent treatment consisted of PCI (70.4 vs 64.3%) and CABG (7.9 vs 7.7%) in the early and cooling-off group, respectively. The primary end point of the trial was death or myocardial infarction at 30 days, and occurred in 5.9% in the early group versus 11.6% in the cooling-off group (p = 0.04). These results were mainly driven by a higher rate of myocardial infarction during the cooling-off period (10.1 vs 5.9%; p = 0.12). Thus, a prolonged cooling-off period in patients selected for an invasive strategy seems both impractical and hazardous.

The recently published Dutch multicenter ELISA-3 trial randomized a relatively high-risk NSTE-ACS population (median GRACE score: 135) to early angiography (n = 269; median delay: 2.6 h) versus delayed angiography (n = 265; median delay: 54.9 h) [80]. Revascularization rates were 66.7 versus 61.9% for PCI and 23.2 versus 25.7% for CABG in the early and delayed groups, respectively. The primary end point of this trial was defined as death, reinfarction or recurrent ischemia at 30 days and was expected to have an incidence of 25%. However, it occurred in 9.9% in the early group versus 14.2% in the delayed group (p = 0.135), mainly driven by a trend towards lower recurrent ischemia in the early group (7.6 vs 12.6%; p = 0.058). Hospitalization was 2 days shorter in the early group. The finding of a 30% relative risk reduction in the primary end point with an early invasive strategy in the high-risk population included in ELISA-3 seems to be in accordance with the findings of the TIMACS trial and we argue that lack of statistical significance should be seen in the light of the lower than expected event rate. Finally, two small single-center trials randomized NSTEMI patients to an early invasive versus a delayed invasive strategy. Both of the trials found better outcomes in patients treated with an early invasive strategy, although neither had defined a primary end point [81,82].

Urgent versus early invasive management

Three trials have compared urgent (<2 h) and early invasive strategies [83–85]. The first study to do so was the OPTIMA trial [83]. This trial assessed timing of PCI rather than angiography and therefore only included NSTE-ACS patients eligible for PCI. Patients were randomized to urgent PCI (n = 73; median delay: 30 min) versus early PCI (n = 69; median delay: 25 h). The trial aimed to include 566 patients, but was terminated prematurely due to recruitment challenges. Nonetheless, the trial reached its primary end point; a composite of 30-day death, myocardial infarction and unplanned revascularization was seen in 60% of patients in the urgent group versus 39% of patients in the early group (p = 0.004). Notably, there were no deaths and the difference was primarily driven by excess myocardial infarction in the urgent group (60 vs 38%; p = 0.005), which was defined as CK-MB above the upper limit of normal.

The ABOARD trial randomized 352 NSTE-ACS patients with a TIMI risk score ≥3 to urgent angiography (n = 175; median delay: 1.2 h) versus early angiography (n = 177; median delay: 20.8 h) across multiple French centers [84]. PCI was performed in 80.1% of patients in the urgent group versus 69.5% in the early group. These rates were 11.0 versus 11.3% for CABG. The primary end point of the trial was enzymatic infarct size and did not show any difference between the urgent and early group (median peak troponin I 2.1 vs 1.7 ng/ml; p = 0.70). Although the composite clinical end point of 1-month death, myocardial infarction or urgent revascularization was similar in both groups (13.7 vs 10.2%; p = 0.31), there was a trend towards a higher incidence of myocardial infarction in the urgent group (9.1 vs 4.5%; p = 0.09).

Finally, the German multicenter LIPSIA-NSTEMI trial randomized high-risk NSTEMI patients (median GRACE score ~137) to three different treatment strategies: urgent invasive (n = 200); early invasive (n = 200); and initial conservative (n = 200) [85]. In the urgent invasive group, median time to angiography was 1.1 h, PCI was performed in 76% of patients and CABG in 8% of patients. In the early invasive group, median time to angiography was 18.3 h and revascularization rates were 71% for PCI and 13% for CABG. In the conservative group the angiography rate was high with 85% of patients undergoing angiography after a median of 67.2 h with subsequent PCI in 57% and CABG in 13%. The trial was neutral with regard to enzymatic infarct size, its primary end point (median peak CK-MB: 0.94 μkat/l for urgent invasive, 0.78 μkat/l for early invasive and 0.91 μkat/l for initial conservative; p = 0.18). However, at 6-month follow-up, the urgent strategy was associated with a higher rate of nonfatal myocardial infarction (urgent: 16.5%; early: 10.0%; conservative: 8.0%; p = 0.02),

while the early and conservative strategies were associated with a higher rate of refractory ischemia (urgent: 0%; early: 6.5%; conservative: 10.0%; p < 0.001). Hospital stay was 1 day shorter in the urgent and early groups. Bleeding was similar across all groups.

