

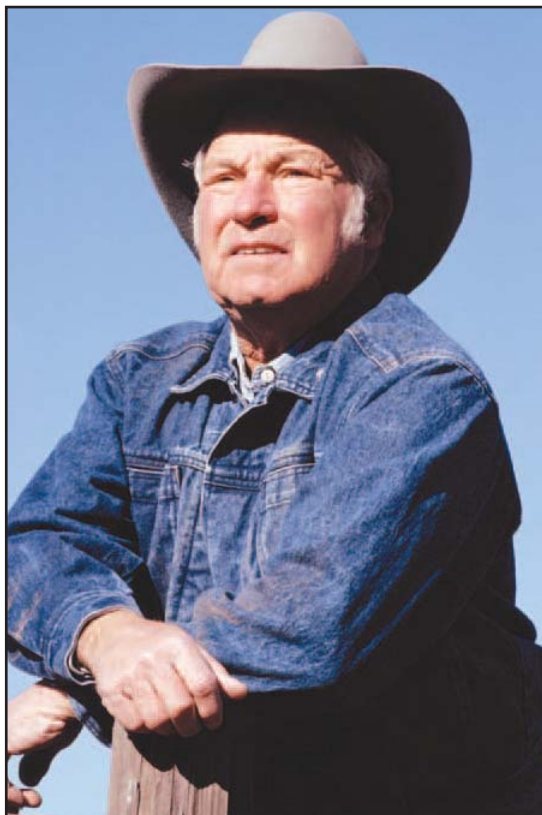


# Clot Stoppers:

## Making the Most of Therapy

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The quote “man lives with atherosclerosis but dies from thrombosis” is axiomatic, as the vast majority of ischemic syndromes result from the formation of thrombus at the site of an active or ruptured atherosclerotic plaque. At this point, the body’s normal hemostatic balance has been overwhelmed by the burden of platelet activation and consequent thrombin-induced fibrin formation. By targeting various steps in the clotting cascade, there is great potential for improving overall outcomes in both the setting of acute ischemic syndromes, and in the long-term secondary prevention of ischemic cardiac events.

### What is the rationale for a long-term antithrombotic strategy after acute chest syndrome?

ST segment elevation (STEMI) and non-ST segment elevation myocardial infarctions (N-STEMI) represent clinical emergencies with high potential for catastrophic events, such as cardiogenic shock, ventricular dysrhythmias, and death. Despite the initiation of appropriate therapies in hospital, research suggests much of subsequent morbidity

### In this article:

1. What is the role of antiplatelet agents?
2. What can be done for long-term anticoagulation?
3. What about atrial fibrillation?
4. What are the current treatment options?

and mortality occurs in the post-hospitalization period. In the case of N-STEMI, more than half of all adverse cardiac events within the first month occur after the initial five days with a subsequent high rate of recurrent ischemia and infarction for up to six months. This may be a result of several factors, including:

- persistent platelet activation and thrombin generation at the site of the clot,
- rebound activation following cessation of anticoagulation, and
- the potential for microembolization of thrombotic debris in the distal coronary vasculature.<sup>1</sup> Intuitively then, optimal management of

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## Mr. Smith's racing heart

Mr. Smith, 74, presents to the emergency department with 45 minutes of moderate retrosternal chest tightness radiating to his arms that developed at rest. He's had a similar episode within the last week, lasting less than 20 minutes, for which no medical attention was sought. There is no shortness of breath or lightheadedness, but his heart has "raced" on occasion over the last several months.

His medical history is significant for longstanding, treated hypertension (hydrochlorothiazide 25 mg daily, and ramipril 5 mg daily). He is a former smoker with no other medical history or medication.

### Examination reveals:

- blood pressure of 134/82 mmHg
- respiratory rate of 18/min
- heart rate of 132 beats per minute that is not often irregular.
- cardiac apex is prominent
- jugular venous pressure is 3 cm above the sternal angle with no appreciable double impulse
- auscultation does not reveal any extra heart sounds or murmurs
- chest is clear to auscultation

### Electrocardiogram reveals:

- atrial fibrillation
- voltage criteria for left ventricular hypertrophy
- non-specific ST-T segment changes in the precordial leads

Mr. Smith is given two baby acetylsalicylic acid (ASA) tablets, sublingual nitroglycerin, intravenous metoprolol, and he is placed on a cardiac monitor.

