Best of the ACC 2009 Scientific Session

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Many of the trials presented at the 2009 American College of Cardiology (ACC) Scientific Session have the potential to change clinical management. Here we discuss new data on heart failure therapies, stroke prevention, statins, immediate versus next-day catheterization and revascularization, predictors of stent thrombosis, aspirin and clopidogrel for atrial fibrillation, omega-3 fatty acids, implantable cardioverter-defibrillator (ICD) therapy, and drug-eluting stents.

Reviewed by Gregg C. Fonarow, MD, FACC, The David Geffen School of Medicine at UCLA, Los Angeles, CA; and Norman E. Lepor, MD, FACC, FAHA, FSCAI, The David Geffen School of Medicine at UCLA, Cedars-Sinai Medical Center, Los Angeles, CA.

The FIX-HF-5 Trial

Patients with advanced heart failure can remain symptomatic and at high risk for mortality despite optimal medical therapy. New therapies are needed. Early studies of isolated cardiac muscle showed that use of voltage clamping techniques to modulate the amplitude and duration of membrane depolarization could modulate calcium entry and contractility in isolated papillary muscles. A conceptual breakthrough occurred with the recognition and experimental demonstration that similar effects could be achieved when extracellular fields with relatively high current densities are applied over relatively long durations during the absolute refractory period. These so-called *cardiac contractility modulation* (CCM) *signals* contain about 150 times the amount of energy delivered in a standard pacemaker impulse. These signals do not initiate contraction, they do not recruit additional contractile elements, and there is no additional action potential.

Preclinical and small uncontrolled clinical studies have demonstrated that CCM increases cardiac contractility, reduces myocardial work, produces left ventricular (LV) reverse remodeling, and induces molecular changes (in genes, proteins, and phosphorylation) indicative of improved calcium handling and contractile function.

The goal of the Multicenter Randomized Controlled Trial of Cardiac Contractility Modulation in Patients With Advanced Heart Failure (FIX-HF-5) trial was to evaluate CCM plus optimal medical therapy compared with optimal medical therapy alone in patients with advanced heart failure.[1] CCM signals are non-excitatory electrical signals delivered during the refractory period with the aim of improving contractility.

The hypothesis tested was that CCM will be more effective at improving certain parameters of metabolism and will be non-inferior with safety endpoints. Patients with New York Heart Association (NYHA) class III or IV heart failure and narrow QRS were randomized to CCM plus optimal medical therapy (n = 215) versus optimal medical therapy alone (n = 213).

Overall, 428 patients were randomized. The mean age was 58 years, 27% were women, 65% were ischemic, 91% were NYHA class III, mean LV ejection fraction was 26%, mean QRS duration was 102 ms, and mean peak VO_2 was 14.7 mL/kg/min. At baseline, 91% of patients used an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 94% used a beta-blocker, and 44% used an aldosterone inhibitor.

The incidence of the primary efficacy endpoint, anaerobic threshold responder analysis (among completers), was 17.6% with treatment versus 11.7% in the control group ($P = .093$). As for secondary endpoints, CCM was associated with a 25 mL/kg/min increase in peak VO_2 (compared with a 40 mL/kg/min decrease in the optimal medical therapy–only group; $P = .024$), a 15% relative improvement in NYHA functional class ($P = .0026$), and a 10-point improvement in quality of life on the Minnesota Living with Heart Failure Questionnaire ($P < .0001$). The incidence of the primary safety outcome of death or all-cause hospitalization by 50 weeks was 52% with CCM versus 48% with optimal medical therapy alone (P for non-inferiority = .03). Findings were more pronounced with CCM among the subgroup of patients with NYHA class III and ejection fraction at or greater than 25%, who showed a 1.3 mL/kg/min improvement in peak VO_2.

In conclusion, among patients with advanced heart failure (NYHA class III or IV), low LV ejection fraction (≤ 35%), and narrow QRS, the use of CCM failed to improve the primary efficacy outcome of anaerobic threshold; however, this therapy was efficacious at improving peak VO_2 and quality of life. This pilot study suggests that CCM has potential, and further studies are indicated.

[Gregg C. Fonarow, MD, FACC]

The PROTECT AF Trial

The goal of the Randomized Prospective Trial of Percutaneous LAA Closure vs Warfarin for Stroke Prevention in AF (PROTECT AF) trial was to compare the effectiveness of a novel left atrial appendage closure device, the Watchman® (Atritech, Plymouth, MN) with that of warfarin in patients with nonvalvular atrial fibrillation.[2] Patients in the treatment group (n = 463) underwent left atrial appendage closure with the Watchman device, followed by warfarin therapy. (Among these patients, 87% were able to end warfarin therapy after 45 days.) Patients in the control group (n = 244) received long-term warfarin therapy only. Two-thirds of the patients had a $CHADS_2$ score of 1 or 2. Mean follow-up was 16 months. Exclusion criteria included contraindication to long-term warfarin therapy, NYHA class IV heart failure, presence or repair of an atrial septal defect, a planned ablation procedure for atrial fibrillation, symptomatic carotid disease, an LV ejection fraction of less than 30%, and left atrial appendage thrombus.