The conclusions of observational studies assessing timing of intervention have varied widely, reporting on benefit [86], equal outcome [87] or harm [88] associated with an early versus delayed invasive strategy. These discordant findings should be seen in the light of the limited ability of observational studies to untangle the clinical impact of treatment strategies that allow for crossover under certain conditions (e.g., earlier treatment in case of hemodynamic instability) [42]. The observational studies could only adopt an as-treated approach, since none of them were primarily designed to assess the timing of treatment and the intentions of the operator on admission were not recorded. Nonetheless, the results of the trials on timing of coronary intervention have shown that a delayed invasive strategy is hazardous compared with an early invasive strategy in high-risk NSTE-ACS patients (e.g., ISAR-COOL and TIMACS). With a total patient number of 894 in all trials combined, the body of evidence comparing urgent invasive with early invasive management is considerably smaller. Even so, all three trials in this field have consistently shown a higher rate of myocardial infarction in the urgent invasive group. Based on these observations, both urgent (<2 h) and delayed invasive (>24 h) strategies may be associated with adverse outcome. Meta-analyses on timing of intervention to date [89–91] have mostly compared earlier with later intervention (with the exception of a sensitivity analysis comparing <20

Study or subgroup	Early invasive (n)		Urgent/delayed invasive (n)		Weight (%)	Odds ratio M-H, random (95% CI)
	Events	*Total*	*Events*	*Total*		
Early vs delayed						
ELISA (2003) [81]	7	109	6	111	7.3	1.20 (0.39–3.70)
ISAR-COOL (2003) [82]	12	203	21	207	14.2	0.56 (0.27–1.16)
TIMACS (2009) [80]	57	1593	59	1438	30.7	0.87 (0.60–1.26)
ELISA-3 (2013) [83]	5	269	2	265	3.7	2.49 (0.48–12.95)
Subtotal (95% CI)		**2174**		**2021**	**55.8**	**0.86 (0.60–1.22)**
Total events	81		88			
Heterogeneity: $\tau^2 = 0.02$; $\chi^2 = 3.28$; df = 3 (p = 0.035); $I^2 = 8\%$						
Test for overall effect: Z = 0.86 (p = 0.39)						
Early vs urgent						
OPTIMA (2009) [86]	26	69	44	73	16	0.40 (0.20–0.78)
ABOARD (2009) [87]	8	177	16	175	11	0.47 (0.20–1.13)
LIPSIA-NSTEMI (2012) [88]	17	200	27	200	17.2	0.60 (0.31–1.13)
Subtotal (95% CI)		**446**		**448**	**44.2**	**0.49 (0.32–0.73)**
Total events	51		87			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.72$; df = 2 (p = 0.70); $I^2 = 0\%$						
Test for overall effect: Z = 3.43 (p = 0.0006)						
Total (95% CI)		**2620**		**2469**	**100**	**0.67 (0.48–0.93)**
Total events	132		175			
Heterogeneity: $\tau^2 = 0.06$; $\chi^2 = 8.52$; df = 6 (p = 0.20); $I^2 = 30\%$						
Test for overall effect: Z = 2.39 (p = 0.02)						
Test for subgroup differences: $\chi^2 = 4.11$; df = 1 (p = 0.04); $I^2 = 75.7\%$						