After eight hours, serum troponin I levels are reported elevated at 2.8 (normal < 0.15).

He is diagnosed with a non-ST elevation myocardial infarction and atrial fibrillation with admission to a monitored unit for 72 hours.

### Medical management includes:

- ASA
- subcutaneous enoxaparin
- ramipril
- simvastatin
- oral metoprolol (which controls his heart rate).

In hospital, he has no recurrence of chest pain, no signs of congestive heart failure, and laboratory investigations (including creatinine kinase) remain normal. Prior to discharge, he successfully completes a low level stress test, and followup is arranged with his family physician.

### What is the most appropriate pharmacologic management of Mr. Smith following his admission to hospital?

For the answer, please go to page 128.

patients following hospitalization for an acute coronary syndrome involves long-term inhibition of platelet activation, and coagulation in a proven, safe, and effective manner.

## What is the role of antiplatelet agents?

By inhibiting cyclooxygenase dependent thromboxane (TXA<sub>2</sub>) synthesis, acetylsalicylic acid



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(ASA) prevents platelet activation and aggregation at the site of an unstable atherosclerotic arterial plaque. Daily ASA doses of 75 mg to 325 mg have proven efficacy in the treatment of acute coronary syndromes, and in the secondary prevention of cardiovascular morbidity and mortality. In a recent comprehensive meta-analysis of over 135,000 patients in 287 studies, the benefit of ASA compared to placebo was unequivocally demonstrated, with relative risk reductions in the range of 26% to 32% for serious vascular events among high-risk patients. Interestingly, lower dose ASA (75 mg to 150 mg) was shown to be as effective as higher dose ASA (160 mg to 325 mg). It has been hypothesized that the lower ASA doses provide some prostacyclin sparing effect which, itself, promotes platelet inhibition and reduces gastrointestinal toxicity.<sup>2</sup>

In the same meta-analysis, the ADP inhibitor clopidogrel reduced vascular events by approximately 10% compared to ASA in patients with a history of coronary disease, stroke or peripheral vascular disease.<sup>2</sup> Although based on relatively few studies, this finding may indicate that clopidogrel is an effective alternative antiplatelet regimen for patients unable to tolerate ASA therapy. Moreover, in the landmark Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, the prolonged use of clopidogrel and ASA demonstrated an early and sustained reduction in combined end point of death, MI or stroke compared to ASA alone among patients that presented with high-risk acute coronary syndromes (those with chest pain and either

electrocardiogram [ECG] changes or cardiac enzyme elevation).<sup>3</sup> Based on the CURE trial results, for every 48 patients treated with clopidogrel,

a major adverse cardiovascular event is prevented at a cost of approximately one major bleeding complication per 100 patients treated. It may, therefore, be appropriate to employ a more aggressive antiplatelet strategy for those patients at significantly higher risk of future events.

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## Resolution for Mr. Smith

Following his discharge from hospital, Mr. Smith is maintained on acetylsalicylic acid 81 mg daily for secondary prevention of myocardial infarction. He also remains on:

- ramipril 5 mg daily
- metoprolol 50 mg twice daily
- hydrochlorothiazide 25 mg daily
- simvastatin 40 mg daily

He remains in atrial fibrillation, and based on his risk profile for thromboembolic stroke (age approaching 75, history of hypertension), a decision is made to initiate long-term anticoagulation with warfarin therapy. It is expected that warfarin may further reduce his future risk of infarction or cardiovascular mortality.

International normalized ratio will be maintained within the 2.0-3.0 range, and, while Mr. Smith is capable of strict medical adherence, frequent monitoring is recommended to minimize the risk of future bleeding complications.

Given his initial acute coronary syndrome presentation with significant chest pain and cardiac enzyme elevation, the addition of clopidogrel to his antithrombotic regimen is considered. However, it is felt that potential benefits may be outweighed by the compounded risk for hemorrhage due to the requirements for warfarin.

