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Routine Invasive Versus Conservative Management Strategies in Acute Coronary Syndrome: Time for a "Hybrid" Approach

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Abstract The acute coronary syndrome is most often caused by plaque rupture and can result in a variety of clinical conditions. There are two general strategies (early invasive versus conservative) currently employed in the treatment of unstable angina or non-ST elevation myocardial infarction. Pooled data from recent clinical trials have demonstrated that high-risk patients benefit from a routine or early invasive approach while certain low-risk subgroups have similar outcomes with a conservative approach. Most patients in the USA are treated aggressively given advances in technology and the relative ease of interventional therapy. The routine invasive approach, however, remains controversial and has important limitations that are not well identified in trials. Furthermore, data from trials are difficult to interpret given their relevance to contemporary practice in today's cost conscious, health care environment. The decision to pursue an invasive or conservative approach should be based upon an individual patient's risk profile, and the level of medical therapy should be based on the underlying pathophysiology. The best strategy incorporates aggressive anti-atherosclerotic therapy with early risk stratification and invasive therapy when appropriate—the so-called hybrid approach. Identifying plaque rupture helps identify patients that would benefit from potent antiplatelet, antithrombotic, and anti-inflammatory therapies, and further insight into the natural history of coronary artery disease coupled with continued advances in diagnostic and interventional approaches will hopefully help guide long-term primary and secondary management.

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Introduction

The acute coronary syndrome (ACS) contributes immensely to the global impact of cardiovascular disease. Each year it is estimated that 1.4 million patients present with ACS [1]. In 2007, cardiovascular disease accounted for one out of every six deaths in the USA [2]. Advances in catheter-based techniques as well as novel antiplatelet and antithrombotic agents have resulted in both aggressive and expeditious management strategies. These aggressive approaches carry with them a small, but measurable risk, and it is not always clear that they actually improve clinical outcomes. Outside of the treatment of ST elevation myocardial infarction (STEMI), and even with analysis of contemporary trials, the optimal timing of interventions in patients with ACS is often unclear. Although some pooled data suggest that higher risk patients appear to benefit from an early invasive approach, randomized trials provide conflicting results when comparing a routine invasive strategy, including coronary angiography with revascularization, to a more conservative strategy in all subgroups. Furthermore, contemporary practice in the USA differs considerably from what is observed in these clinical trials. Economic pressures in concert with both patient and physician preferences impact patient flow through the hospital and result in more timely patient triage and stress testing. While studies demonstrated the average length of stay in the hospital for unstable angina was less than 2 days, the time from presentation to angiography in the "early invasive arm" in trials during the same time period was as high as 4 days [3]. In this way, it is difficult to apply the

knowledge gained from a review of clinical trials to current daily practice. Ultimately, after a review of the pathophysiology of ACS and a comparison of the clinical results from contemporary trials, one may speculate that a combination of aggressive, pathobiologically directed medical therapy with coronary revascularization in selected high-risk patients will lead to improved clinical outcomes.

Background

The acute coronary syndrome represents a variety of clinical conditions that cause myocardial ischemia and necrosis. These conditions represent a disease continuum that range from acute STEMI to unstable angina and non-ST elevation myocardial infarction (UA/NSTEMI). Each of these conditions differs from chronic coronary artery disease in both their abrupt presentation and their associated morbidity and mortality.

Acute ST elevation myocardial infarction can be distinguished from UA/NSTEMI syndromes by the presence of ST elevation on the initial electrocardiographic evaluation. It is most often caused by an acute thrombotic occlusion of the coronary artery. If the obstruction is present for a long enough period of time, myocardial necrosis occurs [4]. Effective management in STEMI has largely been driven by the paradigm that "time is myocardium," in which reestablishing flow either by percutaneous intervention or thrombolytic therapy in a timely fashion clearly improves survival [5, 6]. In fact, current guidelines suggest the goal for patients with STEMI should be to achieve a "door-to-treatment" time within 30 to 90 min of arrival to the emergency room [7].

Conversely, UA/NSTEMI syndromes are usually associated with a partial or transient coronary obstruction that results in a temporary reduction in coronary blood flow [8]. Microemboli have also been implicated in the pathophysiology of UA/NSTEMI [8]. Lower coronary perfusion as seen with hypotension and coronary vasospasm are also contributing factors [9, 10]. Whether at a macro or microvascular level, these syndromes are directly influenced by an imbalance between myocardial oxygen supply and demand.

