Commentary

Debate: Unstable angina – when should we intervene?

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Abstract

The prognosis of patients who present with non-ST segment elevation acute coronary syndromes (ACS) is guarded. These patients can be risk-stratified on the basis of symptom complex, electrocardiographic ST segment depression, obvious hemodynamic compromise and particularly on the basis of serum troponin level. An elevated troponin level determines risk and also predicts the degree of benefit from treatment with either low molecular weight heparin or platelet glycoprotein (GP) IIb/IIIa blockade. Higher risk patients should undergo early coronary angiography and myocardial revascularization as indicated and feasible. Although studies performed before the advent of coronary stenting and adjunctive platelet GP IIb/IIIa blockade suggested increased hazard for patients undergoing early intervention, recent experience cited herein supports an in-hospital and long-term clinical benefit for the aggressive approach. Here, I propose an algorithm for risk stratification and triage of appropriate patients for adjunctive pharmacotherapy and early revascularization.

Keywords: acute coronary syndromes, unstable angina

Introduction

In the current era of coronary stenting and adjunctive platelet GP IIb/IIIa blockade, efficient and effective therapy can be offered to patients who present with non-ST segment elevation ACS. Empirically defined durations of medical 'stabilization' offer no specific advantage to this patient population (unstable angina; non-ST elevation acute myocardial infarction). Unfortunately, prior trials comparing an 'aggressive' (invasive) versus 'conservative' (non-invasive) strategy were performed before the advent of platelet GP IIb/IIIa blockade and coronary stenting [1,2]. These studies identified excess 'hazard' for early intervention and appeared to confirm prior retrospective analyses which had suggested that percutaneous coronary intervention (PCI), performed at the time of diagnostic catheterization (ad hoc) [3,4] or during the first week following presentation for unstable angina [5], was associated with an increased rate of procedural failure and major hospital complications. Thus, the current Agency for Health Care Policy and Research (AHCRP) guidelines published in 1994 promote 'conservatism' to avoid 'early hazard' and, unfortunately, define treatment strategy (invasive versus conservative) before adequately assessing patient risk [6]. In light of recent developments in interventional technology

ACS = acute coronary syndromes; AHCRP = Agency for Health Care Policy and Research; CABG = coronary artery bypass graft; GP = glycoprotein; NHLBI = National Heart, Lung, and Blood Institute; PCI = percutaneous coronary intervention.

and adjunctive pharmacology as well as in our understanding of accurate risk stratification, it is most appropriate at this time to reevaluate our approach to patients with non-ST segment elevation ACS. Let us start by defining the magnitude and significance of this problem.

Non-ST segment elevation ACS has become the most frequent admission diagnosis in the United States Medicare population. In addition, the prognosis of this syndrome with 'conventional' therapy (aspirin, unfractionated heparin, nitrates, beta blockers and no revascularization strategy) remains guarded. Analysis of the control arms for randomized trials of new treatment modalities reveals an incidence of death or nonfatal myocardial infarction of 8–15% at 30 days and 10–20% at 6 months following enrollment [1,7–11]. Observations on the natural history of unstable angina confirm an alarming incidence of death or myocardial infarction (17%) and the requirement for symptom-driven revascularization by either angioplasty (30%) or coronary artery bypass graft surgery (CABG) in 27% of patients at one year following presentation [12]. The ineffectiveness of the conventional-conservative treatment strategy has been compounded by inefficiency. Average published hospital lengths of stay for the diagnosis of unstable angina range from 4–14 days internationally (5 days in the USA) [13–15]. Indeed, recent data from the European ENACT registry of unstable angina demonstrate an average intensive care unit stay of 3.4 days with a total hospital of stay of 8.4 days [15]. These observations point to the need for more effective and efficient treatment strategies for patients who present with non-ST elevation ACS.

Advances in adjunctive pharmacotherapy

Randomized controlled trials have established the superiority of dalteparin (versus placebo) [16] and enoxaparin (versus unfractionated heparin) [8,17] for reducing the occurrence of death or nonfatal myocardial infarction, requirement for urgent revascularization or recurrence of angina pectoris in patients who present with non-ST elevation ACS [18]. The sequence of subcutaneous dalteparin therapy followed by random allocation to early revascularization (average 6 days) reduced the composite endpoint of death or nonfatal myocardial infarction to 6 months compared with subcutaneous dalteparin followed by a conservative (no revascularization) strategy [19]. A preliminary experience with PCI following 48 h subcutaneous enoxaparin therapy, from the ESSENCE trial performed in France, reported an extremely low rate of major cardiac events and supports an 'early invasive' strategy for this patient population [20]. Separately conducted placebo-controlled randomized trials have proven the efficacy of platelet GP IIb/IIIa blockade in reducing ischemic events before and particularly during PCI in patients with non-ST elevation ACS [9,10,21,22]. This benefit of platelet GP IIb/IIIa inhibition is additive to that conferred by aspirin and unfractionated heparin and is most evident in those patients undergoing early PCI (< 72 h following enrollment) [23]. In summary, adjunctive pharmacotherapy with either low molecular weight heparin or platelet GP IIb/IIIa blockade can improve clinical outcomes of patients with non-ST elevation ACS, particularly when administered in sequence with early coronary revascularization.