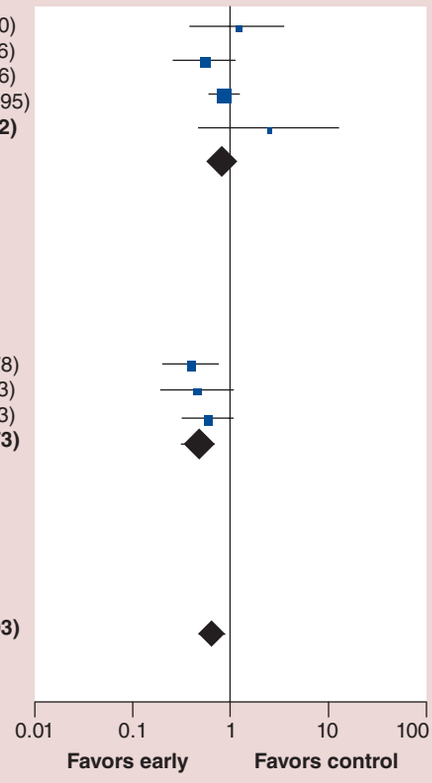

Figure 3. Exploratory meta-analysis of the incidence of early myocardial infarction in 7 randomized clinical trials assessing the timing of intervention in non-ST-elevation acute coronary syndromes. The studies are presented as 'name (year of publication) [reference]' and broken down into early versus delayed invasive management and early versus urgent invasive management. In-hospital myocardial infarction was used for LIPSIA-NSTEMI; 30-day myocardial infarction was used for all other trials. Analyses were conducted assuming a random-effects model [93]. Fixed-effects model analysis yielded similar results. Heterogeneity across studies was tested with Cochran's Q statistic and the I^2 statistic. Analyses were conducted using Review Manager version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark).
df: Degrees of freedom; M-H: Mantel–Haenszel.

and ≥20 h [91]) and therefore have not shown any significant differences in terms of death or myocardial infarction. However, we have demonstrated in an exploratory analysis that significant differences in the incidence of myocardial infarction can be appreciated when urgent, early and delayed management are analyzed separately (Figure 3). A large clinical trial (similar or larger than the TIMACS trial) comparing urgent with early invasive management in high-risk NSTE-ACS patients seems warranted, but we are only aware of two modestly sized ongoing trials in this field (NCT01172990 and NTR3861) [64,92]. In the meantime, it seems most reasonable to perform coronary angiography between 2 and 24 h in NSTE-ACS patients selected for an invasive strategy.

Future perspective

Guidelines and risk scores treat management of NSTEMI patients as a static process with several well-defined steps that occur in a chronological order (i.e., admission, diagnosis and risk stratification, treatment and discharge). Real clinical practice is, however, far more dynamic. The risk of an individual patient may change substantially during hospitalization due to events such as recurrence of angina or the unexpected angiographic finding of severe coronary disease. Surely, we will never be able to fully model the challenges of clinical medicine, but future adaptive risk models that allow for addition of new information during the course of hospitalization may provide more accurate and flexible therapeutic guidance. Troponin and novel biomarkers may play a substantial role in this development as it has recently been shown that they may be used to tailor antiplatelet therapy [94]. Along this line, further development and application of high-sensitivity point-of-care biomarker assays will help to shift initial risk stratification and pharmacological pretreatment to the prehospital setting [95,96]. High-risk NSTEMI patients can then be referred directly to a PCI-capable center to shorten delay to treatment without jeopardizing the 2-h pharmacological pretreatment window that seems to be required to stabilize plaque and optimize outcome in these patients. In fact, the first steps towards such an approach are being taken in an ongoing prospective observational study (NTR4205) [92].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Risk stratification in non-ST-elevation myocardial infarction

- To estimate risk upon admission several clinical risk scores are available, with the Global Registry of Acute Coronary Events (GRACE) risk score being the most widely studied and used.
- Addition of novel biomarkers to these risk scores may further improve their prognostic accuracy.

Initial conservative versus initial invasive management in non-ST-elevation myocardial infarction

- The initial conservative strategy may reduce unnecessary invasive procedures and lower the rate of periprocedural myocardial infarction and bleeding.
- The initial invasive strategy may reduce long-term spontaneous myocardial infarction, length of hospitalization and rehospitalization.
- There does not seem to be a survival benefit from one strategy over the other in a general population, but patients at higher baseline risk benefit most from an initial invasive strategy.

Risk stratification & subgroup considerations in reperfusion strategy selection

- Patients with refractory angina or hemodynamic or electrical instability should be managed invasively.
- Baseline risk should be routinely calculated upon admission using a well-validated clinical risk score.
- Patients with a high baseline risk should be considered for an invasive strategy. An invasive strategy should not be routinely instituted in low-risk patients.
- While women might derive less benefit from an invasive strategy, it may be more effective in the elderly and diabetics.

