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New guidelines for the management of unstable angina and non-ST-elevation myocardial infarction

Part 2: An invasive versus a conservative strategy and long-term management

By CHRISTOPHER P. CANNON, MD

Every year, approximately 1.42 million patients are admitted to hospitals in the United States with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI).[1,2] Over the past several years, there have been numerous advances in the evaluation and management of this large patient population, including numerous effective medical therapies (eg, antiplatelet therapies, cholesterol-lowering therapy) and interventional approaches. Part 1 of this article, presented in the last issue of *Cardiology Rounds*, discussed risk stratification and initial medical management, which is summarized below. Part 2 will discuss the relative benefits of an invasive versus a conservative strategy, and the importance of long-term risk factor modification and medical therapy.

In-hospital management summary

The evaluation of patients with UA/NSTEMI begins with the clinical history, ECG, and measurement of cardiac biomarkers to make an assessment of the likelihood of coronary disease, and the patient's risk of death or recurrent cardiac events. Patients with a *low* likelihood of having UA/NSTEMI should undergo a "diagnostic pathway" evaluation via serial ECGs, cardiac ºaccomplished in an Emergency Department observation/chest pain unit.

For patients with a clinical history that is strongly consistent with UA/NSTEMI, antithrombotic therapy with aspirin, clopidogrel, heparin, or low-molecular weight heparin, beta-blockers, and nitrates are recommended as initial management for all patients (Figure 1). For those patients assessed to be at low risk, an early conservative strategy is adequate, although an invasive strategy is of equal clinical benefit. For intermediate- and high-risk patients (ST-segment changes, positive troponin, TIMI Risk Score ≥3), the above-mentioned medications are beneficial plus GP IIb/IIIa inhibition (thus, 4 antithrombotic agents) are recommended and an early invasive strategy is preferred (Figure 1). Additional studies of the various combinations of treatments are ongoing to further define the safety of these regimens.

An invasive versus a conservative strategy

There are now 9 randomized trials that have assessed the merits of an invasive strategy involving routine cardiac catheterization with revascularization, if feasible, versus a conservative strategy where angiography and revascularization are reserved for patients who have evidence of recurrent ischemia either at rest or on provocative testing. The first three trials failed to demon-

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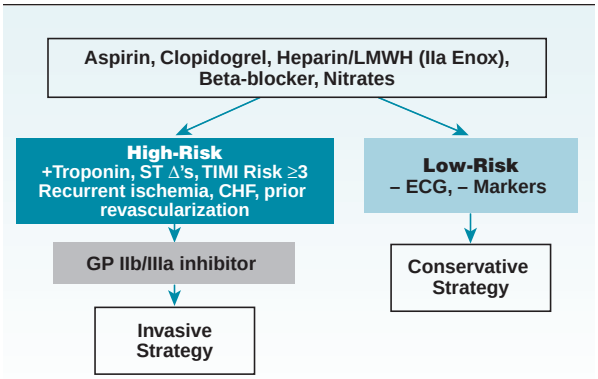
Figure 1: Risk stratification to target therapies in UA/NSTEMI



strate a significant benefit,[3] but the following trials all found a significant benefit with an invasive strategy (Figure 2).[4-6]

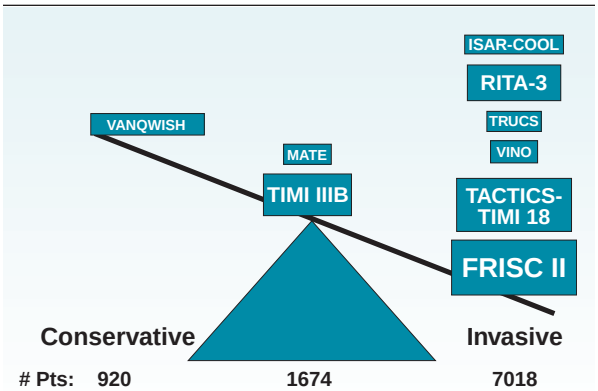
• FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC) II

• Treat Angina with Aggrastat and Determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS)-TIMI 18 trials

• Randomized Intervention Trial of unstable Angina (RITA)

The FRISC II trial – conducted in the late 1990s when stents were available and used in 90% of PCIs – was the first to find a significant *benefit* of an invasive strategy.[4] The primary endpoint, death or MI at 6 months, was significantly lower in the invasive vs. conservative group, 9.4% vs. 12.1%, p=0.031. At one-year there was a significant reduction in *mortality* in the invasive vs. conservative

