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Are statins for everyone?
The JUPITER trial of statins in primary prevention, presented at the American Heart Association 2008 Scientific Sessions, provides potential guidance on how to treat the above patient. This pivotal, multi-site trial showed that treatment of apparently healthy patients with rosuvastatin reduced their relative risk of cardiovascular disease (CVD) morbidity and mortality by almost half (1). The JUPITER trial randomly assigned 17,802 apparently healthy men and women with LDL cholesterol levels of less than 130 mg/dl and hs-CRP levels of 2.0 mg/liter or higher to either rosuvastatin, 20 mg daily, or placebo, and followed them for the occurrence of the combined primary end point of myocardial infarction (MI), stroke, arterial revascularization, hospitalization for unstable angina or death from cardiovascular causes. The data monitoring committee stopped the trial after a median of 1.9 years of follow-up because safety monitoring revealed a significant reduction in cardiovascular morbidity and mortality.

Additionally, rosuvastatin reduced LDL cholesterol levels by 50 percent and hs-CRP levels by 37 percent. The large decrease in total mortality may be because rosuvastatin lowered LDL cholesterol by a much greater degree than that obtained with pravastatin, lovastatin and low-dose atorvastatin in prior primary prevention studies.

It is not correct, however, to conclude from JUPITER that widespread use of statins in all low-risk subjects will yield societal benefits. The treatment benefit in JUPITER was expressed in numbers... Continued on page 2 (see “Statins”)
The JUPITER trial did address whether CVD risk factor.
evident coronary heart disease but have normal LDL-C levels and no clinically 
vascularization procedures in individuals who 
tion for reducing the risk of stroke, MI and re-
approval of rosuvastatin to include the indica-
Food and Drug Administration extended its 
on the trial’s positive outcome data, the U.S. 
C but elevated hs-CRP (> 2.0 mg/liter). Based 
hypothesized in 2001 that 
the JUPITER trial, hypothesized in 2001 that 
expect large treatment benefi ts that may have 
Based on hs-CRP results. They warned not to 
statin therapy on all-cause mortality among 
Interpreting the NNT to fi ve years is prob-
emphasizing the utility of hs-CRP screening, 
assuming that statins have good long-term 
safety and provide benefi ts among low-risk 
people with normal hs-CRP (2).

Patients with elevated hs-CRP
Paul Ridker, MD, the principal investigator of the JUPITER trial, hypothesized in 2001 that 
statin therapy may be effective in the primary 
prevention of coronary events among individ-
uals with relatively low lipid levels but elevated 
levels of hs-CRP. This hypothesis was based on 
an analysis of the Air Force/Texas Coro-
nary Atherosclerosis Prevention Study, which 
was a primary prevention trial that compared 
pravastatin with placebo (3). Dr. Ridker ob-
served that most of the cardiovascular event 
reduction in that trial occurred in patients with 
elevated levels of hs-CRP. He postulated that 
patients with elevated serum levels of hs-CRP 
had an increased extent of systemic inflamma-
tion that led to higher cardiovascular 
event rates.

The JUPITER trial was designed to assess 
whether statin therapy should be given to ap-
parently healthy individuals with normal LDL-
C but elevated hs-CRP (> 2.0 mg/liter). Based 
on the trial’s positive outcome data, the U.S. Food 
and Drug Administration extended its 
approval of rosuvastatin to include the indica-
tion for reducing the risk of stroke, MI and re-
vascularization procedures in individuals who 
have normal LDL-C levels and no clinically 
evident coronary heart disease but have an 
increased risk based on hs-CRP levels, age 
and the presence of at least one additional 
CVD risk factor.

The JUPITER trial did not address whether 
considering hs-CRP in addition to the Fram-

Food and Drug Administration extended its 
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increased risk based on hs-CRP levels, age 
and the presence of at least one additional 
CVD risk factor.

The JUPITER trial did not address whether 
considering hs-CRP in addition to the Fram-

The SHAPE task force algorithm (7). The 
SHAPE task force suggests noninvasive 
atherosclerosis imaging of all asymptomatic 
men age 45 to 75 years and women age 55 
to 75 to add information to conventional risk 
assessment tools (8). 
Carotid ultrasound and cardiac CT can incre-
mentally refine risk assessment and may allow 
for improved adherence and better matching 
of preventive interventions to the magnitude 
of risk. Carotid ultrasound may identify sub-
clinical disease in cerebral circulation. Cardiac 
CT scan (Fig. 2) for coronary artery calcium 
(CAC) may provide a safe and effective way 
of identifying patients with subclinical CAD who 
deserve closer surveillance and treatment.

