CARDIOLOGY Rounds®

AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Non-ST Segment Elevation Myocardial Infarction: Risk Stratification and Early Management

By SAAD ALHASANIAH, MD, and GORDON MOE, MD

Non-ST segment elevation myocardial infarction (NSTEMI) is a common problem encountered in clinical practice. A common question for the clinician is whether patients with NSTEMI would benefit from early intervention as compared to medical therapy, or if intervention should be reserved for unstable patients or those with a positive predischarge stress test. This issue of *Cardiology Rounds* addresses various aspects of NSTEMI, including its definition, risk stratification, major clinical trials that address the clinical question posed above, as well as the recently published American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the use of percutaneous coronary intervention (PCI) in NSTEMI.

Definition

Unstable angina (UA) is defined as "the presence of ischemic symptoms with or without ischemic electrocardiogram (ECG) changes and with negative cardiac markers." NSTEMI differs from UA depending on whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of markers of myocardial injury.[1,2] Since elevated troponin and/or CK-MB may not be detectable for several hours after initial presentation, UA and NSTEMI may be indistinguishable during the initial evaluation. ST segment and/or T wave changes are often persistent in NSTEMI, whereas, in the setting of UA, they are usually transient. Observations from clinical trials have revealed that in UA, the culprit artery is patent in up to 60%-85% of patients and that the thrombus is platelet-rich.[3,4] The principal aims of intervention are to reduce mortality, recurrent MI, and the need for future revascularization.

Risk stratification in NSTEMI

The predictors of adverse outcome in patients with NSTEMI include:

- recurrent or persistent angina at rest despite intensive medical therapy
- hemodynamic instability due to mechanical complications
- unstable ventricular arrhythmia
- left ventricular dysfunction
- renal dysfunction
- elevated cardiac markers
- ischemia ECG changes

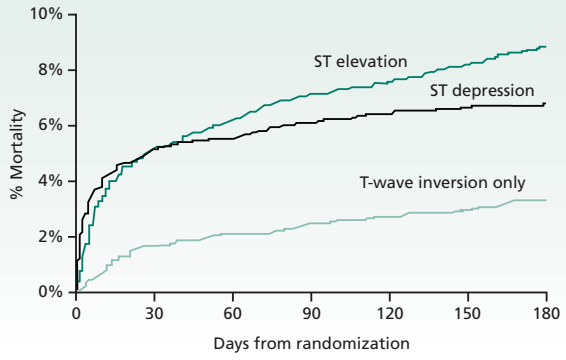
Patients with NSTEMI presenting with heart failure, hemodynamic instability due to mechanical complications, and ventricular arrhythmia carry significant risk and coronary intervention is usually carried out early.[5] Observations from the Global Use of Strategies To Open Occluded Coronary Arteries IV (GUSTO-IV) trial suggest that the higher the B-type natriuretic peptide (BNP), the worse the outcome. Patients with normal creatinine clearance and normal N-terminal pro-BNP (NT-proBNP) levels have a 30-day mortality of 0.3%, whereas those with creatinine clearance <50 mL/min/1.73 m^2 and BNP levels >1869 ng/L have a 30-day mortality of 25.7%.[6] Patients presenting with elevated troponins, which are indicative of myocardial injury, carry a higher risk.

In a GUSTO IV substudy,[7] patients were stratified by quartiles of troponin T (<0.01; 0.01 to 0.12; 0.12 to 0.47; and >0.47). The 30-day mortality rate increased from 1.1% to 7.4% between the first and fourth quartiles of troponin T. There was also a significant increase in the 30-day rate of MI between the first and second quartiles of troponin T (2.5% versus 6.7%), but there was no further increase between the upper three quartiles. Presence of elevated C-reactive protein (CRP) is also associated with a worse outcome. Other risk predictors in patients presenting with NSTEMI, derived from data from the TIMI III registry, include patient demographics (eg, advanced age and Caucasian race have been associated with worse outcomes).[8]

Patients presenting with ischemic ECG changes are at higher risk. While about 50% present with ST segment depression, others present with T wave inversion or mixed ST segment depression and elevation.[9] When comparing patients with NSTEMI to those with ST segment elevation MI (STEMI),