Timing of coronary intervention in patients selected for the invasive strategy

- An early invasive strategy (delay to intervention 2–24 h) is likely to be superior to a delayed invasive strategy (delay 24–72 h) in high-risk patients.
- An urgent invasive strategy (delay <2 h) may be associated with a higher incidence of periprocedural myocardial infarction compared with an early invasive strategy, although a large trial is lacking.
- Current evidence suggests that an early invasive strategy results in optimal clinical outcome.

References

Papers of special note have been highlighted as:
• of interest; •• of considerable interest

1 Roger VL, Weston SA, Gerber Y *et al.* Trends in incidence, severity, and outcome of hospitalized myocardial infarction. *Circulation* 121(7), 863–869 (2010).

2 Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. *N. Engl. J. Med.* 362(23), 2155–2165 (2010).

3 Davies MJ. The pathophysiology of acute coronary syndromes. *Heart* 83(3), 361–366 (2000).

4 Thygesen K, Alpert JS, Jaffe AS *et al.* Third universal definition of myocardial infarction. *Circulation* 126(16), 2020–2035 (2012).

5 Fokkema ML, James SK, Albertsson P *et al.* Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). *J. Am. Coll. Cardiol.* 61(12), 1222–1230 (2013).

6 Fox KA, Steg PG, Eagle KA *et al.* Decline in rates of death and heart failure in acute coronary syndromes, 1999–2006. *JAMA* 297(17), 1892–1900 (2007).

7 Anderson ML, Peterson ED, Peng SA *et al.* Differences in the Profile, treatment, and prognosis of patients with cardiogenic shock by myocardial infarction classification: a report from NCDR. *Circ. Cardiovasc. Qual. Outcomes* 6(6), 708–715 (2013).

8 Roe MT, Messenger JC, Weintraub WS *et al.* Treatments, trends, and outcomes of acute myocardial infarction and percutaneous coronary intervention. *J. Am. Coll. Cardiol.* 56(4), 254–263 (2010).

9 Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 354(9180), 708–715 (1999).

10 Bugiardini R, Manfrini O, De Ferrari GM. Unanswered questions for management of acute coronary syndrome: risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch. Intern. Med.* 166(13), 1391–1395 (2006).

11 Figueras J, Barrabes JA, Andres M, Otaegui I, Lidon RM, Garcia-Dorado D. Angiographic findings at different time intervals from hospital admission in first non-ST elevation myocardial infarction. *Int. J. Cardiol.* 166(3), 761–764 (2013).

12 Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology–National Cardiovascular Data Registry (ACC–NCDR). *Am. Heart J.* 157(1), 141–148 (2009).

13 Roe MT, White JA, Kaul P *et al.* Regional patterns of use of a medical management strategy for patients with non-ST-segment elevation acute coronary syndromes: insights from the EARLY ACS Trial. *Circ. Cardiovasc. Qual. Outcomes* 5(2), 205–213 (2012).

14 Anderson JL, Adams CD, Antman EM *et al.* 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* 61(23), e179–e347 (2013).

15 Hamm CW, Bassand JP, Agewall S *et al.* ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur. Heart J.* 32(23), 2999–3054 (2011).

16 Granger CB, Goldberg RJ, Dabbous O *et al.* Predictors of hospital mortality in the global registry of acute coronary events. *Arch. Intern. Med.* 163(19), 2345–2353 (2003).

17 Eagle KA, Lim MJ, Dabbous OH *et al.* A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 291(22), 2727–2733 (2004).

18 Fox KA, Dabbous OH, Goldberg RJ *et al.* Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ* 333(7578), 1091 (2006).

19 Fox KA, Eagle KA, Gore JM, Steg PG, Anderson FA, GRACE and GRACE2 Investigators. The Global Registry of Acute Coronary Events, 1999 to 2009 – GRACE. *Heart* 96(14), 1095–1101 (2010).

20 D'Ascenzo F, Biondi-Zoccai G, Moretti C *et al.* 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* 33(3), 507–514 (2012).

• **Overview of acute coronary syndrome risk scores and their performance.**

21 GRACE risk score online calculator. www.outcomes-umassmed.org/grace/

22 Boersma E, Pieper KS, Steyerberg EW *et al.* Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 101(22), 2557–2567 (2000).

23 Brilakis ES, Wright RS, Kopecky SL *et al.* Association of the PURSUIT risk score with predischarge ejection fraction, angiographic severity of coronary artery disease, and mortality in a nonselected, community-based population with non-ST-elevation acute myocardial infarction. *Am. Heart J.* 146(5), 811–818 (2003).

