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TAVR matches surgery in intermediate-risk patients

BY MITCHEL L. ZOLER
Frontline Medical News
At ACC16, Chicago

More stories from **ACC 2016** inside! See page 6.

Transcatheter aortic-valve replacement performed as well as surgical-valve replacement in patients with an intermediate mortality risk in a prospective, randomised trial with more than 2000 patients followed for 2 years, the first randomised trial to compare the efficacy and safety of transcatheter aortic-valve replacement against surgical replacement in patients who did not have a high mortality risk.

The results "support TAVR [transcatheter aortic-valve replacement] as an alternative to surgery in intermediate-risk patients similar to those included in this trial," said Dr Craig R. Smith at the annual meeting of the American College of Cardiology. The findings from the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A trial "will increase use of TAVR," predicted Dr Smith, professor and chairman of surgery at New York – Presbyterian Hospital/Columbia University in New York.

Until now, TAVR had been compared with surgical aortic-valve replacement in two prospective, randomised trials that both enrolled either high-risk or inoperable patients with severe aortic stenosis, the PARTNER 1 trial that tested the original Sapien TAVR system, and the US CoreValve High-Risk Study that tested the original CoreValve system (often now called CoreValve classic). The average Society of Thoracic Surgeons (STS) operative risk score of high-risk patients enrolled in PARTNER 1 was 11.8%, and the average risk score in patients enrolled in the CoreValve study was 7.3%. In contrast, the design of PARTNER 2A specified that enrolled patients have a STS risk score of 4–8%, a criterion actually met by 81% of the enrolled patients, and the average STS risk score of all patients enrolled in PARTNER 2A was 5.8%.

Although US labelling for both the Sapien valve and its later iterations, Sapien XT and S3, and for CoreValve and its later iteration, Evolut R, specify

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IN THIS ISSUE

Guideline update shortens minimum DAPT duration in CAD

BY AMY KARON
Frontline Medical News
From an American College of Cardiology/American Heart Association Focused Update

New guidelines decrease the minimum duration of dual-antiplatelet therapy (DAPT) to as little as 3 months after drug-eluting stent placement in certain lower-risk patients with coronary artery disease.

The updated recommendations harmonise and replace six other guidelines, and apply to everolimus and zotarolimus stents, not Cypher or Taxus stents, said Dr Eric R. Bates, who helped author the American College of Cardiology/American Heart Association Focused Update. "The emphasis is on balancing ischaemic risk versus bleeding risk. The recommendations give clinicians guideline coverage to make personalised DAPT recommendations," he said in an interview.

The guidance reflects recent evidence that shorter duration (3–6 months) of DAPT, compared with the standard 12 months of therapy does not increase the risk of stent thrombosis and potentially lessens bleeding risk in select patients. Other studies of an additional 18 or 36 months of DAPT found a decrease in the risk of MI and stent thrombosis, at the cost of greater risk of bleeding. Thus, the updated guidelines call for "a thoughtful assessment of the benefit-risk ratio, integration of study data, and consideration of patient preference" when selecting duration of DAPT. "In general, shorter-duration DAPT can be considered for patients at lower ischaemic risk with high bleeding risk, whereas longer-duration DAPT may be reasonable for patients at higher ischaemic risk with lower bleeding risk," the authors wrote, led by Dr Glenn N. Levine of Baylor College of Medicine, Houston (*J Am Coll Cardiol* 2016 Mar 29. doi: 10.1016/j.jacc.2016.03.512).

The recommendations define DAPT as combination therapy with aspirin and a P2Y12 receptor inhibitor – that is, clopidogrel, prasugrel, or ticagrelor. "When indicated, ticagrelor and prasugrel have a Class IIa preference over clopidogrel," Dr Bates said. The recommended daily dose of aspirin is 81 mg (range, 75–100 mg), which is usually continued indefinitely, regardless of how long patients receive dual therapy.

The shortened durations of dual-antiplatelet therapy include several scenarios. For elective percutaneous coronary intervention, the former Class I recommendation for 12 months of DAPT has been reduced to 6 months, with a Class IIb recommendation for either longer treatment or shorter (3-month) treatment, Dr Bates, professor of medicine at the University of Michigan Health System in Ann Arbor, said. For patients with acute coronary syndrome, the guidelines retain the Class I recommendation for 12 months of DAPT, but also add a Class IIb recommendation for longer or shorter (6 months) DAPT.

