

# PCI or Drug Therapy: Consider Ischemic Burden

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BOSTON — In the ongoing debate over whether patients with chronic, stable angina are better served by revascularization with percutaneous coronary intervention in addition to drug treatment or optimal medical therapy alone, the key variable appears to be ischemic burden, Dr. Daniel S. Berman reported at the annual meeting of the American Society of Nuclear Cardiology.

Last year, investigators in the Clinical Outcomes Using Revascularization and Aggressive Drug Evaluation (COURAGE) trial reported that adding percutaneous coronary intervention (PCI) to optimal medical therapy in patients with stable coronary artery disease did not improve clinical end points, compared with optimal



**COURAGE patients with moderate to severe ischemia showed greater improvement after PCI than after OMT only.**

DR. BERMAN

medical therapy alone (N. Engl. J. Med. 2007;356:1503-16). The results sparked a controversy that led some experts to conclude that PCI is overused and unnecessary in stable coronary disease.

More recently, however, a substudy of the COURAGE trial comprising 314 patients equally distributed between groups treated with PCI plus optimal medical therapy and optimal medical therapy alone showed that the PCI strategy produced a greater ischemia reduction than the optimal medical therapy—only (OMT-only) intervention—particularly among patients with moderate to severe ischemia at baseline.

“Importantly, patients in both groups who experienced ischemia reduction had a significantly lower risk for death or myocardial infarction than patients without ischemia reduction, and the magnitude of residual ischemia was proportional to the overall risk of subsequent cardiac event,” said Dr. Berman, chief of cardiac imaging and nuclear cardiology at Cedars-Sinai Heart Center in Los Angeles.

The main COURAGE trial included 2,287 patients, with a history of angina or documented myocardial ischemia and at least one significant coronary lesion, who were stable on medical therapy. Participants were randomized to continue their medication alone or with PCI, and the study’s combined end points were death or nonfatal myocardial infarction. The composite rates of death or nonfatal myocardial infarction over 4.6 years of follow-up were statistically similar in both groups, at 19.0% for the PCI group and at 18.5% for the patients who received only optimal medical therapy, showing no benefit of PCI over optimal medical therapy in stable coronary artery disease.

In the nuclear imaging substudy, the 314 patients were equally distributed between the PCI and OMT groups and they were well matched with respect to demographics and risk factors, said Dr. Berman.

All of the patients were on medication for a mean 374 days from baseline and all underwent serial myocardial perfusion single-photon emission computed tomography (SPECT-MPI) studies 6-18 months following the baseline examina-

tion to assess the extent and severity of the perfusion defect in the global myocardium, he said.

With myocardial ischemia defined as the total perfusion deficit at stress minus the perfusion deficit at rest, 33% of patients in the PCI group and 20% in the OMT-only group showed a 5% or greater reduction in ischemia.

Among the patients in the imaging substudy with moderate to severe pretreatment ischemia, defined as a perfusion de-

fect involving 10% or more of myocardium, “78% of the PCI patients demonstrated 5% improvement or greater, compared to 52% of the [OMT-only] patients,” Dr. Berman reported.

In considering these changes in terms of their relationship to subsequent outcomes, “we looked at the myocardial infarction rates in patients with and without ischemia reduction and determined that patients in both groups with 5% improvement in ischemia had approximate-

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### The Office of the Surgeon General’s Call to Action Against Deep Vein Thrombosis and Pulmonary Embolism

The high incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), has a devastating effect on patients and their families. The Surgeon General has announced a Call to Action to raise awareness about the risk factors and prevention of VTE.

*“DVT/PE are major national health problems that have a dramatic, negative impact on the lives of hundreds of thousands of Americans each year.”<sup>1</sup>*

Rear Admiral Steven K. Galson, MD, MPH, US Public Health Service, Acting Surgeon General

According to the Surgeon General’s Call to Action, VTE is a major cause of morbidity and mortality among hospitalized patients.<sup>1,2</sup> It is the third leading cause of cardiovascular death in the United States, following myocardial infarction and stroke.<sup>2</sup>

- There are up to 600,000 cases of DVT and PE annually, resulting in at least 100,000 deaths per year<sup>1</sup>
- More annual deaths are attributed to VTE than breast cancer and AIDS combined<sup>3</sup>
- Many patients with VTE do not have any clinical signs or symptoms, with 25% of patients presenting with sudden death<sup>4</sup>

Even when accurately diagnosed, complications due to VTE can be long-standing and reduce quality of life, despite adequate treatment. The first step in reducing the incidence of DVT is to increase awareness among the public as well as health care providers about risk factors that may lead to DVT. By understanding patient risk factors, appropriate prophylaxis may be initiated.

*“The majority of DVT/PE events are related to specific, identifiable triggering events...”<sup>1</sup>*

#### Partial list of risk factors associated with DVT and PE<sup>5,6</sup>

- Restricted mobility
- Age >40 years
- ICU admission
- Obesity
- Surgery
- Varicose veins
- Prior history of VTE (DVT and/or PE)
- Chronic lung disease
- Inflammatory bowel disease
- Smoking

Table 1. Partial list of risk factors. Clinicians are advised to consider other risk factors or conditions that may predispose to DVT/PE.