24 Antman EM, Cohen M, Bernink PJ *et al.* The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 284(7), 835–842 (2000).

25 Conway Morris A, Caesar D, Gray S, Gray A. TIMI risk score accurately risk stratifies patients with undifferentiated chest pain presenting to an emergency department. *Heart* 92(9), 1333–1334 (2006).

26 TIMI risk score online calculator. www.timi.org/

27 de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur. Heart J.* 26(9), 865–872 (2005).

28 Subherwal S, Bach RG, Chen AY *et al.* Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. *Circulation* 119(14), 1873–1882 (2009).

29 Abu-Assi E, Raposeiras-Roubin S, Lear P *et al.* Comparing the predictive validity of three contemporary bleeding risk scores in acute coronary syndrome. *Eur. Heart J. Acute Cardiovasc. Care* 1(3), 222–231 (2012).

30 CRUSADE bleeding score online calculator. www.crusadebleedingscore.org/

31 Chew DP, Junbo G, Parsonage W *et al.* Perceived risk of ischemic and bleeding events in acute coronary syndromes. *Circ. Cardiovasc. Qual. Outcomes* 6(3), 299–308 (2013).

•• **Demonstrates superiority of objective risk measures compared with physician perceived risk, providing a possible explanation for the treatment–risk paradox.**

32 Jarai R, Iordanova N, Jarai R *et al.* Prediction of clinical outcome in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) using the TIMI risk score extended by N-terminal pro-brain natriuretic peptide levels. *Wien. Klin. Wochenschr.* 119(21–22), 626–632 (2007).

33 Widera C, Pencina MJ, Meisner A *et al.* Adjustment of the GRACE score by growth differentiation factor 15 enables a more accurate appreciation of risk in non-ST-elevation acute coronary syndrome. *Eur. Heart J.* 33(9), 1095–1104 (2012).

34 de Mulder M, Gitt A, van Domburg R *et al.* EuroHeart score for the evaluation of in-hospital mortality in patients undergoing percutaneous coronary intervention. *Eur. Heart J.* 32(11), 1398–1408 (2011).

35 Palmerini T, Genereux P, Caixeta A *et al.* A new score for risk stratification of patients with acute coronary syndromes undergoing percutaneous coronary intervention: the ACUITY–PCI (Acute Catheterization and Urgent Intervention Triage Strategy–Percutaneous Coronary Intervention) risk score. *JACC Cardiovasc. Interv.* 5(11), 1108–1116 (2012).

36 The TIMI IIIB Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 89(4), 1545–1556 (1994).

37 Lagerqvist B, Husted S, Kontny F *et al.* A long-term perspective on the protective effects of an early invasive strategy in unstable coronary artery disease: two-year follow-up of the FRISC-II invasive study. *J. Am. Coll. Cardiol.* 40(11), 1902–1914 (2002).

38 Cannon CP, Weintraub WS, Demopoulos LA *et al.* Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N. Engl. J. Med.* 344(25), 1879–1887 (2001).

39 Spacek R, Widimsky P, Straka Z *et al.* Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction: an open multicenter randomized trial. The VINO Study. *Eur. Heart J.* 23(3), 230–238 (2002).

40 Fox KA, Poole-Wilson PA, Henderson RA *et al.* Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 360(9335), 743–751 (2002).

41 de Winter RJ, Windhausen F, Cornel JH *et al.* Early invasive versus selectively invasive management for acute coronary syndromes. *N. Engl. J. Med.* 353(11), 1095–1104 (2005).

42 Hirsch A, Windhausen F, Tijssen JG *et al.* Diverging associations of an intended early invasive strategy compared with actual revascularization, and outcome in patients with non-ST-segment elevation acute coronary syndrome: the problem of treatment selection bias. *Eur. Heart J.* 30(6), 645–654 (2009).

43 Hoenig MR, Aroney CN, Scott IA. Early invasive versus conservative strategies for unstable angina and non-ST elevation myocardial infarction in the stent era. *Cochrane Database Syst. Rev.* 3, CD004815 (2010).

• **Most complete meta-analysis comparing initial invasive and initial conservative revascularization strategies.**

44 Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. *Lancet* 356(9223), 9–16 (2000).

45 Lagerqvist B, Husted S, Kontny F *et al.* 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. *Lancet* 368(9540), 998–1004 (2006).