The guidelines also include a new Class IIb recommendation for 12 months of DAPT started early after coronary artery bypass graft in patients with stable ischaemic heart disease. This strategy "may be reasonable to improve vein graft patency" in these patients, the recommendations state.

The guidance clarifies previous recommendations on the timing of elective noncardiac surgery, and assigns Class IIb support for consideration of such surgeries starting 3 months after implantation of drug-eluting stents, if the risks of delaying surgery outweigh the expected risk of stent thrombosis when it is necessary to stop P2Y12 inhibitor therapy.

The recommendations now distinguish between B and C levels of evidence to increase granularity, according to Dr Bates. The document updates recommendations on duration of DAPT across six previously published guidelines – the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention (PCI); the 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery; the 2012ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischaemic Heart Disease; the 2013 ACC/AHA Guideline for the Management of ST-Elevation Myocardial Infarction; the 2014 ACC/AHA Guideline for Non-ST-Elevation Acute Coronary Syndromes, and the 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery.

The extensive evidence review that informed guideline development was simultaneously reported by Dr John Bittl at Munroe Regional Medical Center in Ocala, Florida, and his colleagues. The investigators synthesised evidence from 11 randomised controlled trials of more than 33,000 patients who received mainly newer generation stents. They also reviewed a randomised controlled trial of more than 21,000 patients with stable ischaemic heart disease who were more than 1 year post-MI, and a post hoc analysis of a trial of more than 15,000 such patients.

These reviews uncovered "moderately strong evidence" that prolonged DAPT after implantation of newer generation drug-eluting stents "entails a trade-off between reductions in stent thrombosis and MI and increases in major haemorrhage," Dr Bittl and his colleagues wrote. Likewise, they found moderately strong evidence that prolonged DAPT helps prevent cardiovascular events at the cost of increased bleeding in patients whose coronary thrombotic risk stemmed from prior MI, not stent implantation. They found weak evidence of increased mortality in stent patients who received prolonged DAPT.

Dr Bates reported consulting relationships with Merck and AstraZeneca. Eight other coauthors disclosed financial relationships with a number of pharmaceutical or device companies. Dr Glenn Levine and seven coauthors disclosed no relationships with industry.

NEWS

Statins inversely linked to colorectal cancer in patients with IBD

BY AMY KARON
Frontline Medical News
From Clinical Gastroenterology and Hepatology

Patients with inflammatory bowel disease who were prescribed statins had 65% lower odds of subsequent colorectal cancer, compared with other IBD patients, even after controlling for multiple potential confounders, researchers reported in *Clinical Gastroenterology and Hepatology*.

"Further confirmation from other cohorts may provide support for the use of statins as a chemopreventive in patients with IBD," said Dr Ashwin Ananthakrishnan of Massachusetts General Hospital in Boston, and his associates.

Patients with long-standing ulcerative colitis or colonic Crohn's disease have about twice the risk of colorectal cancer (CRC), compared with the general population, and up to an 18% lifetime risk of CRC by 30 years after diagnosis, the researchers noted. Early results supporting mesalamine as chemoprophylaxis did not hold up in later trials. Although several studies suggested that statins might help prevent sporadic colon cancer, the only such study in IBD patients was small and did not control for key covariates such as smoking, the investigators added. Therefore, they collected data from 11,001 patients with IBD who were seen at Boston area hospitals between 1998 and 2010. They identified CRC diagnoses based on ICD-9 codes, and analysed electronic prescriptions to see whether and when patients had used statins (*Clin Gastroenterol Hepatol* 2016 Feb 21. doi: 10.1016/j.cgh.2016.02.017).

A total of 1376 patients (12.5%) were prescribed at least one statin. Over 9 years of follow-up, 2% of statin users developed CRC, compared with 3% of nonusers (age-adjusted odds ratio, 0.35; 95% confidence interval, 0.24-0.53). Statin users were more likely to be older, male, white, smokers, and had more comorbidities than nonusers. Nonetheless, the protective effect of statins remained significant after controlling for demographic factors, smoking status, number of colonoscopies, use of steroids and immunomodulators, the presence of primary sclerosing cholangitis, and increases in inflammatory biomarkers (OR, 0.42; 95% CI, 0.28–0.62). The effect occurred for both Crohn's disease and ulcerative colitis. Notably, the inverse association was even stronger among patients who had been prescribed at least two statins or who had at least a 2-year interval between statin use and CRC diagnosis.

