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Scientific Update™

Acute Non-ST Elevation Coronary Syndromes: Open Issues

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The management of the patient with an acute coronary syndrome (ACS) has become more complex as the number of available treatment options increases. Real-world registry observations indicate a very high recurrence rate for coronary ischemic events. The GRACE registry[1] has shown that the 1-year mortality for patients with non-ST segment elevation myocardial infarction (NSTEMI) is 13% and, for those with unstable angina (UA), it is 8%. Approximately 20% of both groups are readmitted to hospital with recurrent cardiac ischemic events that occur despite current treatment, including antithrombin, antiplatelet therapy, and revascularization.

Although management strategies with more effective antithrombotic and antiplatelet agents may result in better outcomes, it is clear that not all treatments are either necessary or appropriate for all patients with an ACS. A risk-guided strategy provides the optimal utilization of treatment and resources and minimizes the risk of exposing a low-risk patient to potentially hazardous, albeit beneficial, treatments. However, with more emphasis on an aggressive invasive approach for a high proportion of patients with ACS, the appropriate choice of medications and the timing of their administration become critical. This issue of *Cardiology Scientific Update* addresses a number of topical issues in the assessment and management of the patient with non-ST segment elevation ACS.

Single or multiple biomarkers for risk stratification?

The use of biomarkers in the assessment of patients with suspected ACS allows for risk assessment, guidance for optimal therapy, and evaluation of the long-term risk. Three well-validated markers are currently available for these applications:

- troponin T or I (cTnT or cTnI)
- B-type natriuretic peptide (BNP) or N-Terminal-proBNP (NT-proBNP)
- C-reactive protein (CRP).

Troponin (I or T) is highly sensitive and specific for the detection of myocardial necrosis and is superior to creatine kinase MB fraction (CK-MB). A meta-analysis[2] in patients with UA (with normal CK and CK-MB) revealed that elevation of cTnI or cTnT was associated with a 9-fold increase in the short-term (30-45 days) risk of death and MI. Yet, many of the studies in this analysis were single measures taken at the time of presentation or randomization into a clinical trial and the overall risk estimate may underestimate the true value of the test. At least 2 measurements of troponin – 4-8 hours after presentation – are necessary for an accurate diagnosis and risk stratification. Hamm et al[3] demonstrated that 9% of patients complaining of chest pain had an elevated troponin at the time of presentation to the emergency department and, after 4-6 hours, this proportion rose to 16%. Troponin elevation at the time of presentation is associated with a worse prognosis than if the cTn rises to an abnormal level later.[4] In contrast, patients with persistently negative cTn during the

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first 8 hours after presentation have a low risk of an adverse outcome,[3] particularly in the absence of other high risk-features such as ST-segment depression.[5] Patients with elevated cTn benefit from an early invasive strategy and the pre-intervention use of small molecule glycoprotein (GP) IIb/IIIa inhibitors[6] and low molecular weight heparin (LMWH).[7]

BNP and NT-proBNP are indicators of myocardial hemodynamic stress and their plasma levels increase with heart failure. Recent studies have documented the prognostic value of BNP in patients with ACS. An elevated NT-proBNP at the time of clinical presentation heralds a 3.5-fold greater risk of 30-day death or MI, with an almost 5-fold greater predictive value from a sample taken 72 hours later (Heeschen et al, *Circulation,* in press). Elevated NT-proBNP is independently predictive of mortality at both 30 days and 1 year. However, on multivariate analysis, increased cTn, elevated creatinine, prior MI or angina, and ST depression, but not NT-proBNP, were predictive of MI at 30 days.[12]

CRP: This marker of systemic inflammation in ACS predicts events over the longer-term. Both CRP and cTn are independent predictors of death or MI at 6-12 months.[8-10] In patients with UA, a high incidence of recurrent instability over the next year is related to the CRP level at hospital discharge;[11] the risk of recurrent UA or MI by 1 year is estimated to be 13%, 42%, and 67% for CRP values <2.5 mg/L, 2.6-8.6 mg/L, and >8.7 mg/L, respectively. A CRP level might be used in patients with a suspected ACS – but without troponin elevation or other high-risk features – to determine if they should undergo coronary angiography or receive statins. The application of such a strategy needs prospective testing.