46 Fox KA, Poole-Wilson P, Clayton TC *et al.* 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 366(9489), 914–920 (2005).

47 Hirsch A, Windhausen F, Tijssen JG *et al.* Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. *Lancet* 369(9564), 827–835 (2007).

48 Yusuf S, Flather M, Pogue J *et al.* Variations between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without initial ST elevation. OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) Registry Investigators. *Lancet* 352(9127), 507–514 (1998).

49 Cho L, Bhatt DL, Marso SP *et al.* An invasive strategy is associated with decreased mortality in patients with unstable angina and non-ST-elevation myocardial infarction: GUSTO IIb trial. *Am. J. Med.* 114(2), 106–111 (2003).

50 Puymirat E, Taldir G, Aissaoui N *et al.* Use of invasive strategy in non-ST-segment elevation myocardial infarction

is a major determinant of improved long-term survival: FAST-MI (French Registry of Acute Coronary Syndrome). *JACC Cardiovasc. Interv.* 5(9), 893–902 (2012).

51 Pride YB, Mohanavelu S, Zorkun C *et al.* Association between angiographic complications and clinical outcomes among patients with acute coronary syndrome undergoing percutaneous coronary intervention: an EARLY ACS (Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndrome) angiographic substudy. *JACC Cardiovasc. Interv.* 5(9), 927–935 (2012).

52 Fox KA, Clayton TC, Damman P *et al.* Long-term outcome of a routine versus selective invasive strategy in patients with non-ST-segment elevation acute coronary syndrome a meta-analysis of individual patient data. *J. Am. Coll. Cardiol.* 55(22), 2435–2445 (2010).

•• **Patient-level meta-analysis of three large trials showing that an initial invasive strategy is superior to an initial conservative strategy in patients with high baseline risk.**

53 Damman P, Hirsch A, Windhausen F, Tijssen JG, de Winter RJ; ICTUS Investigators. 5-year clinical outcomes in the ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) trial a randomized comparison of an early invasive versus selective invasive management in patients with non-ST-segment elevation acute coronary syndrome. *J. Am. Coll. Cardiol.* 55(9), 858–864 (2010).

54 National Institute for Health and Care Excellence (NICE). *Unstable Angina and NSTEMI: the Early Management of Unstable Angina and non-ST-Segment-Elevation Myocardial Infarction. National Clinical Guidelines Centre 2010. Clinical Guideline 94*. National Clinical Guidelines Centre, London, UK (2010).

55 Bhatt DL, Roe MT, Peterson ED *et al.* Utilization of early invasive management strategies for high-risk patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. *JAMA* 292(17), 2096–2104 (2004).

56 Fox KA, Anderson FA, Jr, Dabbous OH *et al.* Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart* 93(2), 177–182 (2007).

57 Dokainish H, Pillai M, Murphy SA *et al.* Prognostic implications of elevated troponin in patients with suspected acute coronary syndrome but no critical epicardial coronary disease: a TACTICS-TIMI-18 substudy. *J. Am. Coll. Cardiol.* 45(1), 19–24 (2005).

58 Steg PG, FitzGerald G, Fox KA. Risk stratification in non-ST-segment elevation acute coronary syndromes: troponin alone is not enough. *Am. J. Med.* 122(2), 107–108 (2009).

59 Savonitto S, Cavallini C, Petronio AS *et al.* Early aggressive versus initially conservative treatment in elderly patients with non-ST-segment elevation acute coronary syndrome: a randomized controlled trial. *JACC Cardiovasc. Interv.* 5(9), 906–916 (2012).

60 Avezum A, Makdisse M, Spencer F *et al.* Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). *Am. Heart J.* 149(1), 67–73 (2005).

61 Kolte D, Khera S, Palaniswamy C *et al.* Early invasive versus initial conservative treatment strategies in octogenarians with UA/NSTEMI. *Am. J. Med.* 126(12), 1076–1083.e1 (2013).

62 Angeli F, Verdecchia P, Savonitto S, Morici N, Servi SD, Cavallini C. Early invasive versus selectively invasive strategy in patients with non-st-segment elevation acute coronary syndrome. impact of age. *Catheter. Cardiovasc. Interv.* doi:10.1002/ccd.25307 (2013) (Epub ahead of print).