Figure 3: The "weight of the evidence" showing benefit of an invasive vs. conservative strategy in patients with UA/NSTEMI. The size of the boxes for each of the 9 randomized trials corresponds to the number of patients enrolled.



groups (2.2% vs. 3.9%, respectively, p=0.016). Then, in the TACTICS-TIMI 18 trial, in which both stents and GP IIb/IIIa inhibition were used, the early invasive strategy reduced the rate of death, MI, or rehospitalization at 6 months from 19.4% in the conservative group to 15.9% in the early invasive group, odds ratio (OR) 0.78, p=0.025.[5] Similarly, death or non-fatal MI was significantly reduced at 30 days, (7.0% to 4.7%, respectively, p=0.02), and at 6 months (p=0.0498). Similarly, RITA 3 found a 34% reduction in death, MI or refractory angina at 4 months, 14.5% vs. 9.6%, p=0.001 (Figure 3).[6]

The benefits of an early invasive strategy were seen in intermediate- and high-risk patients, and especially in

Figure 2: Rates of death or MI during ~1 year follow-up in the major trials of invasive vs. conservative strategy

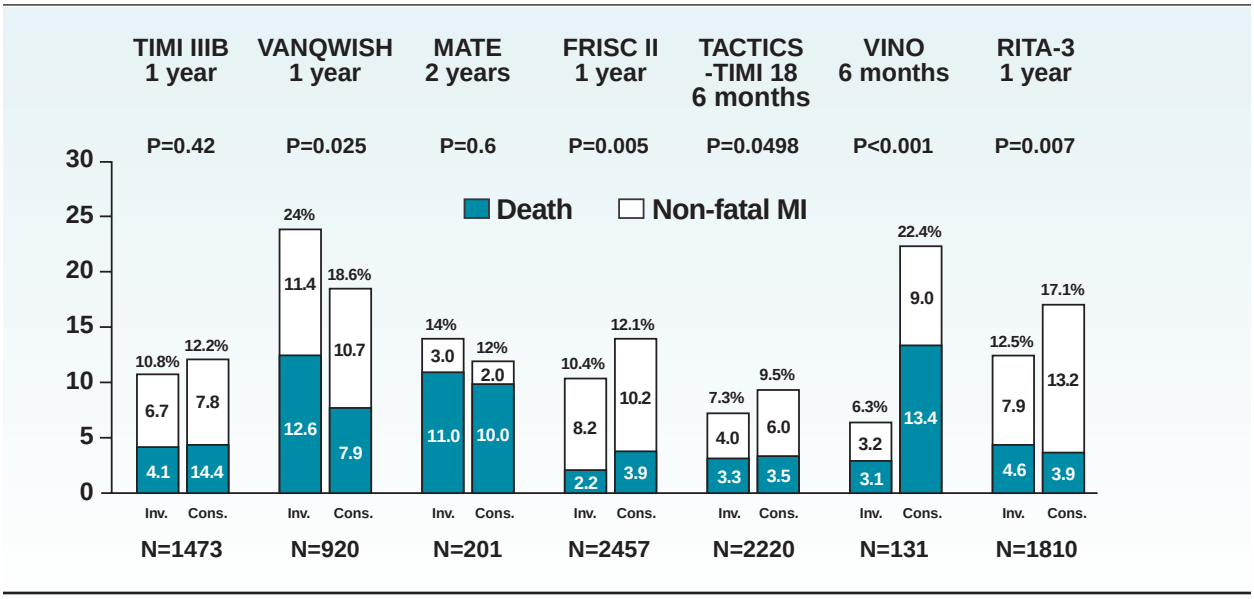
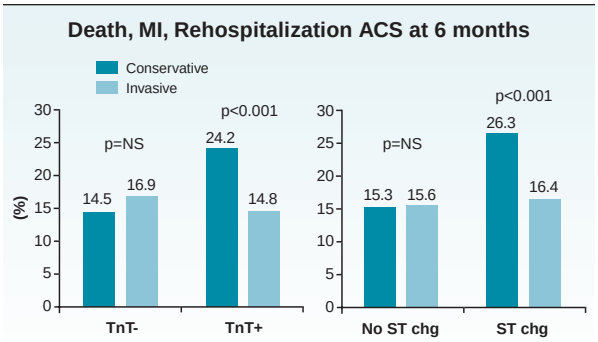