The primary efficacy outcome—cardiovascular death, stroke, or systemic embolism—was 3.4 events per 100 patient-years in the device group versus 5.0 events per 100 patient-years in the control group (P for noninferiority < .05) (Figure 1). The

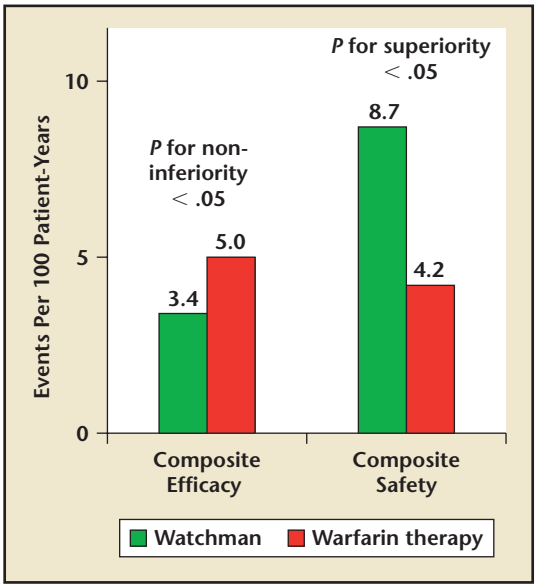


Figure 1. *The Randomized Prospective Trial of Percutaneous LAA Closure vs Warfarin for Stroke Prevention in AF (PROTECT AF) trial compared the effectiveness of a novel left atrial appendage closure device, the Watchman, with that of warfarin in patients with nonvalvular atrial fibrillation. The device seemed to prevent thrombotic complications. Data from Holmes D.[2] Adapted with permission from Cardiosource.*

primary safety endpoint was defined as device embolization that required retrieval, pericardial effusion that required intervention, intracranial or gastrointestinal bleeding, or any bleeding that required transfusion. The primary composite safety outcome was 8.7 events per 100 patient-years in the device group versus 4.2 events per 100 patient-years in the control group (P for superiority $< .05$). This outcome was primarily related to complications (pericardial effusions) at the time of device implantation.

The use of the Watchman device seems to be an effective treatment to prevent thrombotic complications in patients with nonvalvular atrial fibrillation. It would be expected that as experience with the device increases, so will the safety associated with its placement. With longer follow-up, it would be expected that the efficacy-to-safety ratio will be even better, allowing for the accumulation of warfarin-related complications to balance out the initial morbidity associated with device implantation.

The AURORA Trial

The goal of A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) was to evaluate treatment with rosuvastatin as compared with standard therapy in patients with end-stage renal disease (ESRD) on hemodialysis.[3,4] Patients ages 60 to 80 years with ESRD who had received hemodialysis for at least 3 months were randomized to treatment with rosuvastatin 10 mg/d (n = 1391) or placebo (n = 1385). Mean follow-up was 3.2 years. Exclusion criteria included statin therapy within the previous 6 months, expected kidney transplant within 1 year, life expectancy of less than 1 year, a history of malignancy, alanine aminotransferase that was more than 3 times the upper limit of normal, or unexplained elevation in creatine kinase that was more than 3 times the upper limit of normal.

Although rosuvastatin therapy resulted in reductions in greater total cholesterol, low-density lipoprotein cholesterol, triglycerides, and C-reactive protein than placebo, there was no significant difference in the primary composite endpoint of time to cardiovascular death, nonfatal myocardial infarction (MI), or stroke (9.2 events per 100 patient-years in the rosuvastatin group vs 9.5 events per 100 patient-years in the placebo group; $P = .59$) (Figure 2). The results from AURORA are consistent with the Deutsche Diabetes Dialyse Studie (4D), which showed no benefit of statin therapy in patients with diabetes on hemodialysis.[5] Because patients on hemodialysis have been excluded from almost all clinical trials involving devices and drugs, we know little about the biology of the patients with ESRD and their response to therapies that we now consider conventional. This study is perhaps a wake-up call for clinical trialists and device and drug manufacturers to open their eyes to this growing and high-risk population of patients, as we can no longer assume that we can extrapolate data on non-ESRD patients to ESRD patients.

The STICH Trial

The Surgical Treatments for Ischemic Heart Failure Hypothesis 2 (STICH) trial compared coronary artery bypass grafting (CABG) therapy to surgical therapy (with CABG plus ventricular reconstruction) for patients with obstructive coronary artery disease and congestive heart failure in reducing death and cardiac hospitalization, and improving quality of life.[6] The 1000 study subjects were randomized and followed for an average of 4 years. Inclusion criteria included coronary artery disease amenable to bypass surgery, an LV ejection fraction at or less than 35%, and dominant anterior wall akinesia or dyskinesia. Patients were excluded if they had a recent MI, need for aortic valve replacement, planned percutaneous coronary intervention, or noncardiac disease resulting in a life expectancy of less than 3 years. Overall, 49% of patients had NYHA class III or IV heart

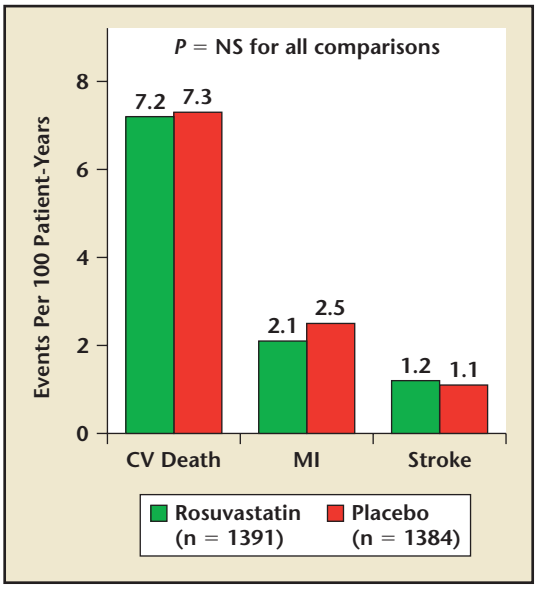


Figure 2. *In A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), rosuvastatin did not reduce the rates of cardiovascular events as compared with placebo. NS, not significant; CV, cardiovascular; MI, myocardial infarction. Data from Fellström BC et al.[4] Adapted with permission from Cardiosource.*