*“Much is known today about how to prevent DVT/PE, and how to minimize the impact for those patients who suffer from these conditions. If this knowledge were applied consistently, the burden could be reduced substantially.”<sup>1</sup>*

#### Advancing DVT Awareness

According to the American Public Health Association Deep-Vein Thrombosis Omnibus Survey, 74% of adults had very little or no awareness of DVT.<sup>7</sup> Even among those mindful of DVT, 57% did not know of any risk factors associated with DVT. Surprisingly, 95% of respondents said their physician had never discussed the importance of DVT with them.<sup>7</sup>

Both patients and physicians must educate themselves about the dangers of DVT. It is important for health care providers to routinely assess DVT risk in hospitalized patients as well as screen high-risk patients more thoroughly. All hospitalized patients are at risk of developing DVT. Patients not receiving prophylaxis and undergoing certain general, urologic, gynecologic, or surgical procedures have a 15% to 40% risk of developing DVT.<sup>5</sup> For hospitalized acutely ill medical patients, the risk is 10% to 20%. Patients having hip or knee arthroplasty are at even higher risk, 40% to 60% without prophylaxis.<sup>5</sup> Given the high prevalence of DVT in hospitalized patients, all patients should periodically be risk assessed for DVT.

*“Individuals, families, and their communities need to understand DVT and PE, the risk factors for these diseases, and how to reduce these risks.”<sup>1</sup>*

#### DVT Prophylaxis Reduces the Incidence of DVT, Which May Lead to PE

The use of anticoagulation therapy has been shown to significantly reduce the risk of VTE by as much as 52%<sup>8</sup>; however, implementation and lack of appropriate prophylaxis in at-risk medical patients continue to be problematic,<sup>9</sup> despite evidence-based DVT/PE guidelines (Table 2).

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ly 50% lower cardiac event rate," he said.

A similarly reduced cardiac event rate was observed in the 105 patients from both groups with moderate to severe ischemia and a greater than 5% reduction in ischemia observed post treatment, he said.

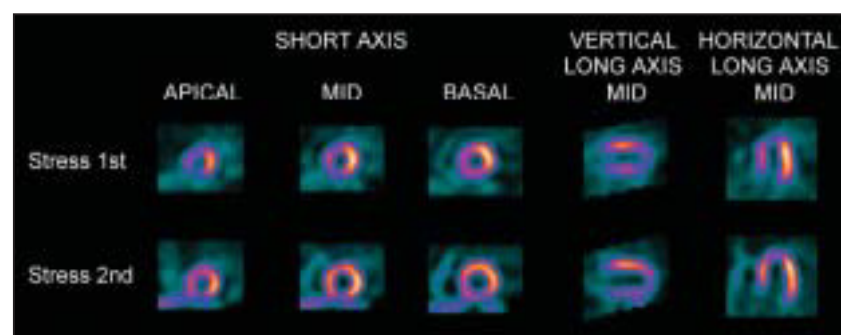
Although the substudy was not sufficiently powered to generalize that reducing ischemia will prevent later cardiac events, "we did see a striking relationship between amount of residual ischemia and the subsequent death or myocardial infarction rate," Dr. Berman stated.

This observation is "definitely a hypothesis generator," warranting a controlled trial comparing the PCI-based strategy with optimal

medical therapy alone in patients with chronic stable angina who would be randomized based on the presence of moderate to severe ischemia, he said.

"We should be studying patients with 10% or more ischemia to determine if there is a subset of patients who would have improved angina and quality-of-life outcomes with revascularization." The findings would be especially important to those patients with documented large amounts of jeopardized myocardia in whom medical therapy does not provide adequate relief, he concluded.

The COURAGE nuclear imaging substudy was supported by Bristol-Myers Squibb Medical Imaging and Astellas Healthcare. ■



The above SPECT-MPI image shows the first and second stress myocardial perfusion from a patient in the nuclear substudy of the COURAGE trial who received optimal medical therapy only. Total perfusion deficit was reduced from 16% to 6%. Patients in both the PCI and OMT-only groups with 5% improvement in ischemia had 50% lower cardiac event rates.