Figure 4: Benefit of invasive strategy by troponin and STΔ's[5,7]



those with ST-segment changes and positive troponin on admission (Figure 4) or a TIMI Risk Score ≥3.[5,6]

Accordingly, the 2002 ACC/AHA guidelines have added ST-segment changes and positive troponin to the list of high-risk indicators that would lead to a Class I recommendation for an early invasive strategy (Table 1).[2] Interestingly, an early invasive strategy is very cost-effective with a cost of approximately $12,739 per life-year saved.[8]

In terms of the exact timing for the invasive approach, preliminary data from the Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL) study recently found a benefit with an "immediate" invasive strategy (average time to catheterization of 2.4 hours), compared with a delayed invasive strategy (average time to catheterization of 4 days).[9] In observational data from TACTICS-TIMI 18, we have not seen a difference in outcomes between patients treated with an "immediate" invasive approach (ie, within hours) versus an early invasive approach (within 12-48 hours). Thus, for the moment, it appears that catheterization any time within the first 48 hours post-admission is beneficial.

Table 1: Early invasive strategy

Class I recommendations

Any of these high-risk indicators:
(Level of Evidence: A)

- Recurrent angina at rest/low-level activity despite Rx
- Elevated TnT or TnI
- New ST-segment depression
- Recurrent angina/ischemia with CHF symptoms, rales, mitral regurgitation
- Positive stress test
- EF <0.40
- ↓ BP
- Sustained VT
- PCI <6 mos, prior CABG

Table 2: Risk factor modification

Class I

- Smoking cessation
- Achieve optimal weight
- Daily exercise
- AHA Diet
- Hypertension control to a BP <130/85 mm Hg
- Tight control of hyperglycemia in diabetics.
- HMG-CoA reductase inhibitor for LDL cholesterol >130 mg/dL.
- Lipid-lowering agent if LDL cholesterol after diet is >100 mg/dL.
- A fibrate or niacin if HDL <40 mg/dL

Long-term secondary prevention

The time of hospital discharge is a "teachable moment" for the patient, when the physician can review and optimize his/her medical regimen. Risk factor modification is key and includes discussions (appropriate for their specific risk factors) about the importance of smoking cessation, achieving optimal weight, daily exercise, following an appropriate diet, good blood pressure control, tight control of hyperglycemia in diabetics, and lipid management (Table 2).

Long-term medical therapy

For medical treatment, there are 5 classes of drugs that have a Class I recommendation in the 2002 ACC/AHA Guidelines for long-term medical therapy (Table 3). The treatments are directed at different components of the atherothrombotic process. For plaque stabilization, statins and ACE inhibitors are recommended for long-term treatment, while beta-blockers are appropriate as anti-ischemic therapy and may help decrease "triggers" for MI during follow-up.[10] Antiplatelet therapy – the combination of aspirin and clopidogrel is now recommended for at least 9 months – will prevent or decrease the severity of any thrombosis that would occur if a plaque does rupture. Thus, a multifactorial approach to long-term medical therapy is directed at preventing the various components of atherothrombosis. The combination of aspirin and clopidogrel is based on long-term follow-up data from the CURE, PCI-CURE, and CREDO trials that demonstrate continued benefit of dual antiplatelet therapy out to 1 year.[11,12] Data

Table 3: Long-term medical therapy: Class I recommendations

- **Aspirin** 75 to 325 mg/d
- **Clopidogrel** 75 mg daily when ASA is not tolerated
- **Combination of ASA and clopidogrel** for 9 months after UA/NSTEMI.
- **ß-Blocker** (Level of Evidence: B)
- **Lipid-lowering agent** and diet in patients with LDL >130 mg/dL
- **Lipid-lowering therapy** if after diet LDL >100 mg/dL
- **ACEI** (Angiotensin converting enzyme inhibitor) for patients with CHF, LV dysfunction (EF< 0.40), hypertension, or diabetes

supporting beta-blockade come from numerous trials of the mid-1980s. Medical therapy includes ACE inhibition for long-term secondary prevention.[13]

Statin therapy, when started early during hospitalization for UA/NSTEMI, has also been shown to be beneficial in reducing recurrent ischemic events.[14] The wealth of data in long-term secondary prevention has made statin use a Class I recommendation for patients with an LDL >130 mg/dL, and they are likely relevant for those with LDL >100 mg/dL, as per the National Cholesterol Education Program (NCEP) – 3 guidelines.[15] New information from the Heart Protection Study showed the benefit of simvastatin 40 mg over placebo during long-term secondary prevention regardless of baseline LDL, including patients with baseline LDLs of <100, suggesting that statin therapy may be indicated in patients with any evidence of coronary or vascular disease.[16]