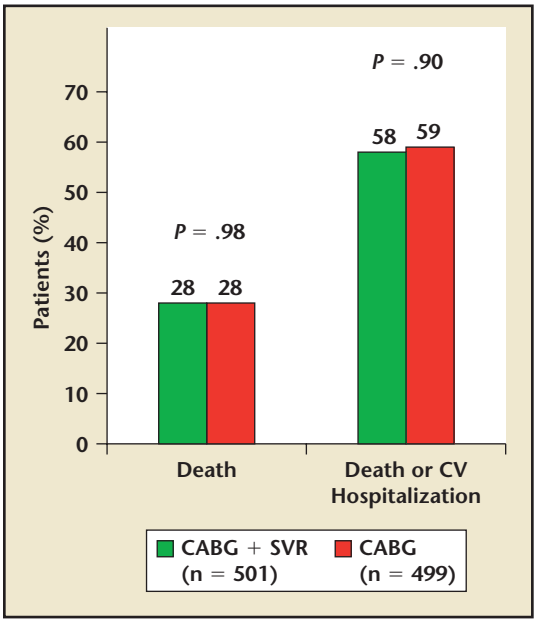


Figure 3. *The Surgical Treatments for Ischemic Heart Failure Hypothesis 2 (STICH) trial compared coronary artery bypass grafting (CABG) therapy to surgical therapy (with CABG plus ventricular reconstruction) for patients with obstructive coronary artery disease and congestive heart failure in reducing death and cardiovascular (CV) hospitalization, and improving quality of life. The addition of surgical ventricular reconstruction to CABG was not associated with improvement. SVR, surgical ventricular reconstruction. Data from Jones R and Mark D.[6] Adapted with permission from Cardiosource.*

failure, and the median ejection fraction was 28%.

The addition of surgical ventricular reconstruction to CABG did not significantly improve the primary endpoint of death and cardiac hospitalization (58% in CABG plus ventricular reconstruction vs 59% in CABG alone; $P = .90$) (Figure 3). There was also no improvement in NYHA heart failure classification or Canadian Cardiovascular Society angina classification in patients who underwent surgical ventricular reconstruction in addition to CABG.

The ABOARD Trial

The goal of the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) trial was to answer a very clinically relevant question: Does a strategy of catheterization and revascularization immediately after admission for non–ST-elevation acute coronary syndrome improve outcome as compared with a less emergent or urgent approach?[7]

The study subjects were 352 patients with non–ST-elevation acute coronary syndrome who were randomized to immediate (n = 175) or next-day (n = 177) catheterization and revascularization. The primary endpoint was level of peak troponin I. All patients had a Thrombolysis In Myocardial Infarction (TIMI) risk score at or above 3 and at least 2 of the following factors: ischemic symptoms, electrocardiographic abnormalities in at least 2 contiguous leads, or positive troponin. Exclusion criteria included hemodynamic or arrhythmic instability requiring urgent catheterization and thrombolytic therapy in the preceding 24 hours.

Median time to catheterization was 1.1 hours in the immediate catheterization group and 20.5 hours in the delayed catheterization group. Percutaneous coronary intervention (PCI) was performed in 80% of patients in the immediate catheterization cohort and in 70% of patients in the delayed catheterization cohort.

After 1 month of follow-up, there was no difference in the primary endpoint of peak troponin I between the groups (median 2.1 ng/mL in the immediate group vs 1.7 ng/mL in the delayed group; $P = .70$) or, for that matter, in the composite endpoint of death, MI, or urgent revascularization or the composite endpoint of death, MI, urgent revascularization, or refractory ischemia. This study does not support the need for emergent coronary angiography and revascularization over a less urgent approach in patients presenting with non–ST-segment elevation myocardial infarction (NSTEMI) acute coronary syndromes who are hemodynamically stable.

New Data From HORIZONS-AMI

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial examined outcomes in 3602 patients with ST-segment elevation myocardial infarction (STEMI) onset within 12 hours who were undergoing primary PCI and were randomized to receive bivalirudin or heparin plus a glycoprotein (GP) IIb/IIIa inhibitor (eptifibatide or abciximab).[8] The analysis presented at the ACC Scientific Session evaluated predictors of stent thrombosis in the 3202 patients from HORIZONS-AMI who received stents.[9,10] Stent thrombosis was defined by the Academic Research Consortium as definite or probable and was categorized as acute (< 24 hours after stent implantation), subacute (1-30 days), or late (1-12 months). Clopidogrel was administered as a 300-mg loading dose and a 600-mg loading dose (Figures 4 and 5).

At 1-year follow-up, stent thrombosis occurred in 107 patients (3.3%) in the entire study population and included acute (0.87%), subacute (1.56%), and late (0.97%) episodes. The 1-year stent thrombosis rate was not significantly different between drug-eluting stents and bare-metal

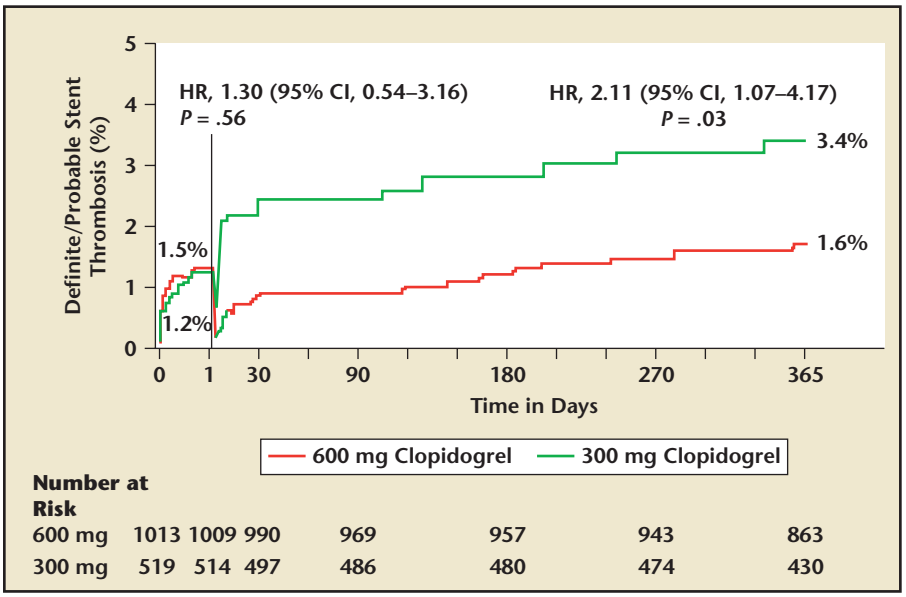


Figure 4. *Impact of clopidogrel loading in combination with bivalirudin in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. HR, hazard ratio; CI, confidence interval. Adapted with permission from Dangas G.*[9]