## What can be done for long-term anticoagulation?

Maintaining long-term anticoagulation after an acute coronary syndrome is re-emerging as a feasible strategy for secondary prevention. Historically, the use of warfarin to achieve sustained anticoagulation post-MI has been the subject of some debate, as earlier studies did not demonstrate a significant benefit in mortality or re-infarction, compared to ASA use alone. It has been suggested by meta-analysis, however, moderate to high dose warfarin, in addition to ASA, is

superior to ASA monotherapy. In a recent large randomized controlled trial, patients treated, post myocardial infarction, with either high intensity warfarin (international normalized ratio [INR] 2.8-4.2) or low intensity warfarin (INR 2.0-2.5) and ASA 75 mg had significantly fewer deaths, re-infarctions or embolic strokes than patients treated with ASA alone. The benefits seen with warfarin regimens were offset, in part, by higher rates of major, non-fatal bleeding events.<sup>4</sup> Although there is potential for improving patients' clinical outcomes by optimizing antithrombotic therapy with long-term anticoagulation, this approach may be confined to a select group of patients who can be reliably monitored to ensure efficacy and safety.

## What are the limitations, concerning warfarin?

The initiation and titration of warfarin has familiar limitations, such as unpredictable dose-response and the requirement for frequent blood tests that make it impractical for use in all patients for whom it may be indicated. While low molecular weight heparins overcome some of the difficulties encountered with warfarin, earlier trials of prolonged outpatient therapy with enoxaparin and dalteparin administration following an acute coronary syndrome were disappointing, with no additional benefit seen beyond the in-hospital management period. An exciting challenge is the recent development and imminent implementation of newer generation anticoagulant therapies; although further research is required to determine whether the theoretical and practical advantages will translate into safer, more efficacious clinical practice.

## What about atrial fibrillation?

In addition to atherosclerotic coronary disease, a high burden of cardiovascular morbidity results from thrombus formation in the setting of atrial fibrillation (AF) with high potential for systemic

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embolization and cardioembolic stroke. AF (non-valvular) is a common condition with greater prevalence among the elderly; it is seen in approximately 10% of 80 year-olds and confers a four to fivefold increased risk of stroke over those without AF.<sup>5,6</sup> Various large-scale clinical trials have demonstrated the benefit of long-term anticoagulation with warfarin, compared to ASA and placebo in patients with AF at high risk of stroke. For example, meta-analyses have shown a relative risk reduction for stroke in the order of 62% to 68% among AF patients on warfarin (INR typically titrated to 2.0-3.0) versus placebo, which translates into an absolute event reduction of approximately 2.7% to 3.1% per year.<sup>7,8</sup> In the same analysis, ASA reduced stroke by 22% compared to placebo, and warfarin was associated with a 36% reduction in stroke over ASA use alone.

A caveat, however, is that major bleeding complications are seen more frequently with warfarin regimens (approximately 2.2% per year compared to 1.3% per year on ASA), especially among the group of patients at highest risk for events, in whom the greatest benefit of long-term anticoagulation is derived.<sup>5</sup> Present guidelines attempt to reflect the available evidence for efficacy and safety, and the use of warfarin is currently recommended for all patients with AF who have a major risk factor for thromboembolic stroke:

- age 65 to 75 (> 75 highest risk),
- prior stroke/transient ischemic attack,
- hypertension,
- left ventricular dysfunction,
- +/- diabetes mellitus, and
- +/- coronary artery disease.<sup>8</sup>

## What lies ahead?

The conversion of fibrinogen to fibrin by thrombin represents the last major sequence in the stepwise activation of clotting factors down the coagulation cascade. This cascade provides various targets for pharmacologic intervention in the secondary prevention of cardiovascular disease, and indeed there are a number of novel agents in development with this aim.