Mortality at 1 year is independently predicted by troponin, BNP, CRP, as well as creatinine levels and heart rate.[12] Additional prognostic information is obtained by the combination of NT-proBNP levels with other markers (Figure 1). Sabatine et al have demonstrated in a validation cohort that the risk of death, MI, or congestive heart failure occurring by 6 months is increased according to the number of markers that are positive:

- 1 marker, relative risk (RR) = 2.1 (p=0.006)
- 2 markers, RR = 3.1 (p <0.001)
- 3 markers, RR = 3.7 (p=0.001).[13]

The use of multiple markers improves both short- and long-term risk stratification and, in the future, may guide treatment. A suggested application of these multiple markers using troponin to ascertain short-term, and BNP and CRP to ascertain long-term risk stratification, is shown in Figure 2.

Figure 1: 1-year mortality in patients with ACS related to quartiles of NT-pro BNP and quartiles of troponin T.[12]

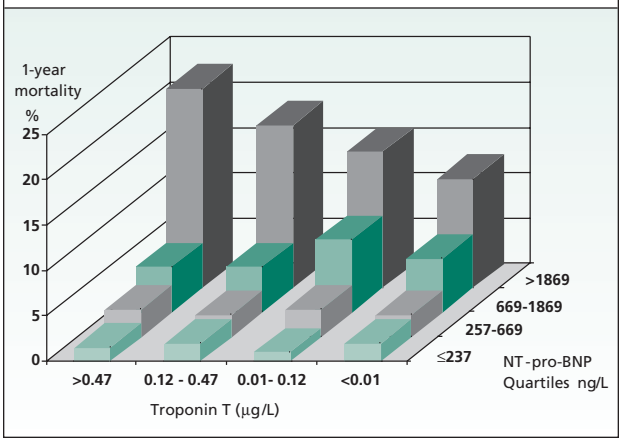


Figure 2: Proposed application of multimarker strategy and possible treatment implications in patients with non-ST segment elevation ACS

Acute	Long-term	
Troponin 2x 0 and 6-12 hours	BNP 72 hours	CRP Pre-discharge
IV GP IIb/IIIa inhibitor	Invasive strategy	? statin ? ACE inhibitor
Early invasive strategy		

Unfractionated or low molecular weight heparin?

Heparin treatment, when added to ASA, reduces the early hazard of death or MI by 39% in patients with NSTE ACS. The ESSENCE[14,15] and TIMI 11B[16,17] trials showed that the LMWH, enoxaparin, reduced both short- and long-term risk without any increase in bleeding. Patient outcomes were shown to relate to the degree of anticoagulation as measured by anti-Xa levels[18] that are reliably achieved with twice-daily subcutaneous injections of enoxaparin. Enoxaparin has subsequently become the heparin of choice, used in >60% of patients with NSTE ACS because of proven efficacy, safety, and convenience of use without the need for frequent monitoring. However, the early trials comparing enoxaparin and unfractionated heparin (UFH) were performed prior to the era of an early invasive approach. Subsequent trials have examined the safety and efficacy of enoxaparin in patients receiving both an intravenous GP IIb/IIIa inhibitor with early cardiac catheterization. The subsequent series of trials – ACUTE II[19] and A to Z[20] – demonstrated no difference for either safety or efficacy, yet the INTERACT trial[21] revealed that enoxaparin-treated patients had less bleeding and better short- and long-term outcomes than patients receiving UFH.