Because the obstruction seen in UA/NSTEMI is transient and often only partially occlusive, the approach is less dependent on reestablishing coronary flow and relies more on the improvement and stabilization of flow. Recognizing this difference is critical when developing management strategies unique to UA/NSTEMI. To understand this difference, evidence suggests a number of factors help determine outcome in these syndromes. These include the type and size of underlying atherosclerotic plaque, the extent and characteristics of platelet aggregation and the superimposed thrombus, the intraluminal inflammatory and hemostatic response, and coronary vasoconstriction [11]. Each factor may contribute more or less significantly in an individual patient, creating a clinical spectrum that can range from new onset chest discomfort to hemodynamic instability and even sudden death, as opposed to a specific disease process [10]. Clearly, the variability in the type, severity, and outcome for UA/NSTEMI calls for a multifaceted and broad approach, and a better understanding of the pathophysiology of ACS will set the stage for a discussion on the optimal management strategy.

The Pathophysiology of ACS

The cardinal event in the vast majority of acute coronary syndromes is the rupture or disruption of atheromatous plaque [12]. Progression of coronary plaque is likely a stepwise process rather than a simple, linear relationship over time. Coronary atherosclerosis begins by the deposition and binding of lipoprotein to proteoglycans in the tunica intima [13]. Monocytes and T lymphocytes begin to adhere to endothelial cells and then enter the tunica intima to combine with lipids. These interactions are governed by various adhesion molecules including selectins, vascular cell adhesion molecules, and intercellular adhesion molecules. Various pro-inflammatory molecules as well as extracellular matrix deposition and destruction by metalloproteinases contribute to the formation of atheroma [14]. Plaques may develop layers of mineralization and calcification and together with smooth muscle cells and connective tissue form a fibrous cap over the atheroma.

Rupture of the fibrous cap and erosion of the intima are the primary mechanisms for transient coronary occlusion. Once the inner prothrombotic elements of the plaque are exposed to blood, the deposition of platelet rich thrombi at the site of disruption can result in a cascade of thrombotic and inflammatory events. The dynamic interplay of platelet deposition, endogenous thrombolysis, and endothelial repair, as well as a number of local and systemic factors determine the amount of luminal obstruction [15]. Platelet aggregation and thrombus may also embolize downstream [16]. The clinical presentation of the acute coronary syndrome is not only based on the extent and duration of ischemia due to these obstructions, but also the distribution of the involved coronary artery and the demand for oxygenated blood. These variable clinical features are also modified by vascular tone and available collateral flow [17] (Fig. 1).

Much attention has focused on which plaques are prone to rupture. These so-called vulnerable plaques include those that have thin fibrous caps, increased expression of matrix matalloproteinases and collagen breakdown, smooth muscle

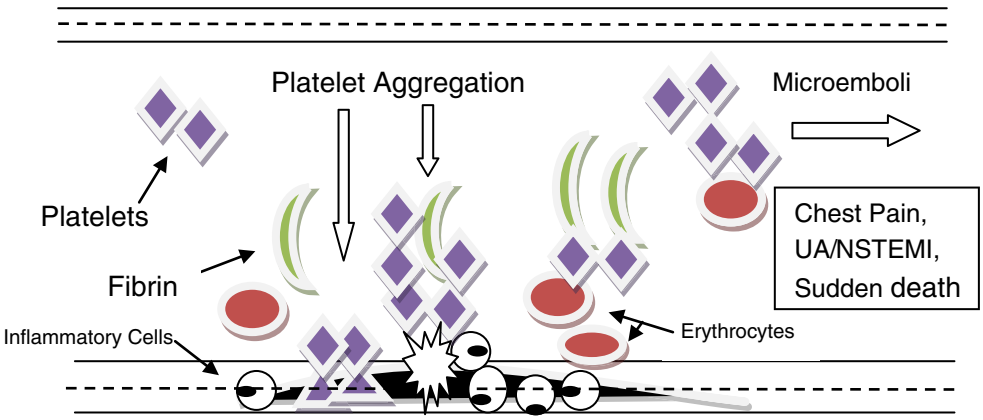

Fig. 1 Pathophysiology of the acute coronary syndrome (ACS). Plaque rupture with platelet aggregation, partial coronary obstruction, and microembolization

cell apoptosis, and amplified inflammatory mediators [11]. Angiographic studies have demonstrated that most plaques that rupture are paradoxically not hemodynamically significant, causing less than 70% diameter stenosis of the artery [18] [19]. Less obstructive plaques may be more responsible for acute clinical syndromes not only because they may be more prone to rupture, but because they may be greater in number than those lesions that cause a severe coronary stenosis [20, 21]. It has also been observed that vulnerable plaques tend to rupture at the shoulder region of the plaque, where large lipid cores and activated macrophages exert mechanical stress in an area of less stability [11]. In one study, thin-cap fibroatheromas represented an independent correlate of major adverse cardiovascular events related to a non-culprit or a non-significant lesion during 3 years of follow-up [22]. There is still much ongoing investigation that will help identify and characterize atherosclerotic plaques at high risk for rupture earlier that is beyond the scope of this review.