> Statins might help prevent CRC through HMG-CoA reductase inhibition and other mechanisms.

Statins might help prevent CRC through HMG-CoA reductase inhibition and other mechanisms, according to the researchers. By inhibiting HMG-CoA reductase, statins lower production of farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are needed for post-translational activation of Ras, Rho, and other proteins that are overexpressed in CRC and that have been linked to tumour invasion. Statins also might help prevent CRC through antioxidant effects or by inhibiting inflammation, cell adhesion, and angiogenesis, the investigators added. "Although we did not see a difference in median C-reactive protein levels between statin users and nonusers, statin users were less likely to require immunomodulator or biologic therapy for their IBD, supporting a potential anti-inflammatory role for statins."

Because patients mainly were treated at two tertiary referral hospitals, they may have had more severe disease than the general population of patients with IBD, the investigators acknowledged. They noted that in some meta-analyses, referral centre studies yielded chemopreventive effects that did not hold up in population-based cohorts.

The study was funded by the US National Institutes of Health, the American Gastroenterological Association, and the Harold and Duval Bowen Fund. The researchers had no disclosures.

Psoriasis tied to abdominal aortic aneurysm in nationwide study

BY AMY KARON
Frontline Medical News
From Arteriosclerosis, Thrombosis, and Vascular Biology

Patients with severe psoriasis were nearly 70% more likely to develop abdominal aortic aneurysms compared with the general population, according to a Danish population-based cohort study.

The findings augment existing evidence linking psoriasis and cardiovascular diseases, wrote Dr Usman Khalid of Copenhagen University Herlev and Gentofte Hospital, Denmark. The report was published online April 14 in *Arteriosclerosis, Thrombosis, and Vascular Biology.*

While the mechanisms for the link are unclear, "emerging evidence suggests that AAA is a focal representation of a systemic disease with a distinct inflammatory component, rather than a mere consequence of atherosclerosis," wrote Dr Khalid and his associates.

Several case series have linked AAA with other autoimmune disorders, including systemic lupus erythematosus and rheumatoid arthritis, they noted. Their study comprised nearly 5.5 million adults in Denmark between 1997 and 2011. The researchers identified 59,423 patients with mild psoriasis and 11,566 patients with severe psoriasis (*Arterioscler Thromb Vasc Biol* 2016 April 14. doi: 10.1161/ATVBAHA.116.307449).

The incidence of AAA in the reference population was 3.72 cases per 10,000 person-years, with an average follow-up period of 14.4 years. In contrast, the incidence of AAA in patients with mild psoriasis was 7.30 cases per 10,000 person-years, and the rate in patients with severe psoriasis was 9.87 cases of per 10,000 person-years, with average follow-up periods of 5.7 years. Both mild and severe psoriasis were significantly associated with AAA after the researchers accounted for age, sex, comorbidities, medications, socioeconomic status, and smoking, with adjusted incidence rate ratios of 1.20 (95% confidence interval, 1.03–1.39) and 1.67 (95% CI, 1.21–2.32), respectively.

The historical view that AAA is caused mainly by atherosclerosis has largely been upended, the researchers noted. Instead, AAA appears to be a multifactorial process involving inflammation, matrix degradation, thrombosis, and aortic wall stress. Furthermore, inflammation in both AAA and psoriasis is centrally mediated by T-helper-17 cells and interleukin-17. Together, the data suggest that shared inflammatory mechanisms link psoriasis and AAA, especially because the association correlates with psoriatic disease activity, they said. "This finding clearly requires independent replication, and the clinical consequences are unclear at present."

The LEO Foundation and the Novo Nordisk Foundation funded the study. Dr Khalid had no disclosures. Four coinvestigators reported financial ties with Abbott, Pfizer, AstraZeneca, Bayer, and several other pharmaceutical companies.

