The changing face of acute coronary syndromes

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Abstract

There have been significant advances in the definition, diagnosis, and management of acute coronary syndromes over the past decade. The roles of both medical management and revascularization have been examined in several large scale randomized controlled trials. As such, the management of STsegment elevation myocardial infarction is well established. Until this year, agreement over the most appropriate management of non-ST segment elevation myocardial infarction also seemed close, but the recent publication of the 5-year follow-up of the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial seems to have again cast doubts over current practice. Here, we explore the current practice and future management of acute coronary syndromes.
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Introduction

Over the past decade, significant advances have been made in the care of patients with acute coronary syndromes (ACS). The improvements encompass diagnosis (cardiac biomarkers, non-invasive angiography, functional imaging), management (medical and revascularization), and secondary prevention. Despite these advances, the best early management of the largest class of ACS (non-ST-segment elevation myocardial infarction [NSTEMI]) remains uncertain. In this review, we explore the pathophysiology, current best management, and future perspectives of the acute coronary syndromes.

Pathophysiology of acute coronary syndromes

ACS arise due to inadequate oxygen supply to the myocardium and can be attributed to five interacting variables: thrombosis, mechanical obstruction, dynamic obstruction, increased myocardial oxygen demand and inflammation or infection [1], but the formation of atherosclerotic plaques within coronary arteries underlies most ACS. Plaque formation is the result of a chronic immune-inflammatory process driven by lipid accumulation within the walls of medium-sized and large arteries. This causes either gradual luminal narrowing leading to a relatively fixed and irreversible lesion or rapid and potentially reversible occlusion as a result of thrombosis [2], vasospasm [3], or both.

Atherosclerotic plaques initially form as precursor lesions, known as fatty streaks, which appear in infancy. The transition from these benign lesions to plaques prone to rupture is a continuous process with relative phases of stability and instability. Unstable plaques typically have a large lipid core, a high concentration of inflammatory cells and a thin fibrous cap [4]. Triggered by multiple patient-specific genetic and environmental factors, the final common pathway of plaque rupture, exposure of the necrotic prothrombotic core and coagulation cascade activation [5] leads to intraluminal thrombosis and ACS.

STEMI or NSTEMI: who decides?

Myocardial infarction (MI) has historically been defined as a combination of two of three characteristics: typical symptoms, a typical ECG pattern with development of Q waves, and a rise in cardiac enzymes. This definition became outdated in terms of risk stratification and lagged behind the development of new diagnostic techniques. The European Society of Cardiology/ American College of Cardilogy/American Heart Association (ESC/ACC/AHA) consensus conference of 1999 [6] therefore re-classified ACS based on the presence or absence of ST elevation and the subsequent detection of necrosis, whether that be via electrocardiographic, biochemical, pathological, or imaging modalities. Patients without ST elevation during the acute phase and without Q wave development could now be classified as MI, with wide-ranging therapeutic and epidemiological implications. The terminology for MI developed by the conference has been adopted with ACS now classified as ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina (UA), in which there is no evidence of myocardial necrosis.

The clinical entities of STEMI and NSTEMI also differ in the underlying pathological processes and the relative contributions of thrombus formation and vasospasm (*Figure 1*). STEMI is usually associated with complete vessel occlusion [7] and unstable angina or NSTEMI with subtotal occlusion [8]. The components of the thrombus have also been found to be different in patients with STEMI compared to those with NSTEMI [9]. The former is predominantly fibrin-rich and the latter platelet-rich.

The importanceof the ability to classifyaproportionof ACS as MI that were previously attributed to unstable angina can be seen in both the prevalence and mortality statistics. In the United States, unstable angina and NSTEMI account for over four times the number of admissions to hospital than STEMI [10] and despite STEMI having a worse 30-day mortality than NSTEMI, they have similar 1-year [11] and 5-year mortality rates [12]. Although hospitalization rates due to MI remain largely stable, the proportion of STEMI does seem to be falling while that of NSTEMI appears to be increasing [13]. One hypothesis for the changing epidemiology of STEMI/NSTEMI is that treatment and prevention strategies are largely directed toward plaque disease and thrombosis, and not toward other important factors involved in the pathogenesis of NSTEMI (*Figure 1*). Alternatively, better reporting arrangements to large national registries may reveal previously unidentified cases of NSTEMI. Nevertheless, together these findings underline the importance of identifying best-practice management of NSTEMI.