How Can We Tell It is Plaque Rupture Clinically?

It is difficult to identify plaque rupture clinically as several non-coronary-mediated mechanisms may mimic a clinical history suggestive of plaque rupture and acute coronary syndrome. However, the vast majority of patients with myocardial infarction and sudden death demonstrate disrupted atherosclerotic plaque as a primary cause [23]. Prodromal chest pain or a syndrome of pre-infarct angina in these patients identifies a cohort with an increased frequency of plaque rupture and coronary thrombi as a cause of their event [24]. Triggers such as physical activity, snow shoveling, anger, and emotional stress have also been associated with vulnerable plaque rupture and coronary thrombus [25, 26]. An associated history of cigarette smoking, peripheral vascular disease, and previously known coronary disease may also suggest underlying plaque formation and disruption as the cause of acute coronary syndromes [11, 27, 28]. Recently, it was found that the metabolic syndrome, and more specifically abdominal obesity, was an independent predictor of rupture of a culprit plaque in patients presenting with ACS [29]. The character of the pain, the location, duration, alleviating factors, and presence or absence of triggers can all be helpful in determining the likelihood of underlying plaque rupture [30].

In addition to historical features, cardiac biomarkers may provide evidence for plaque rupture as a causative mechanism for ACS. Recently, myocardial infarction was more specifically defined to include a typical “rise and fall” pattern consistent with the timing of symptoms in addition to other clinical features suggestive of ischemia [31]. This paradigm shift in the definition of ACS reflects the primary ischemic cardiac injury caused by plaque rupture and distinguishes itself from sustained myocardial injury such as that seen in myocarditis or other non-coronary-mediated elevations [32]. The degree of change in these biomarkers within the first 2 h of presentation may also improve the specificity in the diagnosis and long-term prognosis of high-risk patients with suspected ACS [33]. More sensitive biomarker assays can increase the diagnostic accuracy of ACS and have been shown to have negative predictive values of over 99% for myocardial infarction when drawn at presentation [34]. Elevations in N-terminal proBNP and inflammatory cytokines have also been observed early after pain onset in suspected ACS patients [35]. Although inflammatory markers are currently not standard practice in the evaluation of these patients, their role in this setting may expand as more is understood regarding the clinical implications of plaque rupture and the underlying inflammatory processes that contribute to this syndrome.

Dynamic electrocardiogram changes and focal wall motion abnormalities on echocardiography, although in some cases nonspecific, may also suggest higher risk features that can identify patients with plaque-mediated ACS versus non-coronary syndromes. Patients with objective evidence of ischemia either by electrocardiogram or

noninvasive testing demonstrate better outcomes with more aggressive antiplatelet and antithrombotic therapies compared to their lower risk counterparts [36]. These data are consistent with the underlying mechanisms of plaque disruption which would predict the benefit of plaque-directed therapies in certain higher risk patient subgroups. Global left ventricular dysfunction, pericardial disease, and pulmonary disease with right ventricular abnormality may also suggest other etiologies for chest pain and electrocardiographic changes.

Despite an increased understanding of vulnerable and ruptured plaque, it is still difficult to clinically identify these patients. More than half of the chest pain visits to an emergency room are not secondary to an acute coronary syndrome [37]. In addition, a significant portion of patients with ACS do not exhibit chest pain, and this atypical presentation is more frequently found in the elderly, women, and diabetics [38]. A significant proportion of elevated cardiac biomarkers are ultimately found to be due to non-coronary or secondary disturbances [39]. Heart failure, pulmonary emboli, and hypertensive urgencies are common causes of non-coronary-related chest pain and biomarker elevation. Both in trials and in practice, the significance of chest pain or an angina equivalent with or without a positive biomarker must be put into the context of the clinical presentation. Clinical assessment to distinguish primary plaque rupture versus secondary causes of symptoms and biomarker elevation remains essential [32].