NEW DRUGS AND DEVICES LISTING

Newly Listed	Indication
Therapeutic Goods Administration (TGA) tga.gov.au	
Follitropin alfa (rch) *Afolia/Bemfola*, Finox Biotech Australia	In adult women: For the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated. Controlled ovarian hyperstimulation in women undergoing assisted reproductive technologies In adult men: indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.
Eltrombopag *Revolade*, Novartis Pharmaceuticals	For the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.
Liraglutide *Saxenda*, Novo Nordisk	Indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of • greater than or equal to 30 kg/m^2 (obese); or • greater than or equal to 27 kg/m^2 to less than 30 kg/m^2 (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.
Pharmaceutical Benefit Scheme (PBS) pbs.gov.au	
Nadroparin *Fraxiparine*, Aspen	For prophylaxis and treatment of deep vein thrombosis.
Rituximab *Mabthera* SC, Roche	For patients with CD20 positive, B-cell non-Hodgkin's lymphoma.
Sumatriptan *Imigran* FDT, Aspen	For the relief of migraine.
Trastuzumab *Herceptin* SC, Roche	For the treatment of HER2-positive breast cancer.

Please consult the full Product Information before prescribing.

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Arterial calcium findings on mammograms can predict heart disease risk

BY MICHELE G. SULLIVAN
Frontline Medical News
At ACC16, Chicago

Findings that are easily visible on mammograms – but never shared with patients – could be employed as a powerful new tool for cardiovascular risk assessment, a study showed.

In this prospective imaging study, breast arterial calcification in women without heart disease correlated with cardiovascular risk at least as well as the Framingham Risk Score, and a bit better than the 2013 Cholesterol Guidelines Pooled Cohort Equation.

It also increased the accuracy of both of these models for detecting women at high risk for heart disease, Dr Laurie Margolies said at a press teleconference leading up to the annual meeting of the American College of Cardiology.

If validated in a larger cohort, the findings could well be "practice changing," said Dr Margolies, director of breast imaging at Mt. Sinai Hospital, New York.

She compared its potential impact to that of the now-critical breast density measurement for cancer detection. Until 2008, breast density was a visual, yet unreported and unemployed, mammographic finding.

"This is the same type of practice-changing, revolutionary way of reporting risk," said Dr Margolies. "We have a practical way of assessing coronary artery disease risk that adds no extra cost, no radiation, and very little time, and is superior to standard ways of [coronary artery disease] risk assessment. And since prevention is key to decreasing cardiovascular mortality, it would be very simple to report this score on all mammographies," to give both patients and physicians a heads-up that cardiovascular health needs some quick attention.

The study was simultaneously published online (*JACC Cardiovasc Imag* 2016 Mar 24. doi: 10.1016/j.jcmg.2015.10.022).

The cohort comprised 292 women who underwent digital screening mammography and a noncontrast chest CT scan during the same year. None had a history of coronary artery disease. Cardiovascular risk was assessed with three tools: the Framingham Risk Score (FRS), the 2013 Cholesterol Guidelines Pooled Cohort Equation (PCE), and the breast arterial calcification (BAC) score. The BAC score encompassed measurements of number of involved vessels, length of involved segments, and calcification density. Scores ranged from 1 to 12 and were classified by increasing severity: 0, 1–3, and 4–12.

Women were a mean of 61 years old; none had a history of coronary artery disease. Hypertension and hyperlipidaemia were common (179 and 104 subjects, respectively). Diabetes was present in 79, smoking in 53, and chronic kidney disease in 57.

Any BAC was present in 42.5% of the group. Those with BAC were significantly older and more likely to have hypertension and kidney disease. Coronary artery calcification (CAC) was present in 47.6% of the overall group, but in 70% of those with BAC. These patients were also significantly older than those without CAC. Hypertension, chronic kidney disease, and diabetes were also more common.

The mean BAC score was 2.2. As women aged, the score was more likely to increase. A BAC score greater than 0 was present in 27% of those younger than 60 years, 47% of those aged 60–69 years, and 69% of those aged 70–92 years.

The mean CAC score was 1.6 ,and this also increased with age. The incidence of CAC for the three age groups was 28%, 55%, and 79%, respectively.

In a multivariate model, a severe BAC score of 4–12 conferred a threefold risk for CAC (odds ratio, 3.2), while older age and hypertension conferred a doubling of risk. "This shows us that BAC is a more powerful predictor than these standard risk factors," Dr Margolies said.

The mean 10-year Framingham Risk Score was 4.6. Most women in the cohort (85%) were low risk. Of these, 59% had a BAC of 0, and 63% had a CAC of 0. However, there was some disagreement in the models. Among the FRS low-risk group, 15% had an intermediate-risk BAC score of 1–3, and 22% had a high-risk BAC of 4–12. The CAC was intermediate risk in 29% and high risk in 13%.