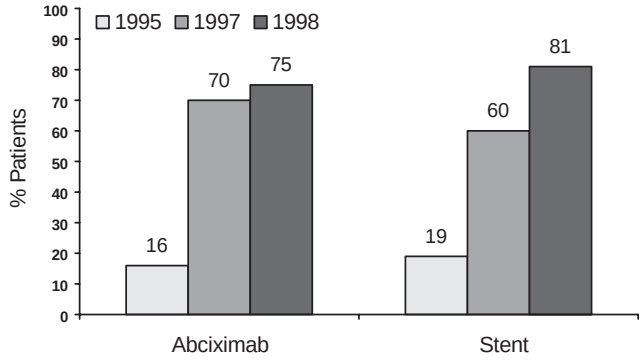
Revascularization strategies

Coronary stents may improve clinical outcomes in patients with unstable angina pectoris when compared with the results obtained with standard balloon angioplasty. In a nonrandomized observational experience, stents (versus balloon angioplasty) improved procedural success and reduced death or the requirement for CABG in hospital [24]. Nevertheless, major adverse cardiovascular events are increased in patients with unstable angina following coronary stent deployment [25,26]. Patients with non-ST segment elevation ACS have abnormalities in platelet size and function [27,28] that may be protracted following presentation [29]. This state of 'platelet hyperactivity' may in part explain the previously observed hazard of early PCI [3–5]. Conversely, adjunctive pharmacotherapy with prophylactic abciximab during PCI (particularly stent deployment) significantly reduces periprocedural complications, improves clinical outcomes and confers a long-term (≥ 1 year) survival advantage in patients with ACS [30–32]. The survival advantage accrued by patients treated with abciximab cannot be ascribed to stent deployment alone [33]. In the absence of adjunctive abciximab therapy, coronary stents have not been associated with a mortality reduction [34].

'Hazard' of early intervention: dispelling the myth

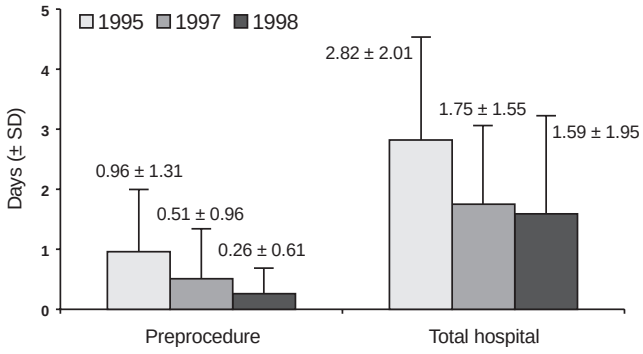
Recent data lead us to question the prior doctrine that early coronary revascularization is fraught with hazard in patients with non-ST elevation ACS. For example, the 1999 United States National Heart, Lung, and Blood Institute (NHLBI) Dynamic Registry demonstrates no increase in major hospital complications following 'ad hoc' PCI [35], despite the more frequent presence of unstable angina and angiographically demonstrable coronary thrombus in these patients. Coronary stents were deployed in almost 70% and adjunctive platelet GP IIb/IIIa blockade was administered in 36% of patients undergoing ad hoc PCI [35]. In a separate report from the NHLBI Dynamic Registry [36], major hospital complications (death, Q-wave myocardial infarction or urgent bypass surgery) were infrequently observed in patients undergoing PCI for non-ST segment elevation myocardial infarction. Adjunctive platelet GP IIb/IIIa blockade was administered in 45% of these PCI procedures. These observations reflect improvements in interventional technology and adjunctive pharmacology. Furthermore, the 1996 New York State Cardiac Surgery database for CABG following non-Q wave myocardial infarction