Medical Therapy

Multiple medical interventions are now available for the treatment of plaque rupture and the subsequent acute coronary syndromes. Most therapies direct their effect on platelet aggregation, the thrombotic response, or hemostasis. As alluded to previously, platelets play a key role in the formation of thrombus and have therefore served as attractive therapeutic targets. The most fundamental of antiplatelet agents is aspirin. While the evidence for the benefit of aspirin in the management of UA/NSTEMI is not as robust as in the setting of STEMI, there are trials that have shown clear benefit. The RISC trial enrolled 796 patients with non-ST elevation myocardial infarction and randomized them to therapy with low-dose aspirin, intravenous heparin infusion, or placebo [40]. The percentage of the combined endpoint of acute MI or death was at least three times higher for those patients receiving placebo compared to aspirin. Likewise, the Veteran's Administration Cooperative Study showed a 51% reduction in acute MI or death in patients with non-ST elevation myocardial infarction randomized to full-dose aspirin (325 mg/day) versus placebo [41].

Irreversible platelet P2Y12 antagonists such as clopidogrel and prasugrel have also demonstrated a reduction in myocardial infarction, stroke, and cardiovascular death in ACS patients [41–43]. The CURE study was a landmark trial that clearly demonstrated an important role for clopidogrel in the management of UA/NSTEMI and resulted in an update in the treatment guidelines for ACS [44].

Glycoprotein IIB/IIIA inhibitors, which work by inhibiting fibrin-mediated cross-linking of platelets, provide benefit in high-risk ACS patients prior to percutaneous coronary intervention [45]. Abciximab, eptifibatide, and tirofiban are all approved for use in UA/NSTEMI. Benefit with abciximab was demonstrated in the EPIC trial which compared abciximab versus placebo in a subset of patients with NSTEMI prior to PTCA. The group receiving abciximab had a 62% reduction in the primary endpoint of MI, urgent revasularization, and death relative to the placebo group [46]. The major benefit of therapy with these potent agents appears to be in high-risk patients destined for percutaneous coronary intervention (PCI) as determined by various risk scores [47–49]. Of course, these benefits have to be weighed against the risk of bleeding inherent in their mechanism of action. For this reason, glycoprotein IIB/IIIA inhibitors are most favored in high-risk patients who did not receive a platelet P2Y12 antagonist such as clopidogrel or prasugrel [50].

Anticoagulation therapy including unfractionated heparin (UFH), low molecular weight heparin (LMWH), and direct thrombin or factor Xa inhibitors also decrease ischemic complications associated with ACS [51–53]. In contrast to UFH and LMWH, direct thrombin inhibitors offer the advantage of being able to neutralize clot bound thrombin. The ACUITY trial established that the direct thrombin inhibitor bivalirudin was noninferior to UFH and LMWH plus a glycoprotein IIb/IIIa inhibitor in the prevention of ischemic complications at 30 days in patients with NSTEMI. At the same time, there were lower rates of major bleeding in patients treated with bivaluridin alone [54].

In addition to antiplatelet and antithrombotic therapy, patients with UA/NSTEMI should also receive anti-ischemic therapy and aggressive risk factor modification. Standard anti-ischemic therapy consists of beta-blockers and nitroglycerin. Of note, beta-blockers have not been directly evaluated in large clinical trials in the setting of UA/NSTEMI. They do have proven benefit in STEMI and the current guidelines recommend their use in virtually all patients with an acute coronary syndrome and no clear contraindications. That being said, it should be noted that the prior standard of intravenous beta-blocker therapy is no longer recommended as first-line therapy and that oral beta-blocker therapy should be used if appropriate instead. This

latest ACC/AHA guideline recommendation was based on the fact that intravenous beta-blocker therapy was associated with hypotension and significant bradycardia [50].

Finally, plaque-modifying agents such as HMG-CoA reductase inhibitors may also play a role in stabilizing plaque and preventing further plaque rupture [55]. Statins are thought to reduce the activation of macrophages and ameliorate the inflammatory process associated with plaque disturbance. Furthermore, they have been shown to lower the activity of matrix metalloproteinases in animals and to promote plaque healing and endothelial function [13].

The constituents of the ruptured plaque and the degree of platelet activation may account for the variable responses to certain therapies such as antiplatelet agents or thrombolytics in patients with different acute coronary syndromes. Angiographic studies have demonstrated that higher risk patients have more complex lesions and evidence of intracoronary thrombus [56]. The thrombus in UA/NSTEMI is often described as "platelet rich" and is less influenced by fibrin. These findings predict that high-risk ACS patients benefit from more intense anti-platelet-directed therapy, and fibrinolytic therapy does not improve outcomes as shown in trials. In TIMI 3B, the addition of a thrombolytic agent not only did not improve outcomes but it may have increased risk in ACS patients [57]. Thrombolytic therapy is not indicated in the treatment of UA/NSTEMI [50].