PE resulting from DVT is the most common cause of preventable death among hospitalized patients.<sup>5</sup> In the DVT FREE study funded by sanofi-aventis, which included 5451 patients with ultrasound-confirmed DVT, 71% did not receive any prophylaxis within 30 days of diagnosis.<sup>10</sup> Moreover, nonsurgical patients were much less likely than surgical patients to receive appropriate DVT prophylaxis.<sup>10</sup> The American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines recommend that, for every general hospital, a formal, active strategy that addresses the prevention of VTE be developed (Grade 1A).<sup>5</sup>

"Providing preventive treatment (or primary prophylaxis) to these individuals can dramatically reduce the likelihood of a blood clot or PE."<sup>11</sup>

## Recommendations for VTE Prophylaxis in Select Hospitalized Patients<sup>5</sup> (Adapted From 2008 ACCP Guidelines)

### Prophylaxis of DVT in medical patients with restricted mobility during acute illness<sup>5,11,a</sup>

- For acutely ill medical patients admitted to hospital with congestive heart failure (CHF) or severe respiratory disease, or who are confined to bed and have one or more additional risk factors, including active cancer, previous VTE, sepsis, or inflammatory bowel disease: ACCP recommends thromboprophylaxis with low-molecular-weight heparin (LMWH) or low-dose unfractionated heparin (LDUH) (all Grade 1A)

### Prophylaxis of DVT following abdominal surgery<sup>5,11,a</sup>

- For higher-risk general surgery patients undergoing a major procedure for cancer: ACCP recommends thromboprophylaxis with LMWH or LDUH three times daily (each Grade 1A)
- For patients undergoing major general surgical procedures: ACCP recommends thromboprophylaxis continue until discharge from hospital (Grade 1A)

### Prophylaxis of DVT following hip- or knee-replacement surgery<sup>5,11,a</sup>

- For patients undergoing total hip replacement (THR) or total knee replacement (TKR): ACCP recommends routine thromboprophylaxis with LMWH (at the usual high-risk dose) or adjusted-dose vitamin K antagonist (VKA) (international normalized ratio [INR] target, 2.5; INR range, 2.0 to 3.0) for at least 10 days (all Grade 1A)
- For patients undergoing THR: ACCP recommends thromboprophylaxis be continued beyond 10 days and up to 35 days after surgery with LMWH (Grade 1A) or a VKA (Grade 1B)

Table 2. ACCP 2008 Guidelines: recommendations for VTE prophylaxis.

LOVENOX® (enoxaparin sodium injection) is indicated for the prophylaxis of DVT, which may lead to PE:

- In medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications
- In patients undergoing hip-replacement surgery, during and following hospitalization
- In patients undergoing knee-replacement surgery

## Two Clinical Trials Showed LOVENOX® Provided Effective VTE Prophylaxis in Medically Ill Patients

MEDENOX (Prophylaxis in Medical Patients With Enoxaparin) was a multicenter, multinational, double-blind study that included 1102 acutely ill medical patients randomized to either LOVENOX® or placebo for 6 to 14 days during hospitalization.<sup>12</sup>

The incidence of DVT or PE was significantly lower in patients treated with LOVENOX® than placebo (5.5% vs 14.9%, respectively).<sup>12</sup> The use of LOVENOX® was associated with a 63% reduction in risk of VTE.<sup>12</sup>

There was no statistically significant difference in major bleeding events<sup>b,c</sup> or thrombocytopenia comparing LOVENOX® with placebo.<sup>12,13</sup>

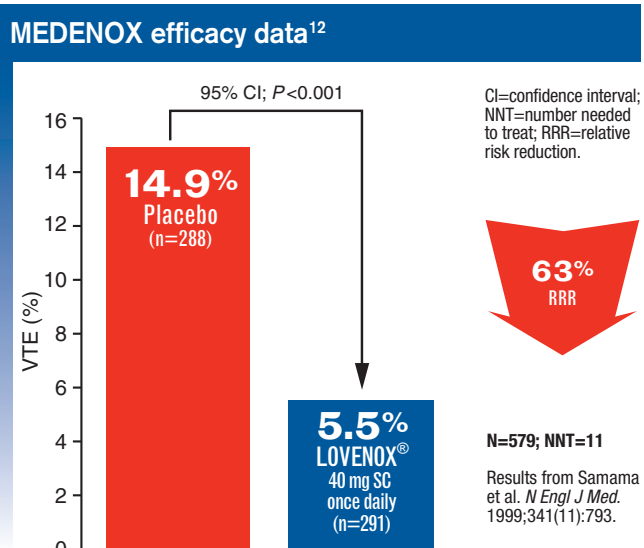


Figure 1. Short-term incidence and RRR of VTE in medical patients treated with LOVENOX® (40 mg) vs placebo. P values are for RRR.

<sup>a</sup> Grades of recommendation – 2008 Guidelines: ACCP Evidence-Based Clinical Practice Guidelines (8th edition)—Grade 1A—strong recommendation based on high-quality evidence; Grade 1B—strong recommendation based on moderate-quality evidence; Grade 1C—strong recommendation based on low- or very low-quality evidence.<sup>11</sup>

<sup>b</sup> Based on the rate of major bleeding on LOVENOX® up to 24 hours after the last dose.<sup>13</sup>

<sup>c</sup> Hemorrhage was classified as major if bleeding was overt and was associated with the need for transfusion of 2 or more units of packed red blood cells or whole blood, or with a decrease in the hemoglobin concentration of 2.0 g/dL or more from baseline, or if bleeding was retroperitoneal, intracranial, or fatal.<sup>12</sup>

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