Selective inhibition of clotting factor Xa (prothrombinase) is an attractive mark for antithrombotic pharmacotherapy. The best studied agent in this class, the pentasaccharide fondaparinux, has been shown to be superior to enoxaparin for the prevention of deep venous thrombosis (DVT) in orthopedic surgery patients.<sup>9-11</sup> In coronary artery

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disease, fondaparinux has shown a trend towards improved vessel patency compared to unfractionated heparin when given with thrombolytic for STEMI, and has shown a trend toward improved outcomes for major cardiac events in N-STEMI acute coronary syndromes compared to enoxaparin.<sup>12,13</sup> Noted improvements do not seem to occur at the expense of increased rates of bleeding, making these agents appealing for further study across a broader range of applications, including the post-hospitalization period following an acute coronary syndrome.

## What are other options concerning prothrombinase inhibition?

Other novel agents with factor Xa inhibition include the direct prothrombinase inhibitor DX-9065a which is under investigation in coronary artery disease patients, and sodium N-amino caprylate

(SNAC)/heparin, which is an orally delivered heparin. This latter agent allows intestinal carriage and absorption of heparin with effective in vivo anticoagulation, including inhibition of Xa and IIa as seen with the parenterally administered compound.<sup>14</sup> It remains to be seen whether these agents will prove effective for long-term anticoagulation in arterial and venous thrombotic disease.

## What other anticoagulants are going through trials?

Recombinant nematode anticoagulant protein c2 (rNAPc2) is another unique anticoagulant undergoing clinical investigation for patients with coronary artery disease, and in patients at risk for DVT. NAPc2, originally isolated from a hookworm species, acts upstream in the coagulation cascade by inhibiting the activity of tissue factor/factor VIIa complex. This effectively inactivates the extrinsic limb of the clotting pathway resulting in significantly impaired thrombin generation. Early phase II trials have shown rNAPc2 to be effective for DVT prophylaxis in surgical patients, and effective in vivo anticoagulants among patients with coronary disease undergoing elective PCI.<sup>15,16</sup> As with other new generation antithrombotic agents, further investigation is warranted to determine what place tissue factor/factor VIIa inhibitors will have in the management of patients with known atherosclerotic coronary disease.

## Are long-term direct thrombin inhibitors feasible?

The use of direct thrombin inhibitors for long-term secondary prevention of cardiovascular disease may be feasible with the development of newer oral agents (such as ximelagatran, which does not require routine anticoagulation monitoring owing to predictable pharmacokinetics). Results from phase III trials of perioperative (DVT) prophylaxis have shown good efficacy and safety compared to standard prophylactic therapy with low-

## Take-home message



### ASA is important, concerning coronary syndromes, according to various studies:

- Daily ASA doses of 75-325 mg have proven efficacy in the treatment of acute coronary syndromes, and in secondary prevention of cardiovascular morbidity and mortality.
- Lower dose ASA (75-150 mg) has shown to be as effective as higher dose (160-325 mg).
- It has been hypothesized lower ASA doses provide prostacyclin sparing effect, which itself promotes platelet inhibition and reduces gastrointestinal toxicity.
- Clopidogrel is an effective alternative antiplatelet regimen for patients unable to tolerate ASA therapy.
- Prolonged use of clopidogrel and ASA have demonstrated early, sustained reduction in combined end point of death, MI or stroke compared to ASA alone.
- Moderate to high dose warfarin, in addition to ASA, has proven to be superior to ASA monotherapy.

molecular weight heparins.<sup>17</sup> Currently, the Stroke Prophylaxis using an ORal Thrombin Inhibitor in atrial Fibrillation (SPORTIF) trials are underway, and will assess the safety and efficacy of anticoagulation with ximelagatran in patients with AF. In the recently completed SPORTIF III trial, ximelagatran reduced stroke and systemic embolic events by 41% compared to warfarin in non-valvular atrial fibrillation patients by “on-treatment” analysis, and demonstrated non-inferiority by “intention to treat” analysis. There was also a trend towards fewer bleeding complications in the ximelagatran group. Following these encouraging early results, the outcome from further trials in this series is most eagerly anticipated. **CME**



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## Net Readings

- CareInternet.net:  
[www.careinternet.com](http://www.careinternet.com)
- Mission International Medical Group:  
<http://mimg.com/cardiology>