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Figure 1: Ischemic ECG changes as predictor of mortality[9]



although patients with STEMI carry a higher early risk for major cardiac adverse events, over the long-term, patients with NSTEMI have a higher rate of cardiac mortality and recurrent MI (Figure 1).[9] In the GUSTO IIB trial, the mortality rate at 1 year was significantly higher in patients with NSTEMI than in those with STEMI (11.1% versus 9.6%). Similar observations have been made in a community-based study in almost 6000 patients with first MI who were observed over a 23-year period. In this study, patients with an NSTEMI had a higher 2-year mortality than those with an STEMI (20% versus 11%).[10]

In the international randomized controlled trial of lamifiban, heparin, or both in UA – the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network (PARAGON) study – patients with ST segment depression of >2 mm had worse outcomes than those with a 1-2 mm ST segment depression; the best outcomes were in those with normal ST segment on presentation (Figure 2).[11,27] Similar findings were observed in the GUSTO IIB trial.[27] Patients with NSTEMI tend to have more multivessel disease when compared to patients presenting with STEMI.[9]

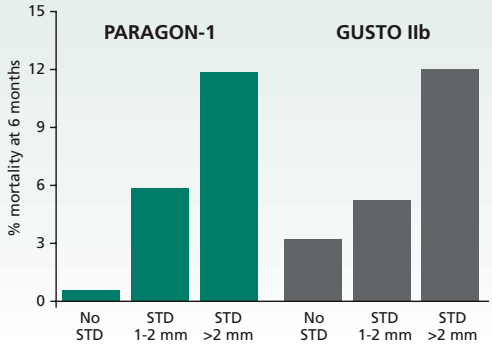
TIMI risk score

From an analysis of data from the TIMI 11B and ESSENCE trials, Antman et al described 7 variables that were independent predictors of outcome in patients with UA or NSTEMI.[12] These criteria were defined as the Thrombolysis In Myocardial Infarction (TIMI) risk score. To calculate the score, a value of "1" is assigned to each of the variables present. The criteria include:

- age 65 years
- presence of at least 3 risk factors for coronary heart disease
- prior coronary stenosis of 50%
- presence of ST segment deviation on admission ECG
- at least 2 anginal episodes in the prior 24 hours
- elevated serum cardiac biomarkers
- use of aspirin during the prior 7 days.

The TIMI risk score was validated in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) database. A similar predictive value has been noted for post-discharge events at 6 weeks and for major cardiac events at 30 days in patients who have undergone PCI. Higher TIMI risk scores have been correlated with more severe angiographic disease. In an analysis from PRISM-PLUS, an increase in the TIMI risk score from "0 - 2" (low risk) to "5 - 7" (high risk) was associated with a progressive increase in the frequency of high-risk angiographic findings such as severe (>70%) culprit stenosis (58% to 81%); multivessel disease (43% to 80%); visible thrombus (30% to 41%); and left main disease.[13]

Figure 2: ST segment depression as a predictor of mortality in NSTEMI[27]



STD = ST depression

The GRACE score

The TIMI risk score, while extensively validated as described above, was derived from 2 clinical trial databases and, therefore, may not be fully representative of the spectrum of patients encountered in clinical practice. The Global Registry of Acute Coronary Events (GRACE), a global registry of acute coronary syndrome (ACS) patients from 94 hospitals in 14 countries, developed 2 models to estimate the risk of in-hospital and 6-month mortality among all patients with an ACS. The in-hospital model was based on data from 11,389 patients with either an STEMI or an NSTEMI ACS.[14] This model was then validated using data from an additional 3972 patients from GRACE and 12,142 patients from the GUSTO IIB trial. Eight independent risk factors were found to account for almost 90% of the prognostic information: age, Killip class, systolic blood pressure, presence of ST segment deviation, cardiac arrest during presentation, serum creatinine concentration, presence of elevated serum cardiac biomarkers, and heart rate.

Point scores are assigned for each predictive factor and added together to estimate the risk of in-hospital mortality. A nomogram was published with the GRACE risk model to allow calculation of the risk score. Software is also available online (www.statcoder.com/grace.htm) to enable the calculation of the GRACE risk score with a hand-held device.