Among those with an intermediate-risk FRS, the coronary artery calcification and breast arterial calcification scores were also intermediate risk in 45% and 12%, respectively; the CAC and BAC were high risk in 36% and 64%, respectively.

For the entire cohort, the FRS categories agreed with the BAC categories 55% of the time, and with the CAC categories 57% of the time.

The mean Cholesterol Guidelines Pooled Cohort Equation risk score was 11.8. This score tends to overestimate CAC presence, Dr Margolies noted, an issue supported by the finding that only 42% of the cohort scored as low risk. In this low-risk group, 74% and 76% had CAC and BAC scores of 0, respectively. But in the PCE high-risk group, only 27% had high-risk CAC and 43% had high-risk BAC. In fact, the CAC and BAC scores were actually 0 in 33% and 40%, respectively.

For the entire cohort, the PCE risk agreed with the CAC 47% of the time and with the BAC 54% of the time.

By itself, a BAC score of more than 0 predicted a CAC score of more than 0 as well as both the Framingham Risk Score and the Pooled Cohort Equation score, with an area under the curve of 0.72 and 0.71, respectively.

BAC did, however, increase the accuracy of both these models for detecting high-risk CAC. In an analysis that included an additional 325 women with a history of coronary artery disease, the area under the curve increased to 0.77 when BAC was added to the FRS; it increased to 0.76 when added to the PCE model.

Adding BAC data to every mammogram would be an easy and very effective way to alert patients and their physicians to developing coronary artery disease, Dr Margolies said.

"Even though heart disease kills 10 times more women than breast cancer does, there is no routine screening test for it. But digital mammography screening for breast cancer is a common procedure. I would advocate that we add the BAC data to mammogram reports so that we have a way to assess this risk. Women who were BAC positive could then undergo further risk assessment, preferably with a gated CT scan, with subsequent adjustment or initiation of statins," she said.

Dr Margolies had no relevant financial disclosures.

STAMPEDE: Metabolic surgery bests medical therapy long term

BY SHARON WORCESTER
Frontline Medical News
At ACC16, Chicago

The superiority of metabolic surgery over intensive medical therapy for achieving glycaemic control in patients with type 2 diabetes was largely maintained at the final 5-year follow-up evaluation in the randomised, controlled STAMPEDE trial.

The 150 subjects, who had "fairly severe diabetes" with an average disease duration of 8 years, were randomised to receive intensive medical therapy alone, or intensive medical therapy with Roux-en-Y gastric bypass surgery or sleeve gastrectomy surgery. The primary endpoint of haemoglobin A_{1c} less than 0.06 was achieved in 5%, 29%, and 23% of patients in the groups, respectively. The difference was statistically significant in favour of both types of surgery, Dr Philip Raymond Schauer reported at the annual meeting of the American College of Cardiology.

Furthermore, patients in the surgery groups fared better than those in the intensive medical therapy group on several other measures, including disease remission (defied as HbA_{1c} less than 6% without diabetes medication), HbA_{1c} less than 0.07 (the American Diabetes Association target for therapy), change in fasting plasma glucose from baseline, and changes in high- and low-density lipoprotein cholesterol levels, said Dr Schauer, director of the Cleveland Clinic Bariatric and Metabolic Institute.

Patients in the surgery groups also experienced a significantly greater reduction in the use of antihypertensive medications and lipid-lowering agents, he added.

The "very dramatic drop" in HbA1c seen early on in the surgical patients was, for the most part, sustained out to 5 years, he said.

The results for both surgeries were significantly better than those for intensive medical therapy, but the results with gastric bypass were more effective at 5 years than were those for sleeve gastrectomy, he added, noting that the surgery patients had better quality of life, compared with the intensive medical therapy patients.

As for adverse events in the surgery groups, no perioperative deaths occurred, and while there were some surgical complications, none resulted in long-term disability, Dr Schauer said.

Anaemia was more common in the surgery patients, but was fairly mild. The most common complication was weight gain in 20% of patients, and the overall reoperation rate was 7%.

Of note, patients in the study had body mass index ranging from 27 to 43 kg/m^2, and those with BMI less than 35 had similar benefits as those with more severe obesity. This is important, as many insurance companies won't cover metabolic surgery for patients with BMI less than 35, he explained.