The SYNERGY trial[22] examined the use of enoxaparin in patients with high risk ACS managed with a strategy of very early catheterization. In this scenario, patients given either enoxaparin or UFH had similar clinical outcomes, yet bleeding appeared to be more frequent in the enoxaparin group (TIMI major bleeding: enoxaparin 9.1%, UFH 7.6%, p=0.008). Differences in study design between SYNERGY and prior clinical trials likely explain the findings, including:

- more frequent and earlier catheterizations were observed in SYNERGY 92% and a median of 22 hours, while in earlier trials, catheterization occurred less frequently and later. In INTERACT, 62% underwent catheterization at a median of 4 days and, in ESSENCE, the percentage of patients and the median time to catheterization for patients undergoing the procedure during the index admission is unknown, but likely >2 days.
- an older population, median age: SYNERGY - 68 years, INTERACT - 64 years, ACUTE 2 - 64 years, and ESSENCE - 65 years
- different concomitant medications: early GP IIb/IIIa inhibitor usage – SYNERGY 58%, INTERACT 100%, ACUTE 2 100%, ESSENCE 0%, and early clopidogrel usage – SYNERGY 66%, INTERACT 16.3%, ACUTE 2 7.9%, ESSENCE 0%.

Treatment prior to randomization in the SYNERGY trial may have reduced the possibility of demonstrating any benefit with 1 agent, since 76% of patients had received a heparin prior to randomization. Consequently, 40% of patients had received both enoxaparin and UFH from the time of admission to the completion of the study. Patients that crossed over from one form of heparin to another during the trial had both higher event rates and more bleeding. In an analysis of all enoxaparin trials, there was a significant reduction in 30-day death/MI rates and no increase in transfusion requirements during the first 7 days after randomization for patients receiving enoxaparin instead of UFH (Figure 3).[23] Furthermore, patients who did not receive heparin before randomization, had a more pronounced reduction of death /MI at 30 days.[23]

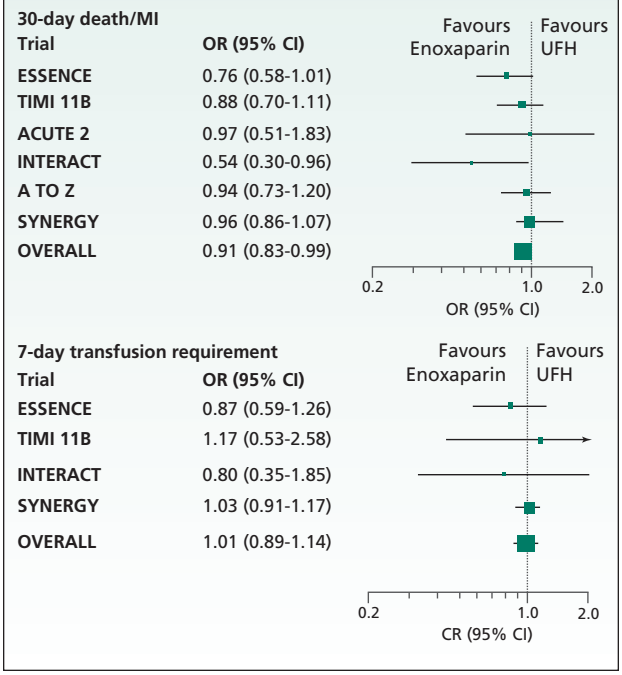
In the antithrombotic management of NSTE ACS where cardiac catheterization is performed early during admission, enoxaparin is easy to use, requires no monitoring before or during cardiac catheterization, and is cost-effective. The SYNERGY study demonstrates the safety and efficacy of enoxaparin used during percutaneous coronary intervention (PCI). However, patients should remain on enoxaparin throughout the hospitalization and not switch to UFH to avoid unpredictable levels of anticoagulation that may be responsible for increased bleeding.

When to start clopidogrel?