Invasive Therapy

Traditionally, coronary angiography helps identify patients that have hemodynamically significant stenosis and require revascularization. Advances in technique have made diagnostic angiography, PCI, and coronary artery bypass surgery (CABG) low risk and well tolerated. Thirty-day mortality for PCI is less than 1% and less than 2% for CABG [58]. Intracoronary stents have lowered the incidence of abrupt coronary closure, procedural myocardial infarction, and restenosis [59]. PCI with stenting at the site of the ruptured plaque not only improves reperfusion at the myocardial tissue level, but also provides a mechanical "scaffold" that stabilizes the site and reduces residual arterial stenosis. In this way, stents locally attenuate the obstructive process of plaque rupture and ensure that the risk of recurrent rupture at the treated site is negligible.

Current indications for coronary angiography in the setting of ACS include those patients that have refractory angina, hemodynamic instability, or electrical instability without serious contraindications to the procedure and those patients that have an elevated risk for recurrent clinical events despite medical therapy [60]. However, there are proponents of an early or routine invasive strategy, even in low- to moderate-risk patients. In this approach, an aggressive invasive strategy provides definitive risk stratification in which appropriate management can be tailored according to the coronary anatomy. Patients with obstructive disease can then be revascularized if appropriate or treated medically if culprit lesions are not present or flow limiting.

There are several important limitations associated with the routine invasive approach and many of these factors should be taken into account when evaluating the most appropriate ACS treatment strategy. Although coronary angiography has been the gold standard in defining coronary anatomy and grading the significance of a stenosis or lesion severity, there is significant inter-observer variability in the interpretation of less than critical disease [61]. Coronary angiography as an anatomical assessment does not necessarily reflect the physiologic significance of a culprit lesion either in its ability to predict flow disturbances or as to whether a plaque is active or unstable. Angiographic interpretation of lesions and functional testing are often discordant and the significance of most moderate lesions cannot be accurately predicted by interventional cardiologists [62]. Recently, intravascular ultrasound and optical coherence tomography have been used to more accurately characterize plaque in ACS and predict lesion instability [63, 64].

As angiography provides an imprecise two-dimensional assessment of the coronary vessel and culprit lesion, it can also grossly underestimate the degree of disease present. Atherosclerosis is a systemic and not local process. Both intracoronary ultrasound and CT imaging studies revealed that there may be multiple plaques along a coronary artery separate from the culprit lesion that are not appreciated by angiography [22, 65, 66]. Focal treatment of a coronary stenosis with stent placement does not address the underlying disease process or the non-culprit plaques. Multi-vessel intravascular ultrasound studies demonstrate a high prevalence of disrupted atherosclerotic plaques in non-culprit arteries in patients presenting with ACS [67]. In a recent post-PCI trial, recurrent cardiovascular events were as likely to occur from the non-culprit plaques as the previously intervened upon culprit lesion [22].

Although the risks of invasive therapy and PCI are low, they are not trivial. With elective PCI, the percentage of patients requiring emergent CABG is low, but this percentage increases with higher patient risk characteristics and can range between 0.3% and 1.2% [68–70]. Rates of major bleeding requiring transfusion can be as high as 3–4% and there is a 0.2–0.4% risk of stroke [71]. Stents are associated with neo-intimal proliferation and restenosis as well as stent thrombosis. The restenosis rates with bare metal stents can range from 15% to 30% [72, 73] and the restenosis rates with drug-eluting stents can range from 3%

to 20% [74]. After stent placement, there is as high as a 2.1% incidence of stent thrombosis, which typically results in acute closure of the coronary artery and subsequent myocardial infarction [75]. Women compared to men have higher peri-procedural complication rates, and guidelines suggest that women who are low risk should be treated conservatively [76].

Invasive Versus Conservative Strategies

There are two general strategies currently employed in the treatment of UA/NSTEMI. The first is an "early invasive approach" in which UA/NSTEMI patients are taken to the cardiac catheterization laboratory within the first 48 h of presentation. Coronary angiography defines the coronary anatomy and revascularization is performed if appropriate. The second strategy is a "conservative approach" in which patients are first treated medically. In this strategy, only those patients that fail therapy or are proven to be high risk are considered for coronary angiography. Despite recent clinical trials, the optimal window of time and long-term benefit of an early or routine invasive approach remains elusive. It is unclear whether improved clinical outcomes can be demonstrated with a more aggressive approach of early invasive therapy in all subsets of patients presenting with ACS. In higher risk patients, it is also unclear as to what defines "early" invasive treatment and if there is benefit to performing angiography urgently—within hours of presentation—or even days after medical therapy and plaque stabilization.