These findings represent the longest follow-up to date comparing the efficacy of the two most common metabolic surgery procedures with medical treatment of type 2 diabetes for maintaining glycaemic control or reducing end-organ complications. Three-year outcomes of STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) were reported in 2014 (*N Engl J Med* 2014;370:2002–13).

The participants ranged in age from 20 to 60 years. The average HbA_{1c} was about 0.09, the average BMI was 36, and most were on at least three antidiabetic medications at baseline. Half were on insulin.

The findings are important, because of the roughly 25 million Americans with type 2 diabetes, only about half have good glycaemic control on their current medical treatment strategies, Dr Schauer said.

Though limited by the single-centre study design, the STAMPEDE findings show that metabolic surgery is more effective long term than intensive medical therapy in patients with uncontrolled type 2 diabetes and should be considered a treatment option in this population, he concluded, adding that multicentre studies would be helpful for determining the generalisability of the findings.

Dr Schauer reported receiving consulting fees/honoraria from Ethicon Endosurgery and The Medicines Company, and having ownership interest in Surgical Excellence.

NEWS

Heart attack patients getting younger, fatter, and less healthy

BY MICHELE G. SULLIVAN
Frontline Medical News
At ACC16, Chicago

Despite advances in the prevention and early detection of cardiovascular disease, heart attack patients are getting younger, fatter, and less health conscious.

A look at 10 years' worth of patient data reveals these and other "alarming trends," according to Dr Samir R. Kapadia of the Cleveland Clinic.

"What we found was so very contradictory to what we expected," he said at a press briefing held in advance of the annual meeting of the American College of Cardiology. "Amazingly, we saw that patients presenting with myocardial infarction were getting younger, and their body mass index was going up. There was more smoking, more hypertension, and more diabetes. And all of this despite our better understanding of cardiovascular risk factors."

The findings seem to point to a serious gap between gathering scientific knowledge and putting that knowledge into practice.

"We have to extend our efforts and put a lot more into educating patients," Dr Kapadia said. "Maybe it's not enough to just tell people to eat right and exercise – maybe we should also be providing them with a structured program. But this is not just the job of the cardiologist. Primary care physicians have to also have this insight, communicate it to the patients, and get them the resources they need to help prevent heart attacks."

His retrospective study comprised 3912 consecutive patients who were treated for ST-segment elevation MI (STEMI) from 1995 to 2014. Data were collected on age, gender, diabetes, hypertension, smoking, lipid levels, chronic renal impairment, and obesity. The group was divided into four epochs: 1995–1999, 2000–2004, 2005–2009, and 2010-2014. The researchers examined these factors both in the entire cohort and in a subset of 1325 who had a diagnosis of coronary artery disease at the time of their MI.

Patients became significantly younger over the entire study period. In epoch 1, the mean age of the entire cohort was 63.6 years. By epoch 3, this had declined to 60.3 years – a significant drop. The change was also evident in the CAD subset; among these patients, mean age declined from 64.1 years in epoch 1 to 61.8 years in epoch 4.

Tobacco use increased significantly in both groups as well. In the overall cohort, the rate was 27.7% in epoch 1 and 45.4% in epoch 4. In the CAD subset, it rose from 24.6% to 42.7%.

Hypertension in the entire cohort increased from 56.7% to 77.3%. In the CAD subset, it increased from 60.9% to 89%.

Obesity increased in both cohorts in overlapping trends, from about 30% in epoch 1 to 40% in epoch 4.

Diabetes increased as well. In the entire cohort, it rose from 24.6% to 30.6%. In the CAD subset, it rose from 25.4% to 41.5%.

Dr Kapadia noted that the proportion of patients with at least three major risk factors rose from 65% to 85%, and that the incidence of chronic obstructive pulmonary disease increased from 5% to 12%, although he didn't break this trend down by group.

He had no financial disclosures.

Sutureless AVR an option for higher-risk patients

BY RICHARD MARK KIRKNER
Frontline Medical News
From the Journal of Thoracic and Cardiovascular Surgery

The first North American experience with a sutureless bioprosthetic aortic valve that has been available in Europe since 2005 and is well suited for minimally invasive surgery has underscored the utility of the device as an alternative to conventional aortic valve replacement (AVR) in higher-risk patients, investigators from McGill University Health Center in Montreal reported in the March issue of the *Journal of Thoracic and Cardiovascular Surgery* (2016;151:735–742).

