The American College of Cardiology’s (ACC) 62nd Annual Scientific Session was held at the Moscone Center, San Francisco, from March 9–11, 2013. The meeting focused on the “transformation of cardiovascular care, from discovery to delivery”, featured over 20 late-breaking clinical trials and 2,000 abstracts. These sessions gave notable exposure and recognition of studies likely to significantly affect clinical practice. There were 21 trials scheduled for presentation in 5 featured Late-Breaking Clinical Trial sessions, but one, the PREVAIL trial, was not presented because of a failure to observe an embargo. I summarize and overview both the late-breaking trials presented at ACC 2013 and the PREVAIL trial. (Circ J 2013; 77: 1139–1145)

Key Words: American College of Cardiology; Congress; Late-breaking clinical trials

**PREVAIL**

This is a randomized controlled study that compares the Watchman Left Atrial Appendage Closure Device to long-term warfarin therapy in patients with atrial fibrillation who are at risk for stroke. However, the results of the trial were not presented because Boston Scientific broke the embargo by releasing a press release announcing the trial results before the session. It is very unusual for a LBCT to be pulled approximately 1 h before it was scheduled to be presented. Although the previous PROTECT AF study showed an increase in perioperative events, mainly pericardial effusion in patients implanted with the device, serious vascular complications were markedly reduced (8.7% vs. 4.4%) in the 7 days post-randomization, as well as cardiac perforation requiring surgical repair (1.6% vs. 0.4%), in the PREVAIL trial.

**HPS2-THRIVE**

This trial is the largest-ever study of niacin, commonly used to raise high-density lipoprotein and lower low-density lipoprotein (LDL) levels. This 4-year study tested a combination of extended-release (ER) niacin with laropiprant in patients at risk for cardiovascular problems such as heart disease and stroke. The 25,673 patients in the study were randomized to receive ER niacin/laropiprant or a placebo, and all received the commonly prescribed LDL cholesterol-lowering medication, simvastatin. The results were disappointing in that it did not meet the primary endpoint of reducing the chance of a major vascular event, defined as the composite of non-fatal heart attack or heart-related death, stroke, or need for angioplasty or bypass surgery. In addition, there were unexpected and significant excesses of bleeding (2.5% vs. 1.9%) and infections (8.0% vs. 6.6%) among the ER niacin/laropiprant patients and significantly higher numbers of patients suffered serious known side effects, including new-onset diabetes, diabetic complications, and gastrointestinal and skin problems.

**Opening Showcase and LBCTs**

**PRATO-ACS**

Previous studies have demonstrated the kidney-protective value of various statins administered before patients undergo angioplasty. In this study, 543 statin-naïve patients with acute coronary syndrome (ACS) who were scheduled for early invasive strategy were randomized to a rosvustatin group or a control group. The primary endpoint was contrast-induced acute kid-
PARTNER II
This is a randomized clinical trial involving the new device for transcatheter aortic valve implantation, the Sapien XT valve, and comparison with the original Sapien design. The redesigned Sapien XT has been commercially available for some time in most parts of the world except the United States and Japan. Three years ago, the first trial reported an almost doubled risk of stroke at 30 days for patients in the Sapien transcatheter system group compared with those who had standard open-heart surgery.\textsuperscript{5,6} PARTNER II’s cohort B compared the original and new Sapien systems in 560 patients with severe aortic stenosis (AS) who were very old, with a mean age >84 years, and deemed unsuitable for surgery. This noninferiority study showed that the new Sapien XT is at least as safe and effective as the old device. At 30 days, all-cause death was 3.5% for Sapien XT and 5.1% for the original device (Figure 2). Stroke rates at 30 days also were low in both groups, at 3.2% for Sapien XT and 3% for Sapien, and much lower than in PARTNER I. Sapien XT significantly reduced vascular complications, with similar mortality and stroke rate at 30 days in PARTNER II. Although it was not evaluated in the presented study, precise evaluation of the aortic root geometry prior to transcatheter aortic valve implantation is also important for procedural success.\textsuperscript{7,8} The approval of the Sapien XT device for clinical use in Japan is eagerly awaited.

NEXT
The NEXT trial assigned 3,235 patients to either biolimus-eluting stent (BES; Nobori, Terumo, n=1,617) or an everolimus-eluting stent (EES, Promus, Boston Scientific, n=1,618) in the largest multicenter, randomized open-label study that was the only LBCT from Japan at ACC.\textsuperscript{13} The BES met the goal of noninferiority to the EES in target lesion revascularization at 1 year, with target lesion revascularization of 4.2% in both groups (Figure 3A). Cumulative incidence of definite stent thrombosis was very low and similar between the BES and EES groups (0.25% vs. 0.06%; P=0.18, Figure 3B). Several panelists pointed out that differences between the 2 devices may be seen after 2 or 3 years because the polymer of the BES dissolves 6–9 months after implantation. Given the equivalent 1-year outcome, long-term follow-up data for the BES will be important and the issue of late stent thrombosis remains a significant concern.
rapid-acting, potent, and reversible, with return of normal platelet function within 1 h. This randomized double-blind trial pitted cangrelor against the oral clopidogrel standard of care in approximately 11,000 patients at 153 centers around the world. In the result, patients in the cangrelor group had a significantly lower rate of the composite of all-cause death, myocardial infarction (MI), ischemia-driven revascularization, and stent thrombosis at 48 h compared with clopidogrel (4.7% vs. 5.9%). Stent thrombosis developed in 0.8% of the patients in the cangrelor group and in 1.4% in the clopidogrel group. The rate of major bleeding tended to be higher with cangrelor, though not significantly so, at 48 h vs. clopidogrel: 0.16% and 0.11%. Thus, cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during percutaneous coronary intervention (PCI), with no significant increase in severe bleeding. This agent may replace heparin in patients prior to coronary angiography and urgent or emergency bypass graft surgery, in patients who are intubated, nauseated or in shock, as well as in situations where absorption may be problematic.