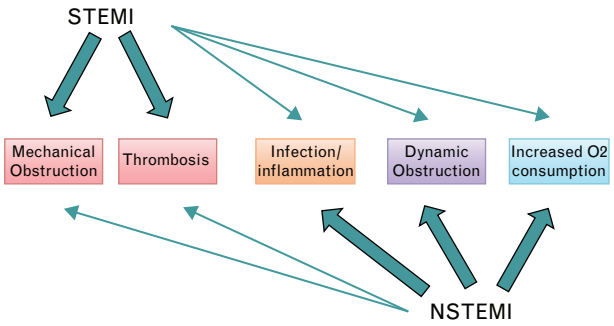

Figure 1. The pathophysiological mechanisms underlying ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). While STEMI is due to acute plaque rupture and thrombus formation, NSTEMI is due to dynamic imbalance between myocardial oxygen demand and delivery.

Management of STEMI

Treatment for STEMI has evolved over the past 30 years with the advent of thrombolysis, percutaneous coronary intervention (PCI), and the optimization of medical therapy. The survival benefit achieved from relieving coronary obstruction by thrombolysis was demonstrated in 1988 by the Second International Study of Infarct Survival (ISIS-2) trial, with the survival benefits of aspirin and streptokinase extending to 10-year follow-up [14]. The concept of a ''golden hour'' in which early intervention provides improved myocardial rescue was confirmed in an analysis of 22 trials comparing thrombolytic therapy to placebo [15]. This analysis found that presentation within 2 hours of symptom onset led to substantially higher benefit from thrombolysis, showing that efficient triage and early intervention improves mortality.

Primary PCI then emerged as a treatment strategy, with a meta-analysis of ten randomized trials [16] comparing primary coronary angioplasty with intravenous thrombolysis finding a 34% reduction in 30-day mortality in the angioplasty group with an associated reduction in stroke and re-infarction. The improved mortality, re-infarction and re-admission rates of PCI were also evident over pre-hospital thrombolysis, and extended to 1-year follow-up [17]. In addition to thrombolysis and PCI, many trials have considered what medications confer a survival benefit post MI. Antithrombotic agents, beta-blockade, inhibitors of the renin-angiotensin system, and lipid-lowering medications have all shown a survival benefit if used in an appropriate context.

Several trials have examined a ''pharmaco-invasive'' strategy, whereby patients presenting with STEMI in non-PCI centers are treated with half dose thrombolysis before urgent transfer to a PCI center. The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) trial

(n = 598) compared such facilitated PCI to rescue PCI after thrombolysis, and found reduced mortality if PCI was performed within 3.35 hr from initial hospitalization [18]. In contrast, the Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events (FINESSE) trial (n = 2452) found nomortality advantage in PCI facilitated with thrombolytic therapy [19]. Subgroup analysis found that high-risk patients (classified by Thrombolysis in Myocardial Infarction [TIMI] score) in the pharmacoinvasive arm did however have a survival advantage at 1-year post treatment. In agreement with these findings, the Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction (TRANSFER-AMI) found fewer ischemic complications in those treated with a pharmaco-invasive strategy than a standard thrombolytic strategy when studying 1,059 high-risk STEMI patients [20]. Hence, a harmaco-invasive strategy could be of benefit in highrisk patients when there is no immediate access to PCI.

The data from these trails has been ratified in international guidelines with both the ESC and the ACC/ AHA recommending PCI as the preferred means of reperfusion, providing it can occur in a timely fashion [21,22]. However, although PCI has been shown to be the intervention of choice for individuals with STEMI, there are continuing debates regarding best practice. Specifically these relate to the preferred site for arterial access, the choice of bare metal or drug-eluting stents, the use of medications post PCI, and the use of thrombolysis prior to PCI.

