Mr. David is a freelance medical writer living in New York City.
cally that OASIS 5 had shown fondaparinux to be an “excellent” regimen for anticoagulation in acute coronary syndrome, he indicated that it was not clear whether the bleeding difference was a result of “intrinsic differences in physical properties of comparative drugs or better dosing with fondaparinux.”

Results of the clinical trial SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors), which became available during the OASIS 5 trial, demonstrated that patients receiving enoxaparin for acute coronary syndrome and UFH when they underwent catheterization for a PCI had multiple bleeding risks. SYNERGY was a prospective, randomized, open-label, multicenter trial involving high-risk patients with acute coronary syndromes. The OASIS 5 regimen required that patients receive UFH during catheterization. Patients with impaired renal function also had greater bleeding risk with enoxaparin.

Dr. Califf stated:

Enoxaparin was disadvantaged by cath lab switching and probably wrong dosing in patients with creatinine clearance of 30–60 ml/minute. . . . Switching to UFH in the cath lab, as was recommended in OASIS 5, is not a recommendation that should be adhered to in this day and time.

Dr. Califf also noted that worse longer-term outcomes of patients with serious bleeding open the possibility that transfusions, rather than the bleeding itself, might confer the added risk.

Enoxaparin and Unfractionated Heparin

Montalescot G: SafeTy and Efﬁcacy of Intravenous Enoxaparin in Elective Percutaneous Coronary Intervention: An International Randomized Evaluation (STEEPLE) (Abstract 2574)

A bright but still indirect light was thrown on the subject of enoxaparin dosing by a later Hot Line session. The STEEPLE trial compared enoxaparin and UFH in patients undergoing elective PCI. The important difference between the use of enoxaparin in both OASIS 5 and SYNERGY and in STEEPLE was that STEEPLE incorporated an intravenous (IV) rather than a subcutaneous route of administration, with a single injection, with a shorter half-life (1.7 hours vs. 4.4 hours). No crossovers to UFH were permitted, according to the lead investigator, professor Gilles Montalescot, M D, at the Hôpital Pitié-Salpêtrière in Paris, France.

The goal of the STEEPLE trial was to demonstrate the superior safety of IV enoxaparin (0.5 or 0.75 mg/ kg) up to 48 hours after the procedure, compared with IV UFH in patients undergoing non-emergent PCI. IV UFH was dosed at 70–100 IU without glycoprotein (GP) IIb/IIIa inhibitors (activated clotting time, 300–350 seconds) or 50–70 IU with GP IIb/IIIa inhibitors (activated clotting time, 200–300 seconds). The primary endpoint, which excluded patients going to bypass surgery, was the occurrence of major and minor bleeding.

The mean age of the 3,528 patients was 64 years (75% men). About 56% had three or more risk factors; 37% had undergone prior PCI. This study population was a “real-world” one because patients were not restricted by age, weight, or renal function.

About 41% of the participants received GPIIb/IIIa inhibitors, and 23% received a clopidogrel loading dose of more than 300 mg; about 47% received chronic thienopyridine therapy.

Major bleeding was reduced significantly with both enoxaparin doses (1.2% for each dose vs. 2.8% for UFH, a reduction of 57%). Combined major and minor bleeding was reduced significantly (P = .014) in those taking enoxaparin 0.5 mg/ kg, with a trend favoring enoxaparin 0.75 mg/ kg (P = .052). Minor bleeding was similar between the patient arms. A secondary endpoint of attaining target anti–factor Xa and target activated clotting time strongly favored enoxaparin (0.5 mg/ kg, 78.8% of patients; 0.75 mg/ kg, 91.7% and UFH, 19.7%).

Clinical endpoints were similar among the patient groups. Dr. M. Montalescot concluded that IV enoxaparin in patients scheduled to have elective PCI was associated with “significantly less bleeding and similar efficacy compared with UFH.”

Discussant Professor Jean-Pierre Bassand, M D, from University Hospital Jean M Injoz in Besançon, France, added: “It is no longer necessary to switch from enoxaparin to UFH in patients with non-ST ACS [acute coronary syndrome] at the time of PCI. That was significantly associated with increased risk of bleeding in SYNERGY and OASIS 5.”