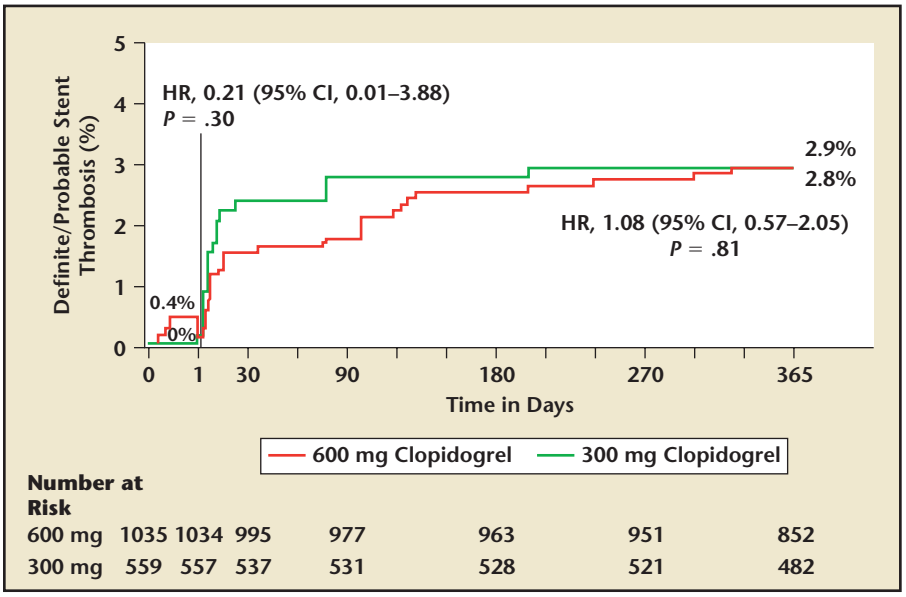


Figure 5. *Impact of a clopidogrel loading dose in combination with unfractionated heparin and a glycoprotein IIb/IIIa inhibitor in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. HR, hazard ratio; CI, confidence interval. Adapted with permission from Dangas G.*[9]

stents (3.3% and 3.4%, respectively). By pharmacologic regimen, the 24-hour stent thrombosis rate was significantly higher in the bivalirudin cohort (1.5%) versus the heparin plus GP IIb/IIIa inhibitor group (0.3%) (P = .0002) (Figure 6). The 1-year stent thrombosis rate was not significantly different, with an incidence of 3.6% in the bivalirudin group and 3.2% in the heparin plus GP IIb/IIIa inhibitor group (P = .53). There was no significant difference in the 1-year stent thrombosis rate within the heparin plus GP IIb/IIIa inhibitor group between eptifibatide and abciximab (3.6% vs 2.8%, respectively; P = .38).

After multivariate adjustments using a Cox model, independent predictors of *acute* stent thrombosis included pre-PCI TIMI 0/1 flow (hazard ratio [HR], 6.1; 95% confidence interval [CI], 1.4-26; P = .01), lesion ulceration (HR, 4.8; 95% CI, 1.4-16; P = .01), bivalirudin use (HR, 4.7; 95% CI, 1.6-14; P = .005), stent number (HR, 1.5; 95% CI, 1.1-2.1; P = .02), and pre-randomization heparin (HR, 0.27; 95% CI, 0.1-0.6; P = .002). Independent predictors of *subacute* stent thrombosis included insulin-dependent diabetes (HR, 4.4; 95% CI, 2.0-10; P = .0002), history of congestive heart failure (HR, 4.2; 95% CI, 1.6-11; P = .003), pre-PCI TIMI 0/1 flow (HR, 2.2; 95% CI, 1.1-4.6; P = .04), final TIMI 0/1 flow (HR, 3.7; 95% CI, 1.1-13; P = .03), ratio of stent to lesion length (HR, 1.4; 95% CI, 1.2-1.7; $P < .0001$), and clopidogrel loading dose of 600 mg vs 300 mg (HR, 0.5; 95% CI, 0.3-0.9; P = .01). Independent predictors of *late* stent thrombosis included active smoking (HR, 4.0; 95% CI, 1.7-9.5; P = .001), prior MI (HR, 3.2; 95% CI, 1.4-7.1; P = .006), and post-stent dilatation balloon use (HR, 2.8; 95% CI, 1.3-5.8; P = .008).

This valuable analysis underscores the importance of periprocedural pharmacology in preventing adverse events following PCI. The increased risk of early stent thrombosis associated with the use of bivalirudin compared with unfractionated heparin plus GP IIb/IIIa seems to be mitigated by the use of a loading dose of clopidogrel. Therefore, loading doses of clopidogrel should be considered