Management strategies in NSTEMI ACS

Many large scale trials have addressed the relative benefit of an early invasive versus a conservative strategy, ie, invasive intervention only if there are signs of ongoing ischemia. Some of the key trials that address this question are reviewed as follows.

TIMI IIIB

The TIMI IIIB trial was a randomized, double-blinded trial of therapeutic strategies and thrombolysis in patients with UA and NSTEMI. TIMI IIIB randomly assigned 1473 patients within 24 hours of an episode of angina at rest in a 2 x 2 factorial design to alteplase or placebo, and to a conservative or early invasive approach. All patients were treated with a standard anti-ischemic regimen including intravenous heparin and aspirin.

- Patients in the conservative arm underwent catheterization only if they developed evidence of recurrent ischemia, including recurrent chest pain with ECG changes, prolonged ST-segment depressions on ambulatory Holter monitoring, or a positive pre-discharge exercise test.
- Patients assigned to the early invasive strategy underwent cardiac catheterization and angiography within 18 to 48 hours, followed by revascularization if indicated.

There was no significant difference in the rates of death and nonfatal MI between invasive and conservative therapy at 6 weeks (7.5% versus 8.2%) or 1 year (10.8% versus 12.2%). The frequency of death, MI, or a positive exercise test at 6 weeks was also similar in the 2 groups, except for patients aged >65 years who had a significant benefit from invasive therapy (8% versus 15%).[15]

The lack of major benefit in TIMI IIIB may be related, in part, to the high crossover rate to invasive therapy in the conservative group. Of the 733 patients assigned to the conservative approach, revascularization was performed in 58% by 1 year.[16] Furthermore, this study was performed in the era prior to the use of coronary stents, glycoprotein (GP) IIb/IIIa inhibitors, and clopidogrel.[15,16]

VANQWISH

The Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial[17] randomly assigned 920 patients with an NSTEMI to:

- an early invasive strategy (coronary angiography followed by revascularization as dictated by anatomic findings) 72 hours after the last episode of chest pain) or
- an early conservative strategy with angiography and revascularization only if there was spontaneous ischemia associated with ST segment changes or if a thallium stress test suggested the presence of residual ischemia (eg, ST segment depression of 2 mm, redistribution defects in ≥2 different territories, or 1 redistribution defect associated with increased lung uptake of thallium).

There was no benefit with the invasive approach, which was performed in only 44% of patients in this arm; to the contrary, at the time of hospital discharge, the primary endpoint of death or nonfatal MI occurred significantly more frequently in the invasive group (7.8% versus 3.2%). Both the primary endpoint and mortality were still increased in the invasive group at 1 year, but not at 2 years. Interpretation of these results should take into account that the study was limited to Veteran's Affairs hospitals' patients, with again, a high crossover rate; the mortality rate from coronary artery bypass graft (CABG) surgery was higher than average.[17]

RITA-3

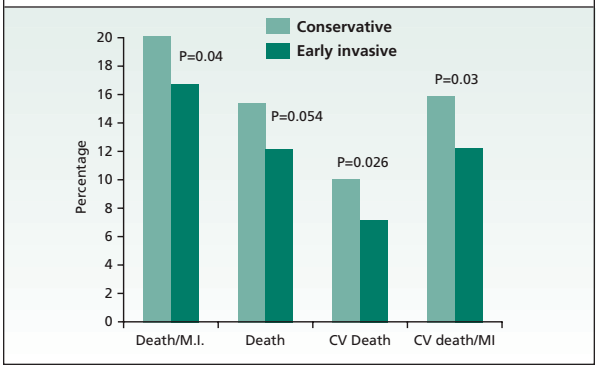
RITA-3 was a UK-based study comparing early angiography and revascularization with conservative therapy in 1810 patients with NSTEMI.[18] All received optimal medical therapy, including enoxaparin as the antithrombotic. Exclusion criteria included the presence of new Q waves, CK or CK-MB enzymes twice the upper limit of normal (ULN) at randomization, MI within the previous month, PCI within the previous year, and CABG at any time. The following describes the principal findings. At 4 months, the early invasive strategy was associated with a lower rate of the co-primary endpoint of death, nonfatal MI, or refractory angina (9.6% versus 14.5%, risk ratio (RR) 0.66, 95% confidence interval (CI), 0.51-0.85; this benefit was entirely due to a reduction in refractory angina (defined as an episode of angina with new ischemic ECG changes) and persisted at 1 year. At 1 year, there was no difference between the 2 groups in the co-primary endpoint of death or nonfatal MI (7.6% versus 8.3%, RR 0.91, 95% CI, 0.67-1.25). However, symptoms of angina were improved in the interventional group and there was a significant reduction in MI at 1 year (9.4% versus 14.1%). At the 5-year follow-up study, published recently, results revealed a reduction in mortality and recurrent MI; the benefit was more profound in patients with a higher risk score (Figure 3).[19]