Management of NSTEMI

As for STEMI, medical management of NSTEMI with anti-ischemic agents (beta-blockers, nitrates) and antithrombotic agents (aspirin, heparin) is well accepted. However, the role and timing of invasive reperfusion techniques in NSTEMI remains less clear. In stark contrast to the results of thrombolysis in STEMI, thrombolysis was early shown in TIMI-IIIB to lead to harm (increased fatal and non-fatal MI) in patients without ST-segment elevation [23]. This trial, from 1994, also ompared the role of ''early invasive'' versus ''early conservative'' strategies in the management of ''non- Q-wave myocardial infarction'', and found no difference in subsequent rates of death, myocardial infarction, or angina. Subsequently, there have beenmany large trials comparing these two strategies and still an overall consensus has not been reached.

In the ''early invasive'' strategy, angiography is routinely performed prior to hospital discharge, while in the ''early conservative'' strategy, best medical management is followed by angiography as indicated by symptoms or recurrent ischemia on provocative testing. Excluding patients with hemodynamic or electrical instability who require immediate angiography, current guidelines recommend risk-stratifying patients with NSTEMI and following an early invasive strategy in those with intermediate to high risk of further events [9,24]. While the European guidelines [9] do recommend against routine angiography in low-risk patients, the American guidelines [24] only recommend limiting the use of angiography in patients with significant co-morbidities, low likelihood of cardiac chest pain, or unwillingness to consent to revascularization. The difference is subtle, but suggests agreement over those patients that should receive early intervention, but not those that are less likely to benefit.

In theory, the early invasive strategy will lead to revascularization (PCI or coronary artery bypass grafting [CABG]) being performed earlier than the early conservative strategy. This supposed advantage must be weighed against the procedural complications and cost in performing greater numbers of invasive procedures. What then is the trial evidence for and against the invasive strategy? In addition to TIMI-IIIB, several other randomized controlled trials (Veterans Affairs Non-Q-wave Infarction Strategies in Hospital [VANQWISH] tiral [25], the Medicine versus Angiography in Thrombolytic Exclusion [MATE] trial [26], and second Randomized Intervention Treatment of Angina [RITA-2] trial [27]) have favored a conservative approach. In VANQWISH there was no difference in death or non-fatal MI between the invasive and conservative arms, and patients randomized to the invasive arm had worse clinical outcome up to 1 year. In MATE, despite revascularization occurring earlier and more often in the invasive group, there was no difference in death or non-fatal MI at 1 year. In RITA-2, there was an improvement in severe angina in the intervention group, but there was also excess mortality in the intervention group, attributed to periprocedural myocardial infarction. More recently, in ICTUS [28] there was a significantly decreased rate of rehospitalization but an increased rate of subsequent myocardial infarction in the interventional arm. This trial is important since it utilized aspirin, heparin and glycoprotein IIb/ IIIa inhibitor (GPI) and encouraged the use of clopidogrel and statins and hence mirrors most closely current best medical management.

While this data seems conclusive, other studies support the use of an early invasive strategy. The Fast Revascularization in InStability in Coronary disease trial II (FRISC-II) [29] and Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)–Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18) [30] demonstrated fewer deaths and non-fatal myocardial infarctions in the invasive arms. RITA-3 [31] identified a reduction in refractory angina, but failed to show an improvement in mortality. There were significant

methodological advantages of RITA-3 over the two prior studies, especially that the definition of myocardial infarction did not differ in the two arms of RITA-3. In FRISC-II and TACTICS-TIMI 18, there were more stringent definitions of MI after PCI than after conservative management perhaps contributing to the apparent reduction in MI by early intervention. These trials also differed in the use of GPIs, with none used in FRISC-II, variable use in RITA-3, and routine use in TACTICS-TIMI 18. All three of these trials did, however, come after the development of intracoronary stents, and hence are more representative of ''current-day'' methods of intervention.