DKCRUSH-III
This is the first head-to-head comparison of double kissing (DK) crush and culotte stent techniques in coronary artery disease (CAD). The culotte technique places stents in the main artery and the side branch, overlapping them in the main vessel before the branch forks. The DK crush technique extends a small piece of the branch stent into the main artery, where it is squeezed against the main artery’s wall. This approach introduces 2 points where the balloons used in stenting inflate in the artery and connect for a “double kiss”. The multicenter study randomly assigned patients with unprotected left main coronary artery distal bifurcation lesions to treatment with DK crush (210 patients) or culotte (209 patients) stenting. At 1 year, major adverse cardiac events (MACE) occurred in 6.2% of the DK crush patients and 16.3% of the culotte patients. The culotte approach had markedly higher rates of repeat intervention at the target lesion and the target vessel (6.7% target lesion vs. 2.4%, and 10.5% target vessel vs. 4.3%).

CHAMPION PHOENIX
Cangrelor is an intravenous ADP receptor antagonist that is...
LBCTs III: Chronic CAD/Stable IHD and ACS

STREAM

The investigators randomized 1,892 patients presenting within 3 h of symptom onset who could not undergo PCI within 1 h of medical contact to primary PCI or fibrinolysis before transport to a PCI-capable hospital. Patients in the fibrinolytic arm received tenecteplase, clopidogrel, and enoxaparin and underwent angiography 6–24 h after randomization, except in the event of failed reperfusion, in which case, emergency angio-
The study will need to evaluate the 20 mg/kg dose powered for clinical outcomes, although these data suggest that the P-selectin antagonist inclacumab reduces myocardial damage after PCI in patients with non-ST-segment elevation MI.

**TERISA**

The primary objective of this trial was to evaluate the efficacy of ranolazine, a partial fatty acid oxidation inhibitor, vs. placebo on angina frequency in subjects with type 2 diabetes, CAD, and chronic stable angina who remain symptomatic despite treatment with 1 or 2 antianginal medications. The primary endpoint was the average weekly number of angina episodes from weeks 2 to 8 of treatment. The key secondary endpoint was the average number of sublingual nitroglycerin doses from weeks 2 to 8. The patients on ranolazine reported 3.8 angina episodes per week vs. 4.3 in the placebo group (P=0.008). Ranolazine patients used 1.7 sublingual nitroglycerin doses per week vs. 2.1 for placebo patients (P=0.003). Interestingly, an exploratory analysis also showed greater reduction in HbA1c for ranolazine vs. placebo. Future studies are needed to explore the potential dual effects of ranolazine on angina and glucose control.

**SELECT-ACS**

P-selectin, a cell adhesion molecule expressed on activated endothelial cells and platelets, plays a critical role in leukocyte and platelet rolling. Inclacumab, a highly selective P-selectin inhibitor, is fully human recombinant monoclonal IgG4 antibody. Among non-ST-segment elevation MI patients undergoing PCI in this SELECT-ACS trial, the preprocedural use of 20 mg/kg inclacumab resulted in a modest reduction in post-PCI cardiac enzyme elevation. Serious adverse events and infections appeared similarly in both treatment groups. Further study will need to evaluate the 20 mg/kg dose powered for clinical outcomes, although these data suggest that the P-selectin antagonist inclacumab reduces myocardial damage after PCI in patients with non-ST-segment elevation MI.

**REMINDER**

The REMINDER trial was a randomized, placebo-controlled trial evaluating the safety and efficacy of early treatment with eplerenone in 1,012 patients with acute ST-segment elevation MI. The primary endpoint of this trial was a composite of cardiovascular mortality, ventricular arrhythmia, clinical or subclinical HF as determined by left ventricular ejection fraction (EF) <40% or elevated brain natriuretic peptide (BNP)/NT-proBNP at ≥1 month after enrollment. After a mean follow-up of 10.5 months, 93 patients (18.4%) in the eplerenone group reached the primary endpoint vs. 150 patients (29.6%) in the placebo group. Eplerenone had an overall hazard ratio of 0.57 (P<0.0001) for the primary endpoint. These results showed that adding eplerenone to standard therapy within 24 h of the onset of symptoms improves the outcome of patients with acute ST-segment elevation MI without evidence of either HF or EF <40%.