FRISC II

The FRagmin and Fast Revascularisation during InStability in Coronary artery disease II (FRISC II) study was a multicentre, randomized trial conducted in the Scandinavian countries.[20] In this trial, 2457 patients with NSTEMI were randomly assigned 48 hours after clinical presentation to an invasive or noninvasive approach. All were treated with aspirin, ß-blockers, and low molecular-weight heparin (LMWH) until revascularization in the invasive group or for at least 5 days in the noninvasive group. At 6 months, the following outcomes were observed: The rate of death or MI was significantly lower in the invasive versus the noninvasive group (9.4% versus 12.1%, respectively); the difference was primarily due to a lower rate of MI (7.8% versus 10.1%). Although the difference in mortality was not significant at 6 months (1.9% versus 2.9%), it was significant at 1 year (2.2% versus 3.9%). The invasive approach was also associated with a 50% reduction in angina and need for readmission. The greatest benefit with invasive therapy was seen in high-risk patients who had ST depression on ECG and/or biochemical markers indicative of myocardial damage; patients with both findings had a marked reduction in death or MI at 1 year (13.2% versus 22.1%). The benefit was primarily seen in patients with more marked or more widespread ST segment depression, particularly if associated with T wave abnormalities in 6 leads. Using the FRISC score system, which includes: age >65 years, male gender, prior MI, elevated serum troponin, ischemic ECG changes, and elevated inflammatory markers, it was found that the higher the score, the higher the event rate. Patients with higher FRISC scores benefited from early intervention more than low-risk patients.[21]

The reduction in the rate of the combined endpoint of death or MI was sustained at 1 year. The differences in each endpoint, when considered separately (death or MI), were both independently significant. At 1 year, there was also a reduction in the readmission rate (37% versus 57%) and in the need for revascularization after the initial admission (7.5% versus 31%). Between the first and second years, there was no further difference in mortality (1.4% versus 1.6%), but there continued to be fewer MIs in the invasive group (1% versus 1.7%).

Figure 3: Five-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome from RITA-3[19]



TACTICS-TIMI 18

The potential role of an early invasive strategy in patients with NSTEMI was evaluated in the TACTICS-TIMI 18 trial, which randomly assigned 2220 patients to an invasive strategy (catheterization within 4 to 48 hours and revascularization with PCI or CABG, if indicated) or conservative medical therapy; all patients received aspirin, ß-blockers, heparin, and tirofiban for 48 hours.

At 6 months, the primary endpoint (death, MI, or re-hospitalization for ACS) was significantly lower with the invasive strategy versus the conservative approach (15.9% versus 19.4%, respectively, RR 0.78). This benefit was due to reductions in MI and rehospitalization for an ACS. There was no mortality benefit

from invasive therapy at either 30 days (2.2% versus 1.6%) or at 6 months (3.3% versus 3.5%).