Coronary calcium scanning
Our experience at Cedars-Sinai with the Early 
Identification of Subclinical Atherosclerosis 
by Noninvasive Imaging Research (EISNER) 
study, under the leadership of Daniel Ber-
man, MD, has shown screening for subclinical 
atherosclerosis with the CAC scan positively 
affects patient treatment with minimal impact 
to the cost of care (8). The EISNER study 
was designed as an ongoing prospective 
registry with the principal objective of assess-
ing whether CAC scanning provides clinical 
benefit, thus improving patient outcomes, in 
asymptomatic patients with intermediate CAD 
risk. The study was also designed to assess 
the value of combining the CAC scan with the Framingham risk score and measurements 
of serum or plasma biomarkers to predict 
outcomes.

Inclusion criteria for EISNER included no 
symptoms of CAD and an intermediate risk 
of CAD defined as either: male, age 55–80; 
female, age 65–80; male, age 45–54 and 
and at least one CAD risk factor; or female, age 
55–64 and at least one CAD risk factor. Risk 
 factors include smoking, high blood pressure,
high total or LDL cholesterol, low HDL chole-
terol, diabetes and family history of early CAD.

The amount of radiation received from a coro-
nary calcium scan is 1–2 mSv, approximately 
half of the natural background radiation in 
Los Angeles over a one-year period. In 
the over-50 age group, the risk of this radiation 
increasing incidence of cancer is extremely 
small. The risk/benefit ratio suggests coronary 
calcium scanning is beneficial in middle-aged 
patients who are at intermediate risk on the 
basis of risk factors and blood testing.

CAC scores vs. hs-CRP levels
The United States Preventive Services Task 
Force 2009 guidelines on nontraditional risk 
factors endorse neither the measurement of 
hs-CRP nor CAC for screening asymptomatic 
patients (10). The strongest evidence of the 
lack of association of hs-CRP with cardiac 
events comes from the Multi-Ethnic Study 
of Atherosclerosis (MESA). This population-
based study included 6,814 asymptomatic 
persons and demonstrated that those pa-
tients with high CAC scores were 10-fold

Figure 2: Non-contrast CT of chest demonstrating extensive coronary calcification (white arrows), which is associated with increased risk of heart attack and death from cardiovascular causes. This patient has a calcium score of more than 1,000.
more likely to suffer cardiac events (11, 12). Almost one-third of the participants classified as intermediate risk by the Framingham risk score had hs-CRP above 3 mg/liter and one-third had moderate coronary calcium (a CAC score >100). Only 9 percent of those at intermediate risk had an elevated hs-CRP above 3 mg/liter and a high coronary calcium score. Compared with CAC scores, hs-CRP did not provide any meaningful incremental risk prediction. Measurement of CAC consistently provides reclassification of patients more accurately to the Framingham risk model (13).

**Conclusion**

Given the conflicting data in the literature on the significance of elevated hs-CRP, what is the clinician to do in the case example provided? Based on the JUPITER trial, we can no longer assume that patients with normal cholesterol levels are at low risk for atherosclerotic disease. The patient presents with a strong family history and an elevated hs-CRP. Risk factor modification, along with primary prevention using statin therapy, would be particularly relevant in a patient with a normal lipid profile and evidence of subclinical atherosclerosis on noninvasive cardiovascular imaging. Many clinicians will start with a generic statin and then re-evaluate the lipid numbers before using the more potent rosuvastatin or atorvastatin. Exercise, low-saturated fat diet and smoking cessation would also be recommended for these patients.

The National Heart, Lung, and Blood Institute is scheduled to release updated cholesterol treatment guidelines in fall 2011. These new guidelines will likely revise the paradigms for the testing and treatment of intermediate-risk patients.

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**Case Report: Spontaneous Coronary Artery Dissection in Low-Risk Patient**

**Prediman K. Shah, MD**

**Case presentation**

A white, 42-year-old pre-menopausal woman, previously healthy and asymptomatic, abruptly developed severe chest pain after modest physical activity. The chest pain radiated to the left arm and to the neck and lasted for approximately 20–30 minutes. She was evaluated soon thereafter at a local hospital’s emergency room. She received sublingual nitroglycerin, which relieved the chest discomfort within several minutes. The patient had been in great health prior to this episode and denied smoking, drug or alcohol abuse, diabetes, high cholesterol, high blood pressure or use of hormones.

On examination at Cedars-Sinai, she was afebrile, her pulse was 90 beats per minute and regular, blood pressure was 110/80 mm Hg, lungs were clear and cardiac examination was unremarkable, with normal heart sounds without any murmurs or rub. The chest X-ray was unremarkable, EKG showed ST-segment elevations in leads II, III, aVF, and V4 to V6 (Figure 1). Admission troponin level was elevated to 30 ng/mL. An urgently performed coronary angiogram was interpreted as showing a filling defect and narrowing (possibly from a thrombus) of a large first obtuse marginal branch of the left circumflex coronary artery. Percutaneous transluminal coronary angioplasty of the narrowed distal segment was performed with improvement in flow. No other coronary angiographic abnormality was noted.