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The MASS COMM trail was designed in 2006, with the Massachusetts Department of Public Health, to provide evidence on which to base regulatory policy decisions about performing non-emergency PCI in hospitals without on-site cardiac surgery. The primary MACE endpoint at 30 days was noninferior between sites with and without on-site cardiac surgery (9.5% vs. 9.4%, P for noninferiority <0.001) and rates of MACE at 12 months were still noninferior (17.3% vs. 17.8%, P for noninferiority <0.001). The results of this trial indicate that nonemergency PCI at sites without on-site cardiac surgery has short-term (30 days) and intermediate-term (12 months) outcomes that are similar to those achieved at sites with on-site cardiac surgery. Current guidelines may need to be reconsidered, as long as they adhere to the strict criteria listed in this trial (ie, minimum procedural volume, quality improvement, participation in outcomes measurement projects).

**CORONARY, GOPCABE and PRAGUE-6**

These 3 trials evaluated off-pump and on-pump technique among patients undergoing coronary artery bypass grafting (CABG). In the CORONARY trial, 4,752 patients who were undergoing CABG were randomized to either on-pump or off-pump procedure. At 1 year, there were no significant differences between the 2 strategies in a composite endpoint of death, MI, stroke, or new renal failure. In the GOPCABE trial, 2,539 patients aged 75 years or older scheduled for elective first-time CABG were randomly assigned to on-pump or off-pump procedure. There were no significant differences between the 2 strategies at 30 days or at 12 months with regard to a composite endpoint of death (13.1% vs. 14%), MI, stroke, repeat revascularization or new renal-replacement therapy. The PRAGUE-6 study was a randomized, single-center trial of 206 patients who were perceived to be at higher risk. Their mean age was 74 years and they had a EuroSCORE 26. Contrary to the former 2 trials, they reported better outcomes at 30 days for the off-pump group. These trails indicate that there is no difference in long-term outcomes between procedures done on-pump or off-pump, if the surgery is performed by experienced surgeons, but off-pump may be better for high-risk patients.

**STOP-HF**

This 5-year study enrolled asymptomatic patients aged >40 years with risk factors for HF and randomized them into an intervention and a control group. Patients in the intervention group were screened for blood levels of BNP and received specialized care if indicated. Control group patients continued to receive standard care from their physicians. It was found that a significantly lower number of patients in the intervention group than in the control group met the primary endpoint of new-onset HF requiring hospitalization or left ventricular dysfunction (5.3% vs. 8.7%, P=0.01). This trial shows that a simple blood-test screening of BNP, followed by targeted care of people at heightened risk of HF, can result in a dramatic reduction in cardiovascular events.

**DIG**

In a post-hoc subanalysis of the original DIG trial, digoxin reduced the risk of 30-day hospital admission in ambulatory older adults with chronic systolic HF and reduced EF receiving angiotensin-converting enzyme inhibitors and diuretics. However, the findings were from an ambulatory population rather than patients who had recently been discharged from hospital and none of the patients was on beta-blockers or aldosterone antagonists, even with reduced EF.

**RELAX**

Because inhibition of the adrenergic and renin-angiotensin-aldosterone systems has been so effective in the treatment of systolic HF, these same therapies have been the subject of recent clinical trials of HF with preserved EF (HFpEF). The RELAX trial tested the effect of the phosphodiesterase-5 inhibitor sildenafil on HFpEF. Disappointingly, there were no differences in the primary endpoint of change in peak oxygen consumption over 24 weeks whether patients took sildenafil or placebo and there was also no difference in exercise capacity. Perhaps HF as we traditionally think of it is the wrong paradigm to pursue as we try to understand HFpEF.

**ASTRAVON**

ASTRAVON tested the hypothesis that neurohormonal modulation with aliskiren in addition to standard therapy during the early post-discharge period, sometimes referred to as the “vulnerable phase”, may improve long-term outcomes. In total, 1,639 patients were randomized to aliskiren 300 mg daily (n=821) vs. placebo (n=818). The primary outcome of cardiovascular death or hospitalization for HF at 6 months occurred in 24.9% of the aliskiren group vs. 26.5% of the placebo group (P=0.41).

**PEITHO**

Tenecteplase is a tissue plasminogen activator produced by recombinant DNA technology using an established mammalian cell line. The primary objective of the PEITHO trial was to investigate the efficacy of thrombolysis with tenecteplase over placebo in normotensive patients with acute intermediate-risk pulmonary embolism (PE). The primary endpoint of all-cause mortality or hemodynamic collapse within 7 days of randomization occurred in 13 (2.6%) of the 506 patients who received tenecteplase plus heparin compared with 28 (5.6%) of the 499 who received placebo plus heparin (P=0.0015). The results justify the concept of risk stratification of normotensive patients with acute PE, and confirm the notion that early recanalization treatment prevents clinical deterioration in patients with evidence of right ventricular dysfunction and myocardial injury.

At this ACC meeting, the efficacy of ultrasound-accelerated thrombolysis for the treatment of acute PE in the ULTIMA trial was also presented. This new technology can be beneficial for PE patients with poor prognosis.

**References**