The reduction in the primary endpoint with the invasive approach was seen only in patients with higher TIMI risk scores. At 6 months, primary events occurred in 19.5% of the patients with high TIMI risk scores (5-7) who underwent early intervention as compared to 30.6% in the conservative group (RR 0.55; 95% CI, 0.33-0.91). This study clearly demonstrated that patients with higher risk scores benefit more from an early intervention strategy, whereas those with low-risk scores do not benefit from early intervention.[22]

ICTUS

The Invasive Versus Conservative Treatment in Unstable Coronary Syndrome (ICTUS), conducted in the Netherlands, included 1200 patients with NSTEMI who had chest pain, an elevated serum cardiac troponin T, and either ECG evidence of ischemia or a documented history of coronary disease.[23] Patients were randomly assigned to an early invasive strategy or a selective invasive strategy. All were treated with aspirin, LMWH, and intensive statin therapy. At the time of PCI, abciximab and clopidogrel were also administered. Inclusion criteria included all three of the following: symptoms of ischemia that were increasing or occurred at rest, with the last episode occurring <24 hours before randomization; an elevated troponin T level (≥0.03 µg/L); and either ischemic changes on ECG or a documented history of CAD as evidenced by previous MI, findings on previous coronary angiography, or a positive exercise test. Exclusion criteria included patients with hemodynamic instability, overt heart failure (HF), and PCI within the past 2 weeks. The primary endpoint was a composite of death, nonfatal MI, or rehospitalization for angina within 1 year. The trial failed to show a benefit from an early invasive strategy. There was no difference in the incidence of the primary endpoint (22.7% versus 21.2% with the selective strategy). Although all patients had elevated serum cardiac troponin T concentrations, the presence of additional high-risk features (eg, older age, ST segment depression, or a more marked elevation in serum cardiac troponin T) did not predict a better outcome with an early invasive strategy in contrast to the other trials above. There was a significant increase in MI with an early invasive strategy (mostly peri-procedural). Although a less stringent CK-MB elevation was required for the diagnosis of MI, the increase in MI persisted when the definitions from FRISC II or TACTICS TIMI 18 were used. Rehospitalization, however, was less common with an early invasive strategy (7.4% versus 10.9%).

When compared to previous trials, patients recruited to ICTUS had higher rates of revascularization in both study groups; at 1 year, 79% in the invasive arm and 54% in the selective arm were receiving some form of revascularization (Figure 4). This may have decreased the difference in benefit from early intervention between early invasive vs. the selective group.

Additionally, patients with CHF or hemodynamically unstable were excluded from the trial; these are high-risk patients who would benefit most from early intervention. Finally, the 1-year follow-up period may have been too short to reveal the benefit of early intervention. For example, RITA-3 did not show early benefit,[18] but when follow-up was extended to 5 years, benefit was demonstrated.[19]

Meta-analysis

A recent meta-analysis of the major trials included 9212 patients and addressed the outcomes of a "routine" versus a "selective invasive" strategy at different time periods.[24] From randomization to hospital discharge, a routine invasive strategy was associated with a significant increase in mortality (1.8% versus 1.1%, RR 1.60, 95% CI, 1.14-2.25), an almost significant increase in nonfatal MI (3.7% versus 3.0%, RR 1.24, 95% CI, 0.99-1.56), and a significant increase in death or MI (5.2% versus 3.8%, odds ratio [OR] 1.36, 95% CI, 1.12-1.66). From hospital discharge to the end of follow-up, a routine invasive strategy was associated with a significant reduction in mortality (5.2% versus 7.3%, OR 0.76, 95% CI, 0.62-0.94), a significant reduction in nonfatal MI (3.8% versus 6.6%, OR 0.56, 95% CI 0.0.46-0.67), and a significant reduction in death or MI (7.4% versus 11.0%, OR 0.64, 95% CI, 0.55-0.75). From randomization to the end of follow-up, a routine invasive strategy was associated with a nonsignificant reduction in mortality (6.7% versus 7.9%, RR 0.92, 95% CI, 0.77-1.09), a significant reduction in nonfatal MI (7.3% versus 9.4%, RR 0.75, 95% CI, 0.0.65-0.88), and a significant reduction in death or MI (12.2% versus14.4%, RR 0.82, 95% CI, 0.72-0.93) (Figure 5).

By the end of follow-up, a routine invasive strategy was also associated with significant reductions in Canadian Cardiovascular Society class III-IV angina (11.2% versus 14%) and in re-hospitalization (32.5% versus 41.3%). In contrast to the long-term benefits overall, there was no significant reduction in death or nonfatal MI among patients without any elevation in serum troponin or other cardiac biomarkers (7.7% versus 8.5%, RR 0.90, 95% CI, 0.72-1.14).