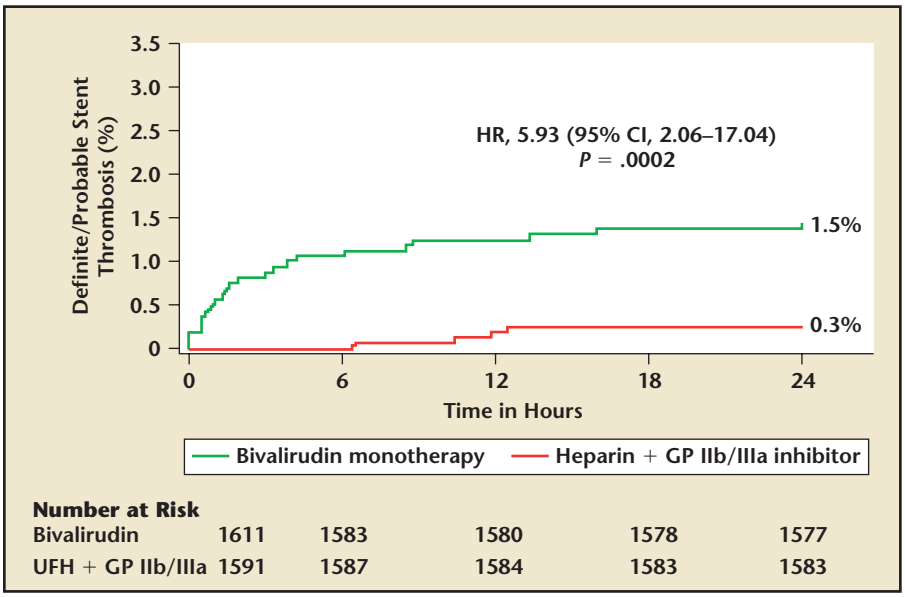


Figure 6. *Impact of antithrombin on rates of acute stent thrombosis (< 24 hours after stent implantation) in the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. GP, glycoprotein; HR, hazard ratio; CI, confidence interval; UFH, unfractionated heparin. Adapted with permission from Dangas G.*[9]

in all patients presenting with STEMI when bivalirudin is to be used as the periprocedural antithrombin. An interesting and unanswered question would be the potential role of loading doses of intravenous GP IIb/IIIa inhibitors compared with clopidogrel in patients with STEMI who are treated with bivalirudin.

The REVERSE Trial

The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) study was a double-blind, parallel-arm, controlled trial that assessed the long-term benefits of cardiac resynchronization therapy (CRT) in patients with NYHA class I (ACC/American Heart Association stage C) or class II heart failure.[11] Inclusion criteria required patients to be stabilized in NYHA class I or II. The class I patients had to be previously symptomatic and have a QRS duration exceeding 120 ms, an LV ejection fraction within 40%, and LV dilatation. Patients had to be on a stable and optimal medical therapy. Patients were randomized to a CRT-on group or a CRT-off group.

At the primary endpoint of 24 months, a deterioration in clinical condition occurred in 19% of the CRT-on patients compared with 34% of the CRT-off patients (P = .01) (Figure 7). Therefore, patients with milder forms of systolic heart failure—who do not meet current guideline recommendations for device-based therapy—who were treated with CRT were less likely to experience deterioration in clinical status.

The ACTIVE A Trial

The Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A) trial examined treatment with a combination of aspirin and clopidogrel as compared with aspirin and placebo in patients with atrial fibrillation at high risk for stroke who were not candidates for warfarin therapy.[12,13] Overall, 7554 patients were randomized and followed for a mean of 3.6 years. The primary endpoint was a composite of stroke, MI, systemic embolus, or vascular death. Patients were included if they had documented atrial fibrillation, were unsuitable for warfarin therapy, and had at least 1 of the following risk factors for stroke: age older than 75 years, hypertension, prior stroke, prior transient ischemic attack, prior systemic embolism, LV ejection fraction less than 45%, peripheral vascular disease, or were ages 54 to 74 years and had diabetes mellitus or coronary artery disease. Exclusion criteria included excessive risk of hemorrhage, prior intracerebral hemorrhage, peptic ulcer disease, use of oral vitamin K antagonist or

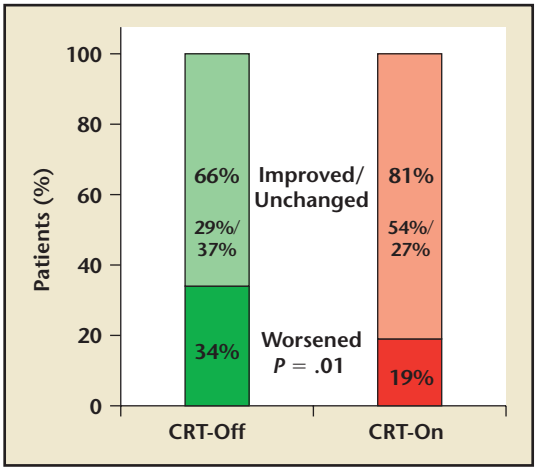


Figure 7. *The Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial assessed the long-term benefits of cardiac resynchronization therapy (CRT) in patients with milder forms of systolic heart failure. At 24 months, patients who were treated with CRT (CRT-On) were less likely to experience deterioration in clinical status than patients who were not treated with CRT (CRT-Off). Adapted with permission from Daubert J-C.*[11]

clopidogrel therapy, significant thrombocytopenia, or ongoing alcohol abuse.

There was a significant reduction in the incidence of the primary endpoint in the combination aspirin plus clopidogrel group (7.6%) compared with the aspirin-alone group (6.6%) ($P = .01$). The secondary endpoint of stroke alone was also reduced in the combination aspirin plus clopidogrel group (3.3%) as compared with the aspirin-alone group (2.4%) ($P < .001$) (Figure 8). This reduction was balanced by an increased risk of hemorrhage in the combination therapy group (2.0) as compared with the aspirin-alone group (1.3%) ($P < .01$).

The study shows that in patients with atrial fibrillation who are at higher risk of stroke and are not candidates for warfarin therapy, the combination of aspirin and clopidogrel reduced the rate of absolute vascular complications by 1.0%, a reduction balanced by a 0.7% absolute increase in the risk of hemorrhage. Warfarin remains the therapy of choice to prevent vascular complications in higher risk patients who can tolerate the use of vitamin K inhibitors with atrial fibrillation, but the combination of aspirin and clopidogrel is an option in intolerant patients at a lower risk of hemorrhage.