Factors predicting success of an invasive strategy in NSTEMI

Subsequent studies have tried to identify subgroups of patients who are likely to benefit most from the early invasive approach. The benefit of early intervention in NSTEMI may occur in men and women equally [30] or may be limited to men with high-risk features [29,32]. This may be explained by the greater severity of coronary artery disease seen in men on presentation [33]. Additionally, systolic dysfunction may represent an independent predictor of good response to an invasive strategy [34].

Another explanation for the differences between these trials is crossover between the invasive and conservative arms. For example, patients randomized to the conservative arm may undergo intervention before hospital discharge dictated by symptoms or recurrent ischemia. The proportion of such patients that effectively ''cross over'' to the alternate arm varies in each of the trials, making analyses extremely difficult. One approach to solving this problem is to interrogate existing databases, as was done in Global Utilization of Strategies To open Occluded coronary arteries trial IV in Acute Coronary Syndromes (GUSTO-IV ACS) [35]. In doing so GUSTO-IV ACS identified a relative risk of death in the invasive arm of almost half that in the conservative arm.

The effect of timing on outcome is also not known. In STEMI, the benefit gained from an immediate interventional approach is well recognized [22], but after the demonstration of harm arising from immediate thrombolysis in NSTEMI [23] few trials have addressed the role of immediate revascularization in NSTEMI. In the Value of First Day Angiography/Angioplasty in Evolving Non-ST Segment Elevation Myocardial Infarction (VINO) trial [36], comparison of first day intervention (at a mean time of 6.2 hours) versus a conservative strategy found reduced mortality and re-infarction at 6 months in the invasive arm. However in contrast to these results, TACTICS-TIMI 18 (in which the mean time to revascularization was 22 hours) had no effect on mortality, but FRISC-II (in which the mean time to revascularization was 4 days) did significantly improve long-term mortality. Furthermore, results from the Global Registry of Acute Coronary Events (GRACE) registry examining early access to catheter laboratories at presentation found an association between early access to intervention and increased mortality at 6 months [37].

Hence, as yet there is no consensus on the ''gold standard'' management of NSTEMI and although incidence of MI is falling overall, the proportion of NSTEMI is increasing. This may be due to changing population demographics with more female gender, diabetes mellitus, old age, and obesity [38], or may be related to the increased use of preventative medications or improvements in the sensitivity of cardiac biomarker assays [39]. Regardless, the impact of the above uncertainty is likely to grow as the relative prevalence of NSTEMI increases.

Future management of acute coronary syndromes

Perhaps then, the current guidelines exist as they do not because they represent the best approach, but because they represent the only approach. Risk stratification certainly can be performed repeatedly and reliably using for example the GRACE or TIMI scores, and on balance the trials above seem to support early intervention (at 4 hours to 7 days) in high-risk patients.

This year has however seen the publication of several further trials, which yet again do not reach consensus. Fox et al [40] performed a repeat analysis of the above trials (selecting FRISC, RITA-3, and ICTUS) and supported the routine invasive strategy based on reduced death or MI in high-risk patients. In contrast, the 5-year follow-up of ICTUS was also published and failed to show any benefit of a routine invasive strategy in death or MI [41]. Perhaps the future will see better selection of patients, or better timing of intervention. A meta-analysis performed by Katritis et al [42] and a randomized trial performed by Shciabasi et al [43] examined the effect of timing and seem to support rapid access to revascularization after presentation. Meanwhile the development of continuous electrocardiography may better predict subsequent mortality and therefore those patients most likely to benefit from the invasive strategy [44].

Conclusions

In summary, the past 20 years have reinforced the correct management of STEMI, but seem to have generated more questions than answers in the management of NSTEMI (*Table I*). Meanwhile, NSTEMI is

Table I. Unanswered questions in the management of NSTEMI.

Which patients with NSTEMI will benefit from an invasive strategy?
Which patients with NSTEMI will not benefit from an invasive strategy?
What is the best way to risk stratify patients with NSTEMI?
At what time after NSTEMI should one attempt revascularization?

becoming more prevalent and hence its correct management is a key question. Due to the long lead time required to follow-up interventional randomized trials, and the rapid development of better medical and interventional therapies, it seems likely that future trials will always be one step behind the best management of the day. ■

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