Table 1: ICTUS trial results. MI related to PCI was present when CK-MB above the upper limit of normal (ULN)

Outcome	Early	Selective	R.R	P-value
Death	2.5%	2.5%	0.99	0.97
M.I.	15%	10%	1.50	0.005
Related to PCI or CABG	11.3%	5.4%	2.09	0.001
FRISC 2 Def*.	12.1%	7.8%	1.56	0.008
TACTIC-TIMI 18 Def**.	8.5%	5.9%	1.4	30.07
Primary E.P	22.7%	21.2%	1.07	0.33
FRISC 2 Def*.	20.2%	19.2%	1.05	0.52
TACTIC-TIMI 18 Def**.	16.9%	17.6%	0.96	0.087

* FRISC 2 definition of MI was CK-MB above the ULN for spontaneous MI and 1.5 times the ULN for MI related to PC.
** The TACTIC-TIMI 18 definition of MI was CK-MB level above the ULN for spontaneous MI and more than 3 times the ULN for MI related to PCI.
EP = endpoint

Figure 4: Comparison of rate of revascularization between ICTUS and prior trials[25]

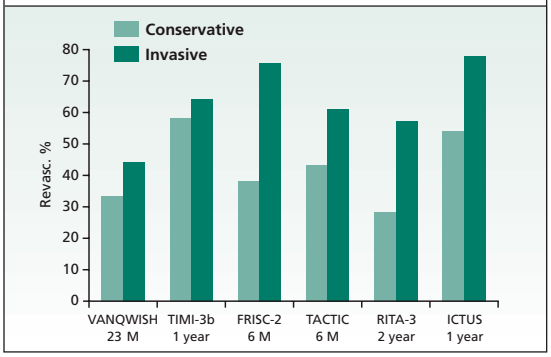
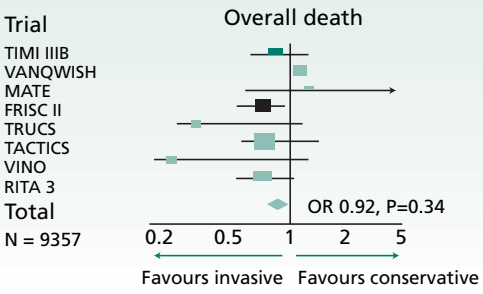


Figure 5: Overall mortality from the meta-analysis comparing routine versus selective invasive strategies in patients with acute coronary syndromes[24]



This finding is consistent with observations discussed earlier with regard to the lack of significant benefit in patients considered low risk (TIMI risk score 0 to 2).

Experience outside the clinical trial setting

CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology and American Heart Association Guidelines, www.crusadeqi.com) is a U.S. quality improvement initiative that collects data on outcomes and usage of proven drugs like aspirin, ß-blockers, heparin, and anti-platelet drugs (eg, GP IIb/IIIa inhibitors), as well as the use of catheterization and angioplasty procedures. The registry focuses on patients with UA and NSTEMI, gathering data from >400 participating U.S. hospitals and provides regular feedback to hospitals with the ultimate goal of improving adherence to the treatment guidelines and patient outcomes.

From the last report (October 2004-September 2005), 31% of the patients have ST segment depression and 95% have positive cardiac markers, 24% have signs of HF, and 82% underwent cardiac catheterization. During hospitalization, 65% underwent cardiac catheterization within 48 hours, 65% underwent revascularization (51% PCI and 12% CABG). Mortality was 4.5% at 1 year, which is higher than the mortality rate in patients in clinical trials.

ISAR-COOL

The only trial comparing "early" versus "delayed" (after "cooling-off" with an antithrombotic regimen) intervention is the German Intracoronary Stenting with Antithrombotic Regimen Cooling-Off (ISAR-COOL) Trial.[25] In this trial, 410 intermediate-to-high risk patients with NSTEMI, plus either ST segment depression or elevated serum troponin T, were treated with intensive antithrombotic therapy, including heparin, aspirin, clopidogrel, and the GP IIb/IIIa inhibitor, tirofiban. Patients were then randomly assigned to a very early (within 6 hours) versus delayed invasive strategy (72 to120 hours); median time to catheterization was 2.4 hours and 86 hours, respectively. The early invasive strategy – when compared with the delayed invasive strategy – was associated with a significantly lower incidence of death or large MI, defined as the presence of new Q waves in ≥2 contiguous leads, new left bundle branch block, or elevated serum CK-MB to at least 5 times the ULN, at 30 days (5.9% versus 11.6%). ISAR-COOL therefore, demonstrates a benefit from an early invasive strategy compared to waiting for 3-5 days. Limitations of this study include the fact that it was a small, single-centre study, the mortality rate was very low compared to other trials, and that there were no measurements of baseline CK-MB in the early intervention group. This may have underestimated the significance of procedure-related MI.