Clopidogrel reduces recurrent cardiac ischemic events both early and late after an NSTE ACS.[24] In this study, patients receiving clopidogrel during the first 24 hours had a 30% reduction in the combined endpoint of death, MI, or severe ischemia. After a period of 9 months, patients receiving clopidogrel had a 20% reduction in death/MI. Pre-treatment with clopidogrel for a median period of 6 days in patients undergoing PCI following ACS resulted in a benefit that persisted despite open-label treatment with clopidogrel for a period of 1 month.[25]

As most recurrent ischemic events occur during the first days following the initial symptoms, maximal benefit is achieved by starting clopidogrel with aspirin at the time of presentation. Benefit is achieved in a wide range of patients with NSTE ACS. Clinical guidelines for the management of ACS recommend the use of clopidogrel in high-risk patients with ECG abnormalities and/or elevated cTn or CK-MB. Some intermediate-risk patients may also benefit from the early use of clopidogrel. Clopidogrel combined with aspirin resulted in a modest (1 patient in 100) increase in bleeding during the 9-month treatment. For patients undergoing coronary artery bypass surgery (CABG) who have received clopidogrel within 5 days of the operation, there is a 50% increase in the incidence of serious bleeding.[26] The recent European guidelines for the management of NSTE ACS recommend avoiding clopidogrel if the patient is likely to go for CABG in the next 5 days;[27] however, this is an unlikely event for most Canadian patients. Furthermore, the international GRACE

Figure 3: Outcome and safety analysis for trials with enoxaparin in NSTE ACS[23]



registry indicates that only 1% of patients undergo CABG within 48 hours of admission.[1]

Perhaps one practical solution is to identify a group of very high-risk patients and use an intravenous, small molecule GP IIb/IIIa inhibitor rather than clopidogrel.[28] Clopidogrel would be administered only when the coronary anatomy is known and CABG is an unlikely course of management. The GP IIb/IIIa inhibitor is continued for 18 hours after the PCI, by which time, clopidogrel would be effective. No clinical trials have yet evaluated this strategy, yet GP IIb/IIIa inhibitors have been shown to reduce death/MI rates before and during PCI in patients with ACS,[29] and to provide additional platelet inhibition beyond that of ASA and clopidogrel.[30]

Resistance to antiplatelet agents is currently a topic of great debate. Clopidogrel resistance, as measured by *in vitro* platelet aggregation studies, is reported to occur in 30%-60% of patients, depending on the time since clopidogrel administration and the baseline degree of platelet reactivity.[31] However, if this apparent level of ineffective treatment had clinical meaning, stent thrombosis would likely be a frequent occurrence. Yet, a recent report has related the degree of clopidogrel-induced platelet inhibition to clinical events after primary PCI for acute MI.[32] It has been suggested that higher loading doses of clopidogrel (600 mg) may overcome some of the early "resistance;"[33] but evidence supporting this approach is modest. Perhaps point of care platelet testing will become more widespread and treatment will be tailored to achieve adequate and immediate platelet inhibition.[34]

How urgent is invasive intervention?

When managing patients with an NSTE ACS, are there benefits from very early invasive intervention as has been proven in patients with STEMI? A meta-analysis examining an invasive approach versus a conservative approach in the management of NSTE ACS revealed a modest 12% reduction in death/MI or recurrent ischemic events with an early invasive strategy.[35] However, the studies were very heterogeneous and many were performed long before current PCI techniques were available. The FRISC 2 study[36] revealed long-term benefit with an early invasive strategy, with a 30% reduction in cardiovascular mortality despite an early hazard, when patients had their cardiac catheterization at 5 days. Although the TACTICS TIMI 18 study[37] also demonstrated benefit for patients randomized to an early invasive strategy, patients undergoing very early catheterization and revascularization had the highest risk of recurrent MI.