The OMEGA Trial

The goal of the Randomized Trial of OMEGA-3 Fatty Acids on Top of Modern Therapy After Acute Myocardial Infarction (OMEGA) was to evaluate treatment with omega-3 fatty acids in addition to standard medical therapy as compared with standard medical therapy alone in reducing the primary endpoint of sudden cardiac death in patients after NSTEMI or STEMI.[14] The 3851 patients had experienced an MI from 3 to 14 days before study entry. They were randomized to receive omega-3 fatty acids and standard medical therapy (n = 1940) or standard medical therapy alone (n = 1911). Of the enrolled patients, 59% had STEMI and 41% had NSTEMI. Coronary angiography was performed in 94% of patients, PCI in 78%, and thrombolysis in 8%. Patients were excluded if they were pregnant or nursing, hypersensitive to the study drugs, or already taking fish oil.

Mean follow-up was for 1 year. The primary outcome of sudden cardiac death occurred in 1.5% of the omega-3 group and 1.5% of the control group ($P = .84$). The data do not support the use of omega-3 fish oils in preventing sudden death following acute MI, despite the existence of studies that have shown an antiarrhythmic potential in other patient populations.

The IRIS Study

The goal of the Immediate Risk-Stratification Improves Survival (IRIS) study was to compare ICD therapy against medical therapy in patients with low ejection fraction or other high-risk criteria early after acute MI.[15] Of the 62,944 patients screened for this study, 898 were randomized, with a mean follow-up of 37 months. The mean ejection fraction of the study population was 35%. The study subjects had experienced an acute MI within the previous 5 to 31 days and had either an LV ejection fraction at or less than 40% and heart rate at or greater than 90 bpm (criterion I) or nonsustained ventricular tachycardia at or greater than 150 bpm on Holter monitor (criterion II). STEMI was the index clinical event for 77% of patients.

The primary endpoint of all-cause mortality was not significantly different between patients treated with an ICD (22.9%) and those treated medically (22%) (Figure 9). An interesting point relates to the secondary endpoint of sudden cardiac death, which was reduced with ICD implantation but counterbalanced by an increase in non-sudden cardiac death. Some of the non-sudden cardiac deaths were related to the actual device implantation. Based on these findings, routine ICD implantation early after MI should not be recom-

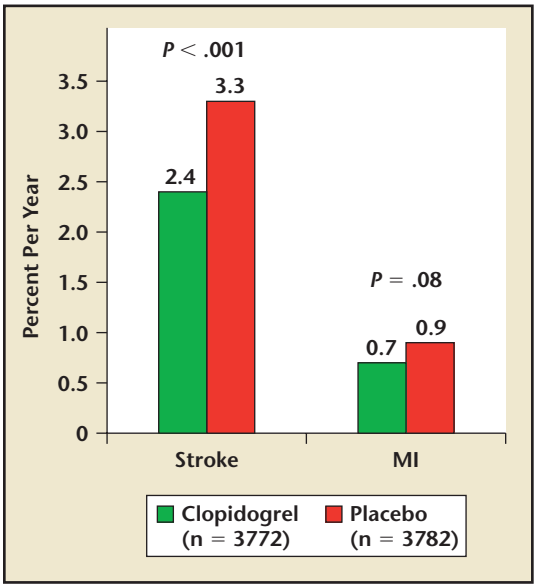


Figure 8. *Data from the Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events (ACTIVE A) trial suggest that the combination of aspirin and clopidogrel is an option in patients with atrial fibrillation who cannot tolerate warfarin. MI, myocardial infarction. Data from the ACTIVE Investigators et al.[13] Adapted with permission from Cardiosource.*

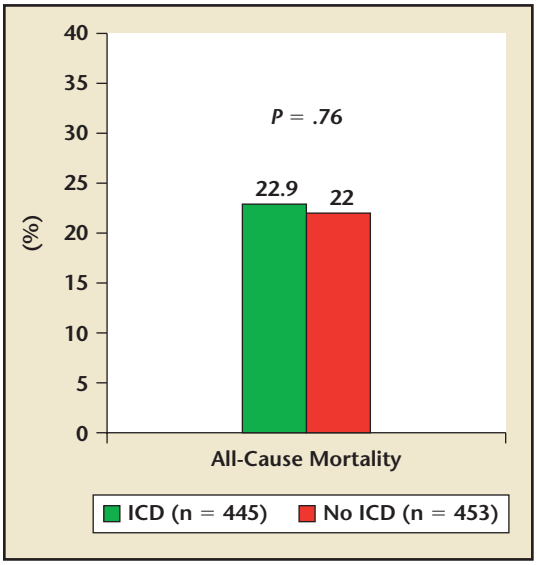


Figure 9. *The Immediate Risk-Stratification Improves Survival (IRIS) study compared implantable cardioverter-defibrillator (ICD) therapy against medical therapy in patients with low ejection fraction or other high-risk criteria early after acute myocardial infarction. All-cause mortality did not significantly differ between the 2 groups. Data from Steinbeck G.[15] Adapted with permission from Cardiosource.*

mended at this time, as is consistent with current guidelines.

The NAPLES II Study

The goal of the Novel Approaches for Preventing or Limiting Events (NAPLES) II study was to evaluate treatment with a loading dose of atorvastatin in statin-naïve patients undergoing elective PCI.[16] The study subjects were 668 patients with coronary artery disease scheduled for elective PCI who were not taking statin therapy. They were randomized to an 80-mg loading dose of atorvastatin within 24 hours prior to PCI (n = 338) or no statin therapy (n = 330). The primary endpoints were a creatine kinase-myocardial band (CK-MB) elevation exceeding 3 times the upper limit of normal at 6 and 12 hours after PCI, or a troponin I elevation exceeding 3 times the upper limit of normal at 6 and 12 hours after PCI. Patients were included if they were being treated for a de novo coronary artery stenosis, were undergoing elective PCI with normal cardiac biomarkers, and were not currently taking statin therapy. Patients were excluded if they were undergoing primary or rescue PCI, had acute coronary syndrome with elevated cardiac biomarkers, were pregnant, were being treated for restenosis, had a saphenous vein graft, or had a left internal mammary artery graft.