Over subsequent days, the patient continued to have recurrences of chest pain, leading to repeat coronary angiography. Careful review of the angiograms suggested a proximal coronary artery dissection involving the large OM1 branch of the circumflex artery. Because of recurrent symptoms, that segment was eventually stented (Figure 2A). However, stenting was followed by renarrowing of the proximal circumflex marginal branch (Figure 2B). Attempts to stent this proximal segment were complicated by retrograde dissection extending into the left main stem coronary artery (Figure 2C). Because of this complication, the patient underwent emergency coronary artery bypass grafting (CABG) with an anastomosis of the left internal thoracic artery to the left anterior descending coronary artery, and right internal mammary artery anastomosis to the left circumflex coronary artery. No evidence for atherosclerosis was noted at surgery and coronary dissection was confirmed.

**Discussion**

The overall clinical, angiographic and operative findings demonstrated that the acute coronary syndrome and infero-posterior myocardial infarction in this otherwise healthy young female with none of the traditional risk factors for atherothrombosis was caused by spontaneous coronary artery dissection (SCAD).

Most acute coronary dissections are secondary to extension of ascending aortic dis-
SCAD: continued from page 3

sections, or occur during cardiac surgery, cardiac catheterization or other coronary interventions, and only rarely result in acute myocardial infarction. Primary SCAD is an important, albeit relatively rare, cause of acute coronary syndrome, especially in young and middle-aged women with minimal or no risk factors for atherothrombosis. Since the first case report of SCAD in a young woman was reported in 1931, more than 300 cases have been reported in the literature. Early on, most cases were diagnosed at autopsy after sudden cardiac death. In recent years, SCAD has been increasingly diagnosed since coronary angiography is frequently performed in patients suspected of an acute coronary syndrome. Angiographic studies show an incidence of SCAD ranging from 0.07 to 1.1 percent.

Nearly 70 percent of SCAD cases reported have been women and nearly 30 percent occurred during late pregnancy or the postpartum period. Among women, the incidence of SCAD has been highest below age 40. Among women under age 50 presenting with an acute coronary syndrome, the prevalence of SCAD has been reported to range from 8.7 to 10.8 percent.

Left coronary dissections are more common in women; right coronary dissections are more common in men. The left anterior descending coronary artery is involved in nearly 60 percent of SCAD cases, with multivessel coronary dissection being noted in nearly 20 percent. Left main coronary involvement is noted in about 12 percent of cases.

The clinical presentation of SCAD depends on the location and extent of dissection, with sudden cardiac death reported in up to 50 percent of cases, especially in those with left main coronary artery dissections. Other patients with SCAD may present with an acute coronary syndrome indistinguishable from that of the garden variety of atherothrombotic acute coronary syndrome.

SCAD may involve separation of coronary intima from media or media from adventitia, resulting in a false lumen with hemorrhage and eventually compressing the true lumen and predisposing it to secondary thrombosis. The exact pathophysiologic mechanism of these dissections is still unclear. It has been postulated that hormones (especially progesterone) can cause weakening of the media; the stress of labor or of strenuous activity may lead to dissection of a weakened vessel. Several reports have demonstrated inflammatory cell infiltration in the walls of the affected vessels—in particular, eosinophils in the adventitia, suggesting a role for a cytokine-mediated inflammatory process. It remains unclear whether these inflammatory changes are the cause or effect of the dissection. Our patient, however, was not in a peripartum period and was not taking oral contraceptives.

A diagnosis of SCAD should be considered when a young patient, particularly a young female, presents with symptoms and signs of an acute coronary syndrome despite absence of known risk factors. Coronary angiography should be performed to establish the diagnosis. At angiography, coronary dissections are graded according to the National Heart, Lung, and Blood Institute classification system developed by the Coronary Angioplasty Registry. This system grades coronary dissections based on angiographic appearance as types A to F:

- Type A: radiolucent areas within the coronary lumen during contrast injection, with minimal or no persistence of contrast after the dye has cleared.
- Type B: parallel tracts or double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance.
- Type C: contrast outside the coronary lumen, with persistence of contrast in the area after clearance of dye from the coronary lumen.
- Type D: spiral luminal filling defects, frequently with extensive contrast staining of the vessel.
- Type E: new, persistent filling defects.
- Type F: those that lead to total occlusion of the coronary artery, without distal antegrade flow.

Recently, the use of intravascular ultrasound imaging and optical coherence tomography have provided unique morphological perspective in patients with SCAD. Non-invasive contrast CT coronary angiography has also been reported to demonstrate coronary dissection and intramural hematoma, and is ideally suited for follow-up evaluation of patients with SCAD who are treated conservatively.

Conservative treatment includes using antithrombotic therapy to prevent superimposed thrombosis when the dissection is non-occlusive without ongoing evidence of flow compromise or ischemic symptoms. In selected cases, percutaneous coronary intervention and stenting is appropriate to restore flow and maintain vessel patency, although on rare occasions such intervention may actually extend the dissection and worsen the angiographic and clinical condition (as was the case in our patient). Most studies support the use of CABG as the treatment of choice for patients with multivessel or left main coronary artery dissections. The prognosis of patients with this condition depends on early diagnosis and the performance of early revascularization procedures.