The definition of "early" invasive therapy varies significantly in trials from 2 h to 4 days after presentation of ACS [77, 78]. Early trials demonstrated no benefit between invasive therapy and conservative therapy but were limited by high crossover rates, lack of stent usage, and suboptimal PCI success rates [58, 79]. FRISC II, which had lower short-term crossover rates, demonstrated a decreased combined endpoint of death or myocardial infarction in the early invasive arm at 6 months and at 5 years [78].

More contemporary studies using stents have also demonstrated inconsistent benefit with early invasive therapy. RITA-3 studied moderate-risk patients excluding those with creatine kinase or creatine kinase MB concentrations twice the upper limit of normal. Although patients had less recurrent ischemia with an invasive strategy, there was no difference in 1-year mortality compared to conservative management [80]. Interestingly, 5-year data in RITA 3 demonstrated a reduction in the combined endpoint of death and myocardial infarction in the invasive arm [81]. TACTICS-18 found higher risk patients including those with ECG changes or positive troponin markers derived the greatest benefit with a more aggressive or early invasive strategy but little if any benefit was seen in low-risk patients [36]. Conversely, both the short-term and 5-year follow-up in the ICTUS trial demonstrated no benefit of an early invasive strategy over conservative treatment in ACS patients with positive troponin markers [82].

Several recent trials have tried to answer the question as to when angiography should be performed if the patient is to be treated invasively. The ISAR-COOL trial compared an early invasive strategy (mean time of 2.4 h) with a delayed invasive strategy (mean time of 86 h) and there was a significantly reduced incidence of combined death and myocardial infarction in the group receiving early intervention [77]. On the other hand, TIMACS [83] compared routine early intervention (less than 24 h) with delayed intervention (greater than 36 h) and found no difference in the composite of death, myocardial infarction, and stroke at 6 months. Higher risk patients in this trial, however, had a significant benefit of early invasive therapy in a prespecified analysis [83]. Notably, a strategy of immediate intervention (70 min) versus delayed intervention (21 h) had no impact on the magnitude of the peak troponin elevation in ACS patients [84]. Thus, although it appears that higher risk patients may benefit from an early invasive approach, the optimal timing of intervention remains uncertain.

Two contemporary meta-analyses demonstrated early invasive strategies reduce short- and long-term mortality, as well as the incidence of non-fatal myocardial infarction and rehospitalization for unstable angina [85]. Similar to individual randomized trials, the largest absolute benefit was seen in higher risk patients [86]. The weaknesses of these integrated studies include the aforementioned differences in the timing and definition of "early" invasive therapy, the rates of intervention, differences in the definition of myocardial infarction, and use of biomarkers (Table 1).

Contemporary Practice: Best of Both Worlds

Today's environment of shortened hospital stays and rising health care costs have fueled a disconnect between clinical trials and real-world practice. Given advances in technology and the relative ease of interventional therapy, many patients are managed aggressively [87]. In the USA, most patients undergo an early invasive approach regardless of their risk profile and even noninvasive risk stratification can occur within hours of admission. Currently, there are emergency room protocols that include stress testing or CT angiograms for low-risk patients such as those with negative point of care biomarkers. This abbreviated strategy results in a "hybrid" approach combining elements of early risk stratification, aggressive medical therapy, and invasive

Table 1 Significant variability among different trials in the definition of "early" in the routine or early invasive strategy for ACS

Trial (year)	The time from presentation to angiography in the early invasive strategy (h)	Enrollment criteria	Mortality benefit
TIMI 3B [57]	36	Chest discomfort concerning for ACS AND objective evidence of ischemic heart disease. EKG changes or documented coronary artery disease (a history of previous myocardial infarction or a 0.70% luminal diameter stenosis on a previous coronary arteriogram or a positive exercise thallium scintigram)	No
VANQUISH [92]	48	Evolving acute myocardial infarction with CK-MB more than 1.5 times upper limit of normal for the hospital and no new abnormal Q waves on serial EKGs	No
FRISC II [78]	96	Symptoms of ischemia at rest or warranting suspicion of ACS (Ischemia verified by EKG or raised biochemical marker CK-MB >6 mcg/L, troponin-T >0.10 mcg/L)	No
TACTICS TIMI 18 [36]	25	Episode of angina or recurrent episodes at rest within preceding 24 h, candidates for coronary revascularization and at least one of the following—EKG changes, elevated cardiac markers, or coronary artery disease by previous cardiac catheterization or myocardial infarction	Yes
RITA 3 [80]	48	Suspected cardiac chest pain PLUS EKG evidence of ischemia or old pathological Q waves or arteriographically proven coronary artery disease	No
ISAR–COOL [77]	2.4	Angina pectoris at rest or with minimal exertion and last episode within 24 h of study entry with EKG changes and/or cardiac troponin-T of 0.03 mg/L or greater	Yes
ICTUS [93]	23	Symptoms of ischemia that were increasing or occurred at rest, with at least one episode occurring no more that 24 h before randomization; Elevated cardiac troponin-T level (≥0.03 mcg/L); Ischemic changes on EKG or documented history of CAD evidenced by previous coronary angiography or positive stress test	No
TIMACS [83]	14	Unstable angina or myocardial infarction within 24 h of presentation to the hospital and at least 2 of the 3—age more than 60, elevated cardiac biomarkers or EKG changes	No