The ICTUS study, presented at the Hotline II clinical trials session of the recent European Society of Cardiology Congress, examined the value of an early invasive strategy versus a selective invasive strategy in patients with NSTE ACS and elevated troponin, receiving current medical treatment with aspirin, enoxaparin, clopidogrel, and statins. All PCI procedures were performed while the patients were receiving abciximab. In the early invasive group, 97% underwent coronary angiography and 73% had a revascularization procedure. In the selective invasive group, 67% had coronary angiography and 47% revascularization, albeit at a later date than the early invasive group. The early invasive group had a greater early hazard for death/MI/re-hospitalization yet, by the end of the first year of the trial, there was no significant difference between the early invasive (21.7%) and selective invasive groups (20.4%; RR 1.06 p=0.59). New or recurrent MI was more frequent in the early invasive group (14.6% vs 9.4%, RR 1.55, p=0.006), yet rehospitalization for ACS was reduced in the early invasive group (7.0% vs 10.9%, RR 0.63, p=0.017). Therefore, using only positive troponin as the indicator of risk, a selective invasive strategy, with coronary angiography performed only in patients with recurrent ischemia or high-risk stress imaging/ECG, appears to be as effective as an early aggressive invasive approach.

The benefit of an early invasive strategy depends on the risk of an adverse outcome as was shown in an analysis of the TACTICS TIMI 18 study. Patients with high, but not low TIMI risk scores, had clear benefit from the early invasive compared to the conservative strategy.[38] However, in Canada and the USA, there is a treatment paradox, with low risk rather than high risk patients more likely to go for early catheterization (CRUSADE, ACS registry).

Is there benefit to be gained from a period of intensive treatment before coronary angiography and revascularization? The ISAR COOL study[39] evaluated the use of antithrombin and antiplatelet drugs for 3 to 5 days, compared to immediate coronary angiography within 6 hours. The study results reported that an early aggressive approach reduced the incidence of large and fatal MI occurring during medical treatment in the delayed group; however, it is unlikely to impact on clinical practice since it was underpowered to allow drawing such a conclusion. Furthermore, it is likely that in the early invasive group, the frequency of recurrent MI was underestimated.

Survival after STEMI is related to the initial patency of the culprit artery.[40] If the vessel is occluded, the outcome is related to the time to opening the vessel;

however, if the vessel is patent, there is no relationship between time to intervention and outcome. In NSTE ACS (when the artery is patent in 79%-87% of patients), it would be surprising if there was a clear relationship between outcome and time to revascularization. In a substudy of TACTICS TIMI 18,[41] the longer the pre-angiography treatment, the better the coronary flow score. Consequently, very early intervention might be expected to result in better outcomes only in patients with refractory ischemia or very high-risk features.

The ELISA (Early or Late Intervention in unStable Angina) trial examined whether very early intervention could improve coronary flow and reduce infarct size compared to delayed angiography after 24-48 hours. The estimation of infarct size was by multiple measures of enzymes before and after PCI and calculation of the area under the enzyme level time curve. The patients undergoing delayed angiography and revascularization had borderline better initial patency, a trend to less thrombus, more TIMI 3 flow, and a significant reduction in infarction size.

Current data suggest that an early invasive strategy in patients with non-ST segment elevation should be reserved for high-risk patients. Most of the conflicting evidence from trials examining an early vs a later invasive strategy likely results from difficulties in determining re-infarction outcomes, thereby favouring the early intervention group. More recent trials support the use of medical treatment for 2-3 days to improve plaque stability and arterial patency and not to rush to very early invasive procedures in the first few hours, except in patients with hemodynamic instability or recurrent refractory ischemia.

Conclusions

• Risk stratification in the short term can be achieved with cTn measured from 2 samples taken within the first 6-9 hours after presentation, together with ECG and clinical observations. Longer-term risk stratification is determined by BNP measurements at 48 hours after presentation and CRP at the time of hospital discharge.

• The LMWH, enoxaparin, improves outcomes and is associated with little or no increase in bleeding compared to UFH if the patient has consistent treatment with the same heparin both before and during PCI and if catheterization is performed at 48-72 hours after presentation.

• Clopidogrel should be given to all patients with NSTE ACS at the time of presentation to prevent early ischemic events unless there is a strong possibility that the patient will require early CABG.

• Early coronary angiography and revascularization in patients with ACS should be reserved for high-risk patients. In most patients, there is an advantage to a 48-72 hour period of treatment with effective antithrombotic and antiplatelet agents prior to intervention to both improve arterial patency and reduce thrombus load.

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