> **The Enable bioprosthesis is an acceptable alternative to conventional aortic valve replacement in higher-risk patients. The early haemodynamic performance seems favourable.**

The investigators, led by Dr Benoir de Varennes, reported on their experience implanting the Enable valve (Medtronic) in 63 patients between August 2012 and October 2014. "The enable bioprosthesis is an acceptable alternative to conventional aortic valve replacement in higher-risk patients," Dr de Varennes and colleagues said. "The early haemodynamic performance seems favourable." Their findings were first presented at the 95th annual meeting of the American Association for Thoracic Surgery in April 2015 in Seattle. A video of the presentation is available.

The Enable valve has been the subject of four European studies with 429 patients. It received its CE Mark in Europe in 2009, but is not yet commercially approved in the United States.

In the McGill study, one patient died within 30 days of receiving the valve and two died after 30 days, but none of the deaths were valve related. Four patients (6.3%) required revision during the implantation operation, and one patient required reoperation for early migration. Peak and mean gradients after surgery were 17 mmHg and 9 mmHg, respectively. Three patients had reported complications: Two (3.1%) required a pacemaker and one (1.6%) had a heart attack. Mean follow-up was 10 months.

Patient ages ranged from 57 to 89 years, with an average age of 80. Before surgery, all patients had calcific aortic stenosis, 43 (68%) had some degree of associated aortic regurgitation, and 46 (73%) were in New York Heart Association (NYHA) class III or IV. At the last follow-up after surgery, 61 patients (97%) were in NYHA class I.

The investigators implanted the valve through a full sternotomy or a partial upper sternotomy into the fourth intercostal space, and they used perioperative transoesophageal echocardiography in all patients. They performed high-transverse aortotomy and completely excised the native valve.

The average cross-clamp time for the 30 patients who had isolated AVR was 44 minutes and 77 minutes for the 33 patients who had combined procedures. Dr de Varennes and colleagues acknowledged the cross-clamp time for isolated AVR is "similar" to European series but "not very different" from recent reports on sutured AVR (*J Thorac Cardiovasc Surg* 2015;149:451–460). "This may be explained partly by the learning period of all three surgeons and the aggressive debridement of the annulus in all cases," they said. "We think that, as further experience is gained, the clamp time will be further reduced, and this will benefit mostly higher-risk patients or those requiring concomitant procedures."

They noted that some patients received the Enable prosthesis because of "hostile" aortas with extensive root calcification.

Dr de Varennes disclosed he is a consultant for Medtronic and a proctor for Enable training. The coauthors had no relationships to disclose. The Enable valve is not available in Australia.

VIEW ON THE NEWS

Sutureless option to conventional AVR

One of the key advantages that advocates of sutureless valves point to is shorter bypass times than sutured valves, but in his invited commentary Dr Thomas G. Gleason of the University of Pittsburgh questioned this rationale based on the results Dr de Varennes and colleagues reported (*J Thorac Cardiovasc Surg* 2016;151:743–744). The cardiac bypass times they observed "are not appreciably different from those reported in larger series of conventional aortic valve replacement," Dr Gleason said.

Dr Gleason suggested that "market forces" might be driving the push into sutureless aortic valve replacement. "The attraction, particularly to consumers, of the ministernotomy (and thus things that might facilitate it) is both cosmetic and the perception that it is less invasive," he said. "These attractions notwithstanding, it has been difficult to demonstrate that ministernotomy or minithoracotomy yield better primary outcomes (e.g., mortality, stroke, or major complication rates) or even quality of life indicators, particularly when measured beyond the perioperative period."

He alluded to the "elephant in the room" with regard to sutureless aortic valve technologies: their cost and unknown durability compared with conventional sutured bioprostheses.

"As health care costs continue to rise and large populations of patients are either underinsured or see rationed care, trimming direct costs may be a more relevant concern for the modern era than trimming cross-clamp time," he said. Analyses have not yet evaluated the increased costs of sutureless valves in terms of shortened hospital stays or lower morbidity, particularly in the moderate-risk population with aortic stenosis, he said.

"Moving forward, there is little doubt that the current value of the sutureless valve will be dictated by the market, but in the end it will be measured by the long-term outcomes of the 'minimally invaded'," Dr Gleason said.

Dr Gleason had no financial relationships to disclose.