ACS acute coronary syndrome, *EKG* electrocardiography

therapy when appropriate. In contrast to clinical trials in which each arm was several days in duration, the entire "hybrid" ACS algorithm is typically performed in less than 48 h (Fig. 2.).

Aggressive anti-atherosclerotic and plaque-stabilizing therapies have the potential to improve both short- and long-term outcomes in ACS patients. Identifying plaque rupture helps identify patients that would benefit from potent antiplatelet, antithrombotic, and anti-inflammatory therapies. High-risk patient subgroups in which plaque disruption is more advanced or complex may develop flow limiting, obstructive disease. Depending on coronary anatomy, these patients may have large areas of ischemia or myocardium at risk and may further benefit from invasive therapy and revascularization. In this way, aggressive medical therapy and invasive therapy work synergistically as opposed to competitively in the treatment of ACS. Moreover, patients deemed to be low risk can be further risk stratified through noninvasive stress testing. Those patients found to have large areas of reversible ischemia or significant left ventricular dysfunction due to obstructive coronary artery disease become candidates for coronary angiography.

If plaque rupture is suspected, the decision to pursue an invasive or conservative approach can be largely based upon an individual patient's risk profile. Two risk assessment scoring systems have emerged for this purpose: The Thrombolysis in Myocardial Infarction (TIMI) risk score and the Global Registry of Acute Coronary Events (GRACE) score. The TIMI risk score, which is based upon an analysis of the TIMI 11B and Essence trials, uses seven variables to assess the risk of myocardial infarction, recurrent ischemia, and death within 2 weeks of hospital discharge [47]. The GRACE score incorporates eight different variables to assess a patient's risk of death or myocardial infarction while in the hospital or over the next 6 months [49]. Patients may fall into a high-, low-, and intermediate-risk category. As discussed, invasive manage-