The primary endpoints were reduced in the patients randomized to statin therapy (Figure 10). The mechanism for this effect is not clear, but most periprocedural "infarctlets" are presumed to be related to distal embolization during the PCI procedure or to perturbations of the microcirculation resulting from the release of vasoactive compounds that can affect myocardial cell perfusion. Interestingly, this reduction did not lead to any difference in mortality or need for unplanned revascularization. In real life, however, it would be anticipated that all patients who had chronic obstructive coronary disease would be on a lipid-lowering agent, such as a statin, including at the time of revascularization.

The ARMYDA-RECAPTURE Study

The Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes (ARMYDA) RECAPTURE study was a randomized, blinded trial that evaluated treatment with a loading dose of atorvastatin in patients undergoing PCI.[17] The patients were on long-term statin therapy (> 30 days). They were randomized to receive 80 mg of atorvastatin within 12 hours prior to PCI and a further 40 mg

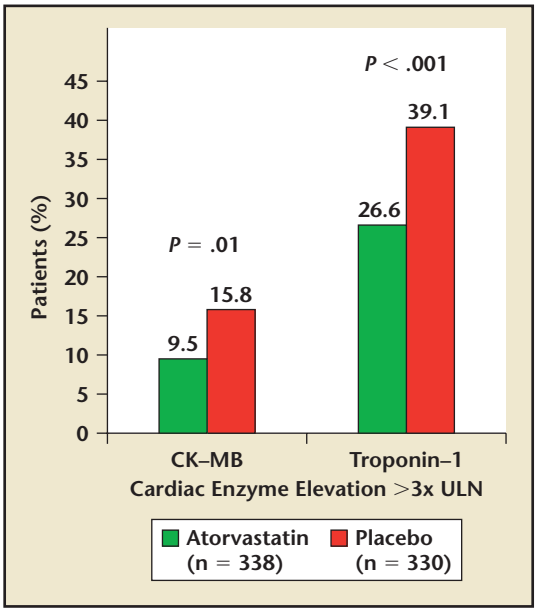


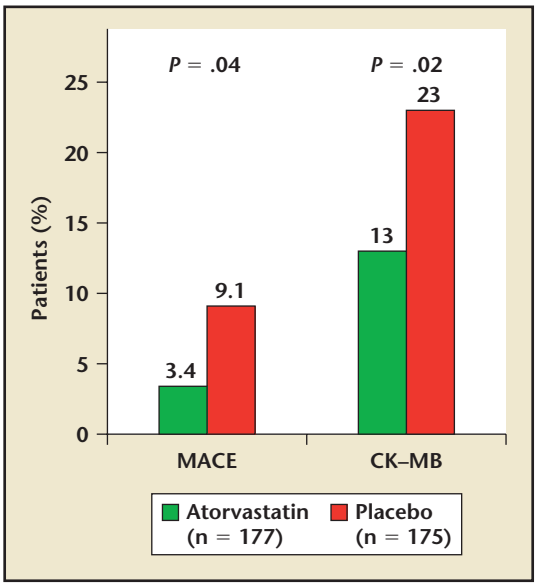
Figure 10. *The Novel Approaches for Preventing or Limiting Events (NAPLES) II study evaluated treatment with a loading dose of atorvastatin in statin-naïve patients undergoing elective PCI. The primary endpoints were a CK-MB elevation exceeding 3 times the ULN at 6 and 12 hours after PCI, or a troponin I elevation exceeding 3 times the ULN at 6 and 12 hours after PCI. Both of these endpoints were reduced in the patients randomized to statin therapy. PCI, percutaneous coronary intervention; ULN, upper limit of normal; CK-MB, creatine kinase-myocardial band. Data from Briguori C.[16] Adapted with permission from Cardiosource.*

during the procedure (n = 177) or placebo (n = 175). The primary endpoint was a reduction in the incidence of major adverse cardiac events (MACE) at 30 days after PCI. (MACE was a composite of cardiac death, MI, or unplanned revascularization.) The patient population included those with stable angina or non–ST-elevation acute coronary syndrome. Patients were excluded if they had STEMI, high-risk non–ST-elevation acute coronary syndrome requiring urgent angiography within 2 hours, serum alanine aminotransferase or aspartate aminotransferase exceeding the upper limit of normal, an LV ejection fraction of less than 30%, serum creatinine greater than 3 mg/dL, or a history of liver or muscle disease.

The incidence of MACE was significantly lower in patients treated with atorvastatin reload prior to PCI (3.4%) than in those who received placebo (9.1%) (P = .04) (Figure 11). Patients in the atorvastatin-reload group also had a lower incidence of CK-MB levels exceeding the upper limit of normal (13% vs 23%; P = .02) and of troponin I elevation greater than the upper limit of normal (36% vs 47%; P = .03).

The ARMYDA trial previously demonstrated that atorvastatin loading prior to PCI reduced postprocedure MI in statin-naïve patients.[18] The results of ARMYDA-RECAPTURE affirm the findings of the NAPLES II study,[16] suggesting that a loading dose of atorvastatin prior to PCI may reduce MACE following PCI, even in patients on background statin therapy.

Figure 11. *The Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes (ARMYDA) RECAPTURE study evaluated treatment with a loading dose of atorvastatin in patients undergoing PCI. Atorvastatin treatment was associated with lower rates of major adverse coronary events and a lower incidence of creatine kinase-myocardial band (CK-MB) levels exceeding the upper limit of normal. Data from DiSciascio G.[17] Adapted with permission from Cardiosource.*



The REVIVAL-3 Trial

The Regeneration of Vital Myocardium in ST-Segment Elevation Myocardial Infarction by Erythropoietin (REVIVAL-3) study was a parallel, randomized, blinded trial that evaluated treatment with high-dose erythropoietin (EPO) compared with placebo after primary PCI in patients with ST-elevation myocardial infarction (STEMI).[19] The 138 patients were randomized to receive intravenous EPO (n = 68) or placebo (n = 70) after PCI. The EPO was 100,000 U divided into 3 doses given at PCI, 24 hours afterward, and 48 hours afterward. The patients had an LV ejection fraction within 50%. Exclusion criteria included cardiogenic shock; previous MI; uncontrolled hypertension; underlying hematological disorders, including polycythemia vera, anemia, or thrombocytopenia; PCI in the last month; or contraindication to magnetic resonance imaging or the study medication.