Clopidogrel


Turning to the opposite challenge, keeping platelet activation from precipitating major cardiac events in patients being treated for ST-elevation MI (STEMI), the CLARITY trial investigators sought to examine the issue of pretreatment with clopidogrel (Plavix®, Bristol-Myers Squibb/ Sanofi). These investigators, also led by Dr. M. Montalescot, hypothesized that after initial pharmacological (fibrinolytic, aspirin, heparin) therapy, clopidogrel pretreatment, hours to days before angioplasty, was superior to clopidogrel therapy in preventing major adverse cardiovascular events when it was initiated at the time of a PCI.

An earlier CLARITY–TIMI 28 analysis among 3,491 STEMI patients had shown that clopidogrel helped to open blocked arteries and decreased the odds of a second heart attack by 31%1 For this analysis, investigators compared 933 patients who were randomly assigned to receive a pre-angioplasty loading dose of clopidogrel 300 mg for two to eight days, followed by 75 mg once daily for those given placebo (n = 930). Following angioplasty, open-label clopidogrel was given in both groups, in accordance with the physician’s recommendation. The patients, whose mean age was 57.5 years, reported to the hospital less than 12 hours from symptom onset. Stents were implanted in 95% of the patients.

The time from randomization to a PCI was significantly longer for the clopidogrel pretreatment group (3.2 days) than the placebo group (2.9 days) (P = .003). Overall, for patients receiving clopidogrel, the risk of having a closed artery or an MI or dying was reduced by 36% before angiography. Infarct-related artery patency occurred in 87% of patients receiving clopidogrel pretreatment and in 81% of those receiving placebo (P < .001). The odds of MI, urgent revascularization, or dying of cardiovascular disease within 30 days was also reduced by 20% in the pretreatment patients (P = .026).

Among PCI patients receiving clopidogrel pretreatment,
the risk of MI, stroke, or cardiovascular death was reduced by 46% (3.6% with clopidogrel vs. 6.2% with placebo; \( P = .008 \)).

No excess in major bleeding or intracranial hemorrhage was reported with clopidogrel pretreatment.

Dr. Montalescot concluded that pretreatment with clopidogrel before a PCI resulted in a consistent benefit for all subgroups. For every 100 patients undergoing PCI, four major cardiovascular events were prevented.

**Fish Oil (Omega-3 Polyunsaturated Fatty Acids)**

Brouwer IA: Study on Omega-3 Fatty Acids and Ventricular Arrhythmia (SOFA) (Abstract 1336)

The SOFA trial examined whether fish oil affected arrhythmias in patients with an implantable cardioverter defibrillator (ICD). The intake of very-long-chain omega-3 polyunsaturated fatty acids (PUFAs), found mainly in fish oil, has been thought to reduce the risk of sudden death, possibly through an anti-inflammatory effect or through changes in conductivity in the myocardium. Approximately 50% of all cardiovascular disease deaths are sudden and result from arrhythmias, stated SOFA lead investigator Ingeborg A. Brouwer, MD, from the Wageningen Centre for Food Sciences in the Netherlands.

Investigators focused on the incidence of recurrent spontaneous ventricular tachycardia (VT) and all-cause mortality in 546 patients with the ICD from 26 European centers. The participants were randomly selected to take 2 g of fish oil daily \((n = 273)\) or placebo oil \((n = 273)\). Follow-up included complete registration of ICD events at 12 months, with a primary endpoint of time to first VT tachycardia/ventricular fibrillation (VT/VF) or death.

An analysis revealed a slight trend in favor of fish oil in event-free survival \((P = .24)\). At 12 months, 30% of the patients taking fish oil had experienced either a life-threatening arrhythmia or death, compared with 33% of the placebo patients. Looking at the subgroups (VT at entry, VF at entry, prior MI, and an ejection fraction of less than 30% at entry), investigators found trends favoring fish oil in each, but none had a significant advantage. Among 342 patients with a prior MI, the trend was strongest \((P = .086)\) for the primary endpoint, occurring in 28% of the fish oil patients and in 35% of the placebo patients. Dr. Brouwer concluded that there was no strong beneficial effect from omega-3 PUFAs on life-threatening cardiac arrhythmias for ICD patients, nor was there any indication of harm from fish oil.

The Society's discussant, Luigi Tavazzi, MD, from San Matteo University Hospital in Aosta, Italy, pointed out that other trials have reasonably demonstrated reductions of life-threatening cardiac arrhythmias in post-MI patients taking fish oil. Dr. Tavazzi's large, open-label GISSI–Heart Failure project had found significant benefits in this population. This ongoing randomized trial is now testing the effects of omega-3 fatty acid supplementation versus placebo in 7,057 patients taking fish oil over a period of three years, he said.

**REFERENCE**