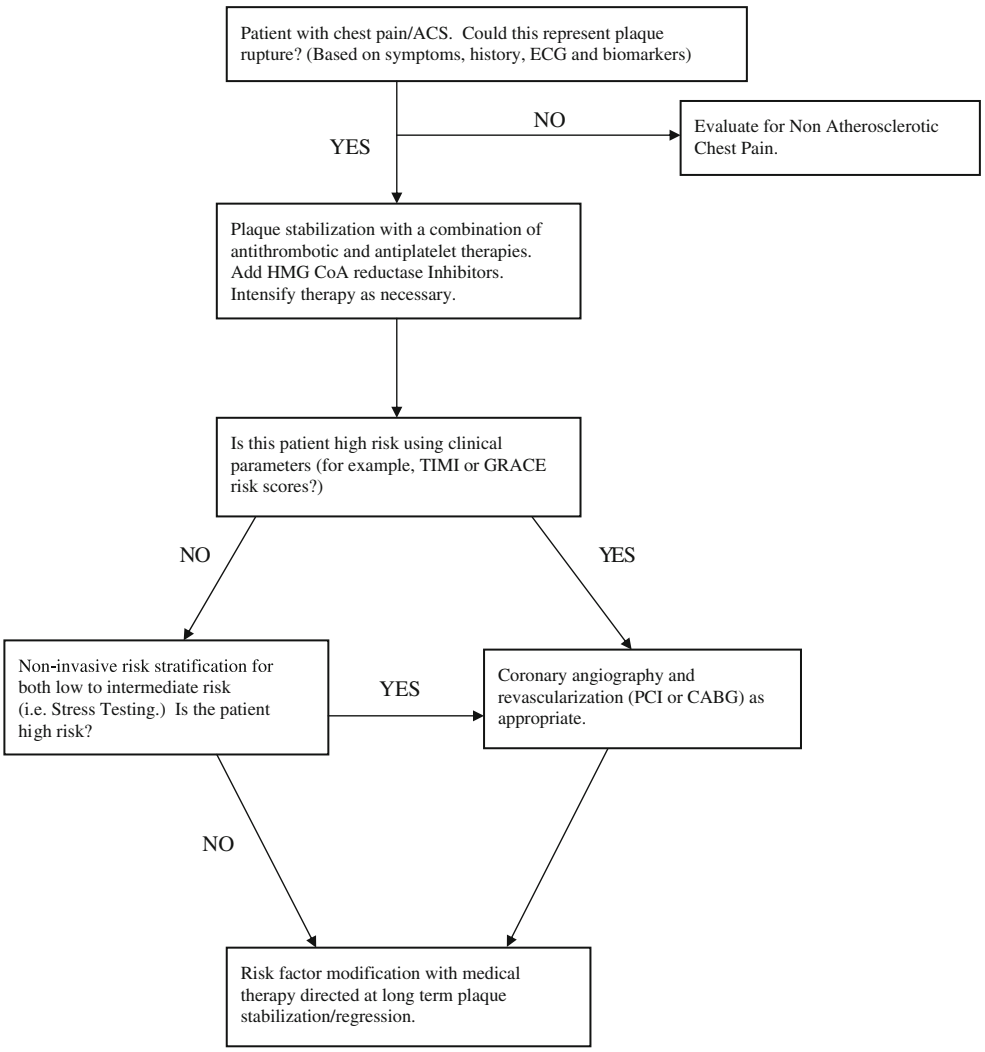

Fig. 2 An algorithm for ACS combining contemporary practice with trial-based evidence and pathophysiology. The entire algorithm could be performed in less than 48 h, i.e., the "hybrid" approach

ment in high-risk patients may be more justifiable. However, low- to intermediate-risk groups are typically further risk stratified using noninvasive testing. Optimal management strategies for these low- or intermediate-risk patients, including conservative management or stress testing in lower risk patients, may depend on physician preference and local practice patterns. Whether or not one chooses to employ these risk scoring systems, risk assessment should still be performed early in the management of ACS patients to help define the type and intensity of both medical and invasive therapies [50].

Several studies, both in the USA and abroad, have documented the shift towards chest pain units and early noninvasive stress testing for low- to moderate-risk subgroups on the basis of cost-effectiveness. In the mid 1990s, Gomez et al. showed that low-risk patients, randomized to a "rapid rule-out" protocol as opposed to routine care, were more likely to have a shorter hospital stay and lower hospital charges both initially and at 30 days [88]. Similarly, Mikhail et al. demonstrated that even mandatory stress testing in low-risk patients assigned to a chest pain center was associated with cost savings [89]. Indeed, patients in the USA presenting with UA/NSTEMI often undergo stress testing within 24 h or less of admission. One clinical trial enrolling patients with unstable angina safely discharged almost half of all patients from a chest pain unit after a low-risk clinical evaluation and negative stress testing with a median length of stay of 9.2 h [3]. In the last decade, the median length of stay for acute myocardial infarction continues to decrease and the majority of high-risk patients with UA/NSTEMI in the USA currently undergo cardiac catheterization [90, 91]. Approximately one third of patients undergoing coronary angiography are revascularized [91].

It is unlikely that the economical considerations and need for rapid evaluation in health care will soon disappear. How then can this hybrid approach best be utilized? The burden will lie heavily on physicians to utilize a high index of

suspicion for ACS based on clinical presentation, risk factors, and objective measures such as ECG and biomarkers. By more accurately triaging those patients at highest risk, we can reserve invasive catheter-based strategies for those most likely to benefit. Certainly, this is a challenging proposition and one that will require more research into novel risk factors and early markers of underlying plaque rupture.

Conclusion

ACS is most often caused by plaque rupture. The mechanism and events surrounding plaque rupture helps predict which medical therapies most benefit these patients. Invasive therapy, including PCI, is safe and often the preferred strategy in the USA, but it has its limitations. Pooled data from recent clinical trials have demonstrated that high-risk patients benefit from an early invasive approach, while certain low-risk subgroups have similar outcomes with a more conservative approach. The best strategy incorporates aggressive antiatherosclerotic therapy with early risk stratification and invasive therapy when appropriate—the "hybrid" approach. Further research into the understanding of the natural history of coronary artery disease coupled with continued advances in diagnostic and interventional approaches will hopefully allow for greater identification of vulnerable plaque and help guide long-term primary and secondary management.

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