63 From AM, Rihal CS, Lennon RJ, Holmes DR Jr, Prasad A. Temporal trends and improved outcomes of percutaneous coronary revascularization in nonagenarians. *JACC Cardiovasc. Interv.* 1(6), 692–698 (2008).

64 US National Institutes of Health Trial Register. http://clinicaltrials.gov/

65 Swahn E, Alfredsson J, Afzal R *et al.* Early invasive compared with a selective invasive strategy in women with non-ST-elevation acute coronary syndromes: a substudy of the OASIS 5 trial and a meta-analysis of previous randomized trials. *Eur. Heart J.* 33(1), 51–60 (2012).

66 O'Donoghue ML, Vaidya A, Afsal R *et al.* An invasive or conservative strategy in patients with diabetes mellitus and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. *J. Am. Coll. Cardiol.* 60(2), 106–111 (2012).

67 Haines DE, Raabe DS, Gundel WD, Wackers FJ. Anatomic and prognostic significance of new T-wave inversion in unstable angina. *Am. J. Cardiol.* 52(1), 14–18 (1983).

68 de Zwaan C, Bar FW, Janssen JH *et al.* Angiographic and clinical characteristics of patients with unstable angina showing an ECG pattern indicating critical narrowing of the proximal LAD coronary artery. *Am. Heart J.* 117(3), 657–665 (1989).

69 Luchi RJ, Scott SM, Deupree RH. Comparison of medical and surgical treatment for unstable angina pectoris. Results of a Veterans Administration Cooperative Study. *N. Engl. J. Med.* 316(16), 977–984 (1987).

70 Cho JY, Jeong MH, Ahn Y *et al.* Different impact of mitral regurgitation on clinical outcomes according to timing of percutaneous coronary intervention in patients with non-ST segment elevation myocardial infarction. *Int. J. Cardiol.* 168(5), 4872–4874 (2013).

71 Goldberg RJ, Spencer FA, Fox KA *et al.* Prehospital delay in patients with acute coronary syndromes (from the Global Registry of Acute Coronary Events [GRACE]). *Am. J. Cardiol.* 103(5), 598–603 (2009).

72 Tymchak W, Armstrong PW, Westerhout CM *et al.* Mode of hospital presentation in patients with non-ST-elevation myocardial infarction: implications for strategic management. *Am. Heart J.* 162(3), 436–443 (2011).

73 Nestler DM, White RD, Rihal CS *et al.* Impact of prehospital electrocardiogram protocol and immediate catheterization team activation for patients with ST-elevation-myocardial infarction. *Circ. Cardiovasc. Qual. Outcomes* 4(6), 640–646 (2011).

74 Mahmoud KD, Gu YL, Nijsten MW *et al.* Interhospital transfer due to failed prehospital diagnosis for primary percutaneous coronary intervention: an observational study on incidence, predictors, and clinical impact. *Eur. Heart J. Acute Cardiovasc. Care* 2(2), 166–175 (2013).

75 Cudnik MT, Frank Peacock W, Diercks DB, Roe MT, Chen AY. Prehospital electrocardiograms (ECGs) do not improve the process of emergency department care in hospitals with higher usage of ECGs in non-ST-segment elevation myocardial infarction patients. *Clin. Cardiol.* 32(12), 668–675 (2009).

76 Berger PB, Ellis SG, Holmes DR Jr *et al.* Relationship between delay in performing direct coronary angioplasty and early clinical outcome in patients with acute myocardial infarction: results from the global use of strategies to open occluded arteries in Acute Coronary Syndromes (GUSTO-IIb) trial. *Circulation* 100(1), 14–20 (1999).

77 Mehta SR, Granger CB, Boden WE *et al.* Early versus delayed invasive intervention in acute coronary syndromes. *N. Engl. J. Med.* 360(21), 2165–2175 (2009).

•• **The TIMACS trial is the largest trial on timing of intervention showing benefit from early invasive over delayed invasive management in high-risk patients.**

78 van 't Hof AW, de Vries ST, Dambrink JH *et al.* A comparison of two invasive strategies in patients with non-ST elevation acute coronary syndromes: results of the Early or Late Intervention in unStable Angina (ELISA) pilot study. 2b/3a upstream therapy and acute coronary syndromes. *Eur. Heart J.* 24(15), 1401–1405 (2003).

79 Neumann FJ, Kastrati A, Pogatsa-Murray G *et al.* Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 290(12), 1593–1599 (2003).