ACC/AHA/SCAI 2005 Guideline Update for PCI

The recently published ACC/AHA/SCAI 2005 guidelines[26] discusses the indications for PCI following UA/NSTEMI. They are summarized in Table 2.

Table 2: ACC/AHA/SCAI 2005 Guideline Update for PCI[26]

Class I

An early invasive PCI strategy is indicated for patients with UA/NSTEMI who have no serious co-morbidity and coronary lesions amenable to PCI. Patients must have any of the following high-risk features:

a. Recurrent ischemia despite intensive anti-ischemic therapy. (Level of Evidence: A)
b. Elevated troponin level. (Level of Evidence: A)
c. New ST-segment depression. (Level of Evidence: A)
d. HF symptoms or new or worsening mitral regurgitation (Level of Evidence: A)
e. Depressed left ventricular (LV) systolic function. (Level of Evidence: A)
f. Hemodynamic instability. (Level of Evidence: A)
g. Sustained ventricular tachycardia. (Level of Evidence: A)
h. PCI within 6 months. (Level of Evidence: A)
i. Prior CABG. (Level of Evidence: A)

Class IIa

a. It is reasonable to perform PCI in patients with UA/NSTEMI and single-vessel or multivessel CAD who are undergoing medical therapy with focal saphenous vein graft lesions or multiple stenoses who are poor candidates for reoperative surgery. (Level of Evidence: C)
b. In the absence of high-risk features associated with UA/NSTEMI, it is reasonable to perform PCI in patients with amenable lesions and no contraindication for PCI with either an early invasive or early conservative strategy. (Level of Evidence: B)
c. Use of PCI is reasonable in patients with UA/NSTEMI with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG. (Level of Evidence: B)

Class IIb

a. In the absence of high-risk features associated with UA/NSTEMI, PCI may be considered in patients with single-vessel or multivessel CAD who received medical therapy and who have 1 or more lesions to be dilated with reduced likelihood of success. (Level of Evidence: B)
b. PCI may be considered in patients with UA/NSTEMI who received medical therapy who have 2- or 3-vessel disease, significant proximal LAD CAD, and treated diabetes or abnormal LV function. (Level of Evidence: B)

Class III

In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have 1 or more of the following:

a. Only a small area of myocardium at risk. (Level of Evidence: C)
b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. (Level of Evidence: C)
c. A high risk of procedure-related morbidity or mortality. (Level of Evidence: C)
d. Insignificant disease (less than 50% coronary stenosis). (Level of Evidence: C)
e. Significant left main disease and candidacy for CABG (Level of Evidence: B)

Conclusion

NSTEMI is likely one of the most common cardiac problems in patients presenting to the emergency room. Prompt risk stratification is crucial in their timely management. The TIMI and GRACE scoring systems are well-validated in various trials. In clinical trials addressing the issue of early intervention versus a conservative approach, data are not always consistent but, among trials favouring early intervention, benefit was maximal in patients with high-risk features in terms of mortality, as well as future adverse cardiac events. Patients at low risk (ie, a low TIMI score) do not benefit from early intervention and, in fact, might fare worse. It is also important to maximize medical therapy in patients with NSTEMI, especially those with high-risk features. Early intervention increases cardiac events in terms of procedure-related MI although, from the recent meta-analysis, there appears to be long-term overall benefit. The merit of early intervention within hours versus maximum medical therapy and then intervention after 3 days in patients with intermediate- to high-risk NSTEMI is a question that needs to be answered in future multicentre randomized trials.