The importance of close follow-up

The ACC/AHA Guidelines have emphasized the importance of ensuring that patients who have recently been hospitalized with UA/NSTEMI are given optimal long-term secondary prevention medications. In part, this is because early initiation of medications is associated with better long-term compliance. Critical pathways are a means of ensuring that all appropriate medications are utilized, mostly as a reminder of all the classes of drugs that have been recommended (Table 4). A simple "cardiac checklist," either in a card format[17] or a Palm Pilot format (Figure 5)[18] is a way for clinicians to have rapid access to guideline-recommended medications that can be used at the bedside.

There are now several studies documenting that use of a critical pathway and, in particular, specific tools such as standardized orders or checklists, can improve the quality of care, including the CHAMP, GAP and the AHA "Get with the Guidelines" programs (Table 4). In the ACC's Guidelines Applied in Practice (GAP) project, they were able to improve the use of aspirin, beta-blockade, and increase the number of patients who had a lipid profile checked during hospitalization (Figure 6).[19]

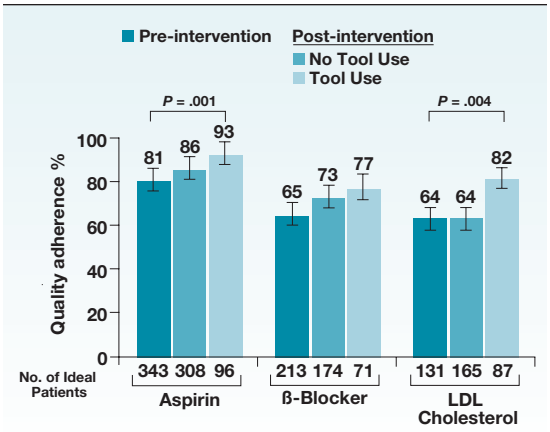
Establishing the optimal secondary prevention regimen is a key function of the cardiologist or internist who discharges the patient, but also of the primary care

Table 4: Critical pathways[17]

- Goal: optimize and streamline patient care
- Standardized treatment protocols for the management of specific disorders
- Emerging Evidence – Pathways work:
  - CHAMP (Cardiac Hospital Atherosclerosis Management Program)
  - Guidelines Applied in Practice (GAP)
  - AHA "Get with the Guidelines" program

Figure 5: Cardiac Checklist for the Palm Pilot[18]

Figure 6: GAP: Adherence improves with tool use[19]



physician who sees the patient in follow-up. Indeed, the Guidelines make two Class I recommendations:

1) Discharge instructions should include a follow-up appointment; and

2) Before hospital discharge patients, and/or designated responsible caregivers, should be provided with easily understandable instructions with respect to medication type, purpose, dose, frequency, and pertinent side effects. The transition from the hospitalization phase to the outpatient phase is critical.

The goal is for the patient to follow the guidelines, which now recommend 5 drugs classes for long-term secondary prevention (as noted above). Thus, it is important for the cardiologist to try to send the patient home on all of these medications. However, given the current very rapid pace of treatment with early invasive strategies, it is sometimes not possible to initiate treatment with all of the therapies (eg, starting ACE inhibitor due to low BP). Thus, if the patient is seen in follow-up by the primary care physician, and he/she is not receiving all of therapies recommended in the ACC/AHA Guidelines (in the absence of any contraindication), it is important that the physician initiates therapy in order to meet the Guidelines. In this fashion, there is a smooth transition of care and high compliance with optimal care as outlined in the Guidelines.

Conclusion

There have been many advances in UA/NSTEMI management. Risk stratification and use of troponin and risk scores to target appropriate therapies are now critical. In addition, many advances in antithrombotic therapy have improved outcomes, eg, clopidogrel, low molecular weight heparin, and selected use of GP IIb/IIIa inhibitors. An early invasive approach is clearly beneficial for intermediate- and high-risk patients and is relatively cost-effective. Finally, it is important to take a second look at the UA/NSTEMI patient at the time of hospital discharge to ensure the patient is on the 5 classes of drugs for secondary prevention and that a comprehensive risk factor modification program has been initiated.

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