Figure 1



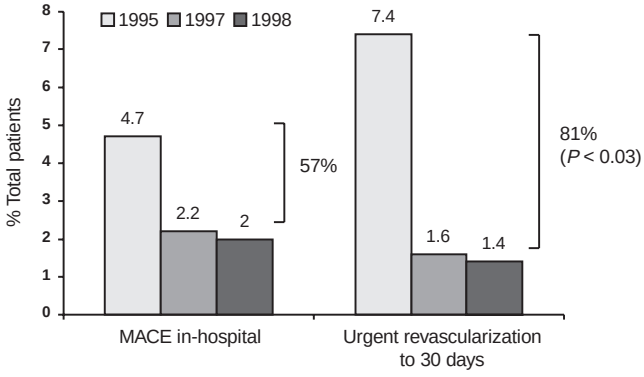
Percentage utilization of abciximab or coronary stents to treat unstable angina by Ohio Heart Health Center Operators at The Christ Hospital, Cincinnati, Ohio, USA for each treatment cohort. Adapted with permission from [39].

Figure 2



Preprocedure (mean ± SD) and total hospital length of stay for each treatment cohort.

Figure 3



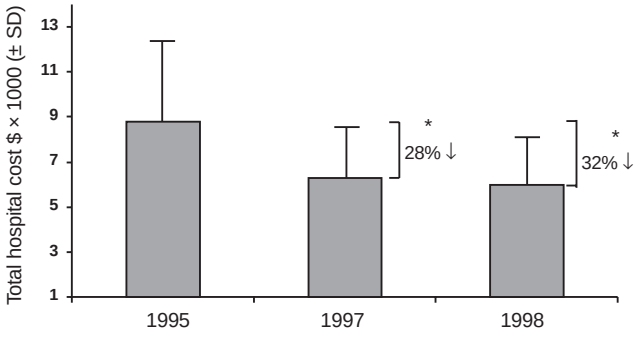
Incidence of occurrence in-hospital of major adverse cardiac events (MACE: death, Q-wave myocardial infarction [QMI], urgent coronary revascularization) following PCI, and the requirement for urgent revascularization (percutaneous or surgical) within 30 days by treatment cohort. Adapted with permission from [39].

demonstrates no increase in risk for mortality (adjusted odds ratio [95% confidence interval] = 1.01 [0.51, 1.98]) when surgery is performed 3–8 days following presentation when compared with CABG for all other classes of angina (mortality 1.3%) [37]. This experience stands in stark contrast to the 12% in-hospital mortality reported from the VANQWISH trial when CABG was performed during the initial hospitalization for non-Q wave myocardial infarction [1].

The Ohio Heart Health Center experience

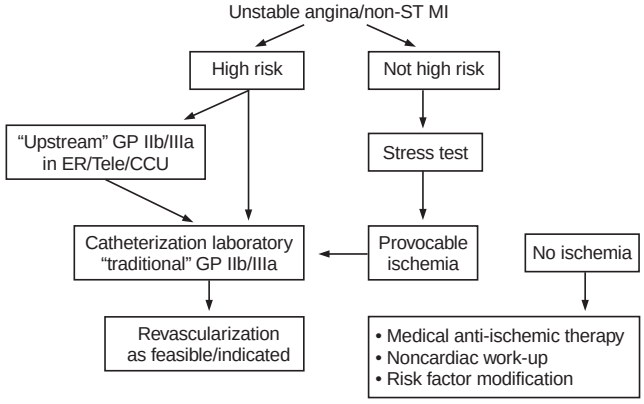
In 1996, abciximab was incorporated into a practice guideline for patients undergoing PCI by Ohio Heart Health Center (OHHC) operators at The Christ Hospital in Cincinnati, Ohio, USA. To assess the impact of this strategy, three separate cohorts of unstable angina patients having PCI either before (1995) or after (1997, 1998) implementation of guideline-driven abciximab therapy were compared [38,39]. No differences in clinical or angiographic demographics were observed between cohorts. The utilization of both abciximab and coronary stents increased in each cohort (Fig. 1). Average preprocedural hospital length of stay was reduced from 0.96 (1995) to 0.26 (1998) days and total hospital stay from 2.82 to 1.59 days, respectively (Fig. 2). This abbreviated hospital length of stay was observed in 352 consecutive patients treated in 1998 and compares favorably with the established 4–14 day length of stay for unstable angina pectoris noted previously [13–15]. The same OHHC operators achieved a 57% reduction in major cardiac events (death, Q-wave myocardial infarction or urgent revascularization) in-hospital and an 81% reduction in the requirement for urgent revascularization within 30 days following PCI (Fig. 3). The cost increment of technology (stents and abciximab) was more than offset by cost savings attributable to the reductions in both hospital length of stay and costly adverse clinical outcomes (Fig. 4). Other factors contributing to the reduced cost of care may have included a dedicated, high volume interventional unit, capitated vendor contracts for catheterization laboratory resources and an active clinical research program. Similar improvement in clinical outcomes and a net cost reduction associated with adjunctive abciximab use during PCI in patients with non-ST elevation ACS was reported by Lundstrom *et al* [40]. These investigators observed a reduction in the requirement for urgent revascularization as well as in total costs to 6 months following PCI with adjunctive abciximab. A recently published observational study lends further support for an aggressive, 'early invasive' approach to patients who present with non-ST elevation myocardial infarction [41]. Patient and procedural demographics, hospital and long-term outcomes in patients treated for