References

1. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined – a consensus document of The Joint ESC/ACC Committee for the redefinition of myocardial infarction. *J Am Coll Cardiol* 2000;36:959-69.
2. Meier MA, Al-Badr WH, Cooper JV, et al. The new definition of myocardial infarction: diagnostic and prognostic implications in patients with acute coronary syndromes. *Arch Intern Med* 2002;162:1585-9.
3. Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-IIIA Trial). *Am J Cardiol* 1994;74:531-7.
4. Roe MT, Harrington RA, Prosper DM, et al. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease.The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators 1. *Circulation* 2000;102:1101-6.
5. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2002;40:1366-74.
6. James SK, Lindahl B, Siegbahn A,et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease: a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;108:275-81.
7. James SK, Armstrong P, Barnathan E, et al. Troponin and C-reactive protein have different relations to subsequent mortality and myocardial infarction after acute coronary syndrome: a GUSTO-IV substudy. *J Am Coll Cardiol* 2003;41:916-24.
8. Stone PH, Thompson B, Anderson HV, et al. Influence of race, sex, and age on management of unstable angina and non-Q-wave myocardial infarction: The TIMI III registry. *JAMA* 1996;275:1104-12.
9. Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. *JAMA* 1999;281:707-13
10. Furman MI, Dauerman HL, Goldberg RJ, Yarzebski J, Lessard D, Gore JM. Twenty-two year (1975 to 1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi-hospital, community-wide perspective. *J Am Coll Cardiol* 2001;37:1571-80
11. Kaul P, Newby LK, Fu Y, et al. Relation between baseline risk and treatment decisions in non-ST elevation acute coronary syndromes: an examination of international practice patterns. *Heart* 2005;91:876-81.
12. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
13. Mega JL, Morrow DA, Sabatine MS,et al. Correlation between the TIMI risk score and high-risk angiographic findings in non-ST-elevation acute coronary syndromes: observations from the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial. *Am Heart J* 2005;149:846-50.
14. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163:2345-53
15. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation* 1994;89:1545-56.
16. Anderson HV, Cannon CP, Stone PH, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial. A randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q wave myocardial infarction. *J Am Coll Cardiol* 1995; 26:1643-50.
17. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *N Engl J Med* 1998;338:1785-92.
18. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet* 2002;360:743-51.
19. Fox KA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. *Lancet* 2005;366:914-20.
20. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. *Lancet* 1999;354:708-15.
21. Lagerqvist B, Diderholm E, Lindahl B, et al. FRISC score for selection of patients for an early invasive treatment strategy in unstable coronary artery disease. *Heart* 2005;91: 1047-52.
22. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med* 2001;344:1879-87.
23. de Winter RJ, Windhausen F, Cornel JH, et al. Early invasive versus selectively invasive management for acute coronary syndromes. *N Engl J Med* 2005;353:1095-104.
24. Mehta SR, Cannon CP, Fox KA, et al. Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. *JAMA* 2005; 293:2908-17.
25. Neumann FJ, Kastrati A, Pogatsa-Murray G,et al. Evaluation of prolonged antithrombotic pretreatment ("cooling-off" strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA* 2003;290:1593-9.
26. Smith SC, Jr., Feldman TE, Hirshfeld JW, Jr., et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *J Am Coll Cardiol* 2006;47:e1-121.
27. Kaul P, Fu Y, Chang WC, et al, for the PARAGON-A and GUSTO-IIb Investigators Prognostic value of ST segment depression in acute coronary syndromes: insights from PARAGON-A applied to GUSTO-IIb. *J Am Coll Cardiol* 2001;38:64-71.

Upcoming meetings

21- 22 April 2006
11th Annual Atlantic Canada Cardiovascular Conference
Halifax, NS
Contact: Office of Continuing Medical Education:
Mary Ann Robinson
Tel: 902-494-1560
E-Mail: CME@DAL.CA or mary.ann.robinson@dal.ca

2-6 September 2006
ECS Congress 2006
Barcelona, Spain
Contact: www.esccardio.org
Tel: 011-33-492-947600
Fax: 011-33-492-947601

Disclosure Statement: *Dr. Moe and Dr. Alhasaniah have no disclosures to announce in association with this publication.*

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.