• **The ISAR-COOL trial, showing that a prolonged cooling-off period prior to intervention adversely affects outcome in patients undergoing initial invasive management.**

80 Badings EA, The SH, Dambrink JH *et al.* Early or late intervention in high-risk non-ST-elevation acute coronary syndromes: results of the ELISA-3 trial. *EuroIntervention* 9(1), 54–61 (2013).

81 Sciahbasi A, Madonna M, De Vita M *et al.* Comparison of immediate vs early invasive strategy in patients with first acute non-ST-elevation myocardial infarction. *Clin. Cardiol.* 33(10), 650–655 (2010).

82 Tekin K, Cagliyan CE, Tanboga IH *et al.* Influence of the timing of percutaneous coronary intervention on clinical outcomes in non-ST-elevation myocardial infarction. *Korean Circ. J.* 43(11), 725–730 (2013).

83 Riezebos RK, Ronner E, Ter Bals E *et al.* Immediate versus deferred coronary angioplasty in non-ST-segment elevation acute coronary syndromes. *Heart* 95(10), 807–812 (2009).

84 Montalescot G, Cayla G, Collet JP *et al.* Immediate vs delayed intervention for acute coronary syndromes: a randomized clinical trial. *JAMA* 302(9), 947–954 (2009).

85 Thiele H, Rach J, Klein N *et al.* Optimal timing of invasive angiography in stable non-ST-elevation myocardial infarction: the Leipzig Immediate versus early and late PercutaneouS coronary Intervention triAl in NSTEMI (LIPSIA-NSTEMI trial). *Eur. Heart J.* 33(16), 2035–2043 (2012).

86 Sorajja P, Gersh BJ, Cox DA *et al.* Impact of delay to angioplasty in patients with acute coronary syndromes undergoing invasive management: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial. *J. Am. Coll. Cardiol.* 55(14), 1416–1424 (2010).

87 Ryan JW, Peterson ED, Chen AY *et al.* Optimal timing of intervention in non-ST-segment elevation acute coronary syndromes: insights from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Registry. *Circulation* 112(20), 3049–3057 (2005).

88 Montalescot G, Dabbous OH, Lim MJ, Flather MD, Mehta RH; Global Registry of Acute Coronary Events Investigators. Relation of timing of cardiac catheterization to outcomes in patients with non-ST-segment elevation myocardial infarction or unstable angina pectoris enrolled in the multinational global registry of acute coronary events. *Am. J. Cardiol.* 95(12), 1397–1403 (2005).

89 Katritsis DG, Siontis GC, Kastrati A *et al.* Optimal timing of coronary angiography and potential intervention in non-ST-elevation acute coronary syndromes. *Eur. Heart J.* 32(1), 32–40 (2011).

90 Navarese EP, De Servi S, Gibson CM *et al.* Early vs. delayed invasive strategy in patients with acute coronary syndromes without ST-segment elevation: a meta-analysis of randomized studies. *QJM* 104(3), 193–200 (2011).

91 Navarese EP, Gurbel PA, Andreotti F *et al.* Optimal timing of coronary invasive strategy in non-ST-segment elevation acute coronary syndromes: a systematic review and meta-analysis. *Ann. Intern. Med.* 158(4), 261–270 (2013).

• **Most recent meta-analysis assessing trials and observational studies on timing of coronary intervention.**

92 The Netherlands Trial Register. www.trialregister.nl/

93 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control. Clin. Trials* 7(3), 177–188 (1986).

94 Wallentin L, Lindholm D, Siegbahn A *et al.* Biomarkers in relation to the effects of ticagrelor in comparison with clopidogrel in non-ST-elevation acute coronary syndrome patients managed with or without in-hospital revascularization: a substudy from the prospective randomized Platelet Inhibition and Patient Outcomes (PLATO) trial. *Circulation* 129(3), 293–303 (2014).

95 van der Laarse A, Cobbaert CM, Gorgels AP, Swenne CA. Will future troponin measurement overrule the ECG as the primary diagnostic tool in patients with acute coronary syndrome? *J. Electrocardiol.* 46(4), 312–317 (2013).

• **Elaborates on current state and future challenges of (prehospital) biomarker assessment.**

96 Korley FK, Jaffe AS. Preparing the United States for high-sensitivity cardiac troponin assays. *J. Am. Coll. Cardiol.* 61(17), 1753–1758 (2013).