Figure 4



Average total hospital cost (mean ± SD) for treating a patient with unstable angina for each treatment cohort. Total cost includes the cost of abciximab and coronary stents. *$P \leq 0.00005$. Adapted with permission from [39].

Figure 5



Proposed algorithm for assessment and treatment of patients with unstable angina or non-ST segment elevation myocardial infarction (MI). Patients judged to be at high risk on the basis of symptom complex, electrocardiographic ST segment depression or elevation in serum troponin level are eligible for adjunctive platelet GP IIb/IIIa inhibitor therapy and early coronary angiography. ER, emergency room; Tele, telemetry; CCU, coronary care unit. Adapted with permission from [39].

non-ST elevation myocardial infarction in hospitals favoring an early invasive treatment strategy were compared with similar data derived from hospitals favoring a noninterventional or 'early conservative' approach. Coronary angiography was performed in 90% of patients and early PCI (≤ 6 h) in almost half of all patients admitted to early invasive hospitals [41]. Acknowledging significant differences in baseline demographics between the patients treated at conservative versus invasive institutions, both in-hospital and late (4 year) survival was improved in aggressively treated patients [41].

Appropriate patient selection

Significant improvements in the ability to risk-stratify patients who present with non-ST elevation ACS have evolved. The single most accurate and readily available predictor in this population is the serum troponin level. Elevation in the serum level of either troponin T or I predicts adverse clinical outcomes [42–44]. A quantitative relationship between troponin level and risk of death, myocardial infarction or urgent revascularization has been established [45]. Troponin is a surrogate marker for platelet-thrombus formation, microvascular embolization and minor myocardial injury. In addition to predicting risk, an elevated troponin level also predicts a beneficial response to abciximab therapy [46]. Similar observations have been made between elevation in serum troponin level and a beneficial response to therapy with intravenous tirofiban or subcutaneous dalteparin in patients with non-ST elevation ACS [47]. Thus, troponin predicts magnitude of clinical benefit from therapy with either platelet GP IIb/IIIa blockade or low molecular weight heparin. Another predictor of risk in patients with non-ST elevation ACS is the 12-lead electrocardiogram [2,48]. Both the presence and magnitude of ST segment depression on the 12-lead electrocardiogram correlate directly with mortality in follow-up [2,48]. Patients who manifest signs of left ventricular decompensation or ischemic mitral valve dysfunction during episodes of angina should also be considered high risk. Anginal symptoms (Braunwald classification) define risk for subsequent adverse outcomes. Braunwald Class III angina (rest pain < 48 h) predicts the subsequent occurrence of death or myocardial infarction and Class c (medically refractory angina) adversely affects survival to 30 days [49]. The correlation between Braunwald symptom class and subsequent occurrence of ischemic events may be explained in part by the correlation between symptom class and the presence of thrombus on selective coronary angiography [50,51].

Conclusion: defining appropriate care

Patients with non-ST elevation ACS should be risk-stratified upon presentation. Risk can be assessed by angina symptom class, presence or absence of hemodynamic compromise, electrocardiographic ST segment depression and elevation in serum troponin (Fig. 5). Patients at high risk should undergo early angiography and revascularization as indicated. Patients who have elevated serum troponin should receive therapy with platelet GP IIb/IIIa blockade and/or low molecular weight heparin. If PCI is performed, coronary stent deployment is desirable and adjunctive GP IIb/IIIa blockade is indicated unless a specific contraindication is present. Optimal long-term outcomes, specifically a survival advantage, are conferred by adjunctive abciximab therapy during PCI. Furthermore, CABG performed 3–8 days following presentation for non-ST elevation infarction is not associated with

increased risk for mortality. Patients determined to be not at high risk should undergo appropriate diagnostic testing. Thus, efficient and effective therapy can now be offered to patients with non-ST elevation ACS. Empirically defined periods of medical stabilization most likely add cost without incremental benefit.

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