Mean follow-up was 6 months. The primary endpoint, LV ejection fraction as measured by cardiac magnetic resonance imaging at 4 to 6 months, was 52% in the EPO group and 52% in the placebo group (P = .91).

The ZEST Trial

The goal of the Zotarolimus-Eluting Stent Versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions (ZEST) trial was to evaluate paclitaxel- and sirolimus-eluting stents in comparison with zotarolimus-eluting stents in wide-variety (real-world) patients with obstructive coronary artery disease.[20] Patients were excluded if they presented with severe LV dysfunction (LV ejection fraction < 25%), cardiogenic shock, renal insufficiency, liver dysfunction, left main stenosis, in-stent restenosis of a drug-eluting stent, or a limited life expectancy. Patients were randomized to zotarolimus-eluting stents (n = 883), sirolimus-eluting stents (n = 878), or paclitaxel-eluting stents (n = 884). At 12 months, the primary outcome of death, MI, or target vessel revascularization had occurred in 10.1% of the zotarolimus group, 8.3% of the sirolimus group, and 14.2% of the paclitaxel group (P = .25 for zotarolimus vs sirolimus; P < .0003 for zotarolimus vs paclitaxel) (Figure 12).

Zotarolimus is associated with repeat revascularization rates that are intermediate to sirolimus and paclitaxel. Stent thrombosis rates were low for all stents, although rates of MI were the lowest with zotarolimus.

The PRIMA Trial

The study Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality? (PRIMA) was a parallel-designed, randomized trial of patients with decompensated heart failure that compared a management approach based on levels of the N-terminal portion of pro-brain natriuretic peptide (NT-proBNP) with clinically guided management.[21] The 345 study subjects had decompensated heart failure with an elevated NT-proBNP level on hospital admission, a level that dropped at least 10% during hospitalization. The mean ejection fraction of patients was 31%. Exclusion criteria included significant cardiac arrhythmia, need for urgent surgical intervention, severe chronic obstructive pulmonary disease, recent pulmonary embolism, limited survival, or hemodialysis.

After a mean follow-up of 702 days, the occurrence of the primary outcome—number of days alive outside the hospital—was 685 with NT-proBNP guided management versus 664 with clinically guided management (P = .49). Total mortality was 26.5% for the NT-proBNP guided management group versus 33.3% for the clinically guided management group (P = .20). There was no significant difference between the groups in any of the secondary outcomes.

The use of BNP with the methodologies employed in this trial as an isolated guide to therapy in the outpatient arena seems to be limited. Although BNP levels could be used to trigger effective modification of heart failure therapies known to impact the mortality or morbidity of heart failure—such as the addition or titration of β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, aldosterone inhibitors, and diuretics—BNP would not be expected on its own merits to affect the natural course of the heart failure condition. ■

[Norman E. Lepor, MD, FACC, FAHA, FSCAI]

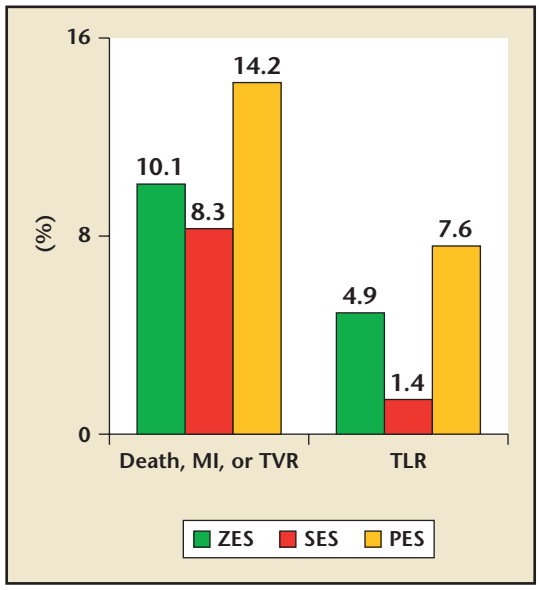


Figure 12. *The Zotarolimus-Eluting Stent Versus Sirolimus-Eluting Stent and Paclitaxel-Eluting Stent for Coronary Lesions (ZEST) trial evaluated paclitaxel- and sirolimus-eluting stents in comparison with zotarolimus-eluting stents in real-world patients with obstructive coronary artery disease. MI, myocardial infarction; TVR, target vessel revascularization; TLR, target lesion revascularization; ZES, zotarolimus-eluting stent; SES, sirolimus-eluting stent; PES, paclitaxel-eluting stent. Data from Park S-J.[20] Adapted with permission from Cardiosource.*

Main Points

- Among patients with advanced heart failure, low left ventricular ejection fraction (≤ 35%), and narrow QRS, the use of cardiac contractility modulation failed to improve the primary efficacy outcome of anaerobic threshold; however, this therapy was efficacious at improving peak VO_2 and quality of life.
- In patients with nonvalvular atrial fibrillation, a novel left atrial appendage closure device seemed to prevent thrombotic complications.
- Rosuvastatin did not reduce a primary composite endpoint of time to cardiovascular death, nonfatal myocardial infarction, or stroke among patients with end-stage renal disease on hemodialysis.
- New data do not support the need for emergent coronary angiography and revascularization over a less urgent approach in patients presenting with non–ST-segment elevation myocardial infarction acute coronary syndromes who are hemodynamically stable.
- A recent study suggests that loading doses of clopidogrel should be considered in all patients presenting with ST-segment elevation myocardial infarction when bivalirudin is to be used as the periprocedural antithrombin.
- A loading dose of atorvastatin prior to percutaneous coronary intervention may reduce major adverse cardiac events, even in patients on background statin therapy.

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