Confidence from Evidence and Real World Experience*

*Xarelto has evidence for its efficacy and safety profile for eligible patients from RCTs and real world studies in SPAF[1-3] and PE/DVT.[4,5] Xarelto is the world's most prescribed NOAC,[6] with over 15 million patients treated across multiple indications.[7,8]

RCT=randomised controlled trial; SPAF=stroke prevention in atrial fibrillation; PE=pulmonary embolism; DVT=deep vein thrombosis; NOAC=non-vitamin K antagonist oral anticoagulant.
Calculation based on IMS Health MIDAS, Database: Monthly Sales June 2015.

Xarelto® rivaroxaban

PBS Information: Authority Required (STREAMLINED). Refer to PBS Schedule for full authority information.

PLEASE REVIEW THE FULL PRODUCT INFORMATION (PI) BEFORE PRESCRIBING. APPROVED PI AVAILABLE AT WWW.BAYERRESOURCES.COM.AU/RESOURCES/UPLOADS/PI/FILE9466.PDF OR UPON REQUEST FROM BAYER AUSTRALIA LTD.

Minimum Product Information. XARELTO® (rivaroxaban) INDICATIONS: Prevention of venous thromboembolism (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limbs (elective total hip replacement, treatment for up to 5 weeks; elective total knee replacement, treatment for up to 2 weeks); 10 mg tablet once daily. Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke; 20 mg tablet once daily (15 mg for patients with CrCl 30-49 mL/min). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for the prevention of recurrent DVT and pulmonary embolism (PE); 15 mg tablet twice daily for 3 weeks, followed by 20 mg tablet once daily. Xarelto 15 mg and 20 mg tablets should be taken with food. Tablets may be crushed and administered orally (mixed with water or applesauce) or given through gastric tubes. See full PI for details. **CONTRAINDICATIONS:** Hypersensitivity to rivaroxaban or to any of the excipients, clinically significant active bleeding, lesions at increased risk of clinically significant bleeding and patients with spontaneous impairment of haemostasis, significant hepatic disease which is associated with coagulopathy, dialysis or severe renal impairment with a creatinine clearance < 15 mL/min for Xarelto 10 mg or < 30 mL/min for Xarelto 15 mg and 20 mg, concomitant treatment with strong inhibitors of both CYP 3A4 and P-glycoprotein, Pregnancy, Lactation. **PRECAUTIONS:** Increased bleeding risk such as general haemorrhagic risk (see PI for list), bronchiectasis or history of pulmonary bleeding, renal impairment, hepatic impairment, surgery and interventions, spinal/epidural anaesthesia or puncture, patients with prosthetic valves (no clinical data), haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy, lactose intolerance. **INTERACTIONS WITH OTHER MEDICINES:** Care to be taken if concomitantly used with medicines affecting haemostasis; concomitant administration with NSAIDs, platelet aggregation inhibitors, other anticoagulants. **ADVERSE EFFECTS:** Please refer to PI for a complete list. Very common and common adverse reactions (≥ 1%) include post procedural haemorrhage, increased transaminases, gingival bleeding, constipation, diarrhoea, nausea, pyrexia, oedema peripheral, contusion, pain in extremity, headache, dizziness, haematuria, menorrhagia, epistaxis, haematoma, anaemia, rectal haemorrhage, fatigue and ecchymosis, haemoptysis, pruritus, conjunctival haemorrhage, abdominal pain, dyspepsia, gastrointestinal haemorrhage, syncope, hypotension, increased gamma-glutamyltransferase, tachycardia, vomiting, asthenia, wound haemorrhage, subcutaneous haematoma and rash. Less frequent but serious adverse reactions include: urticaria, hypersensitivity, hyperglycaemia, cerebral, cerebellar and intracranial haemorrhage, haemorrhagic transformation stroke, jaundice, eye haemorrhage, loss of consciousness, angioedema, allergic oedema, cholestasis, hepatitis and thrombocytopaenia. **DOSAGE AND ADMINISTRATION:** see INDICATIONS above. **BASED ON PI DATED:** 09 Nov 2015.

References: 1. Patel MR *et al. N Engl J Med* 2011;365:883–91. **2.** Camm J *et al. Eur Heart J.* 2015 Sep 1. pii: ehv466. [Epub ahead of print]. **3.** Tamayo S *et al. Clin Cardiol* 2015;38:63–8. **4.** Prins MH *et al. Thrombosis J* 2013;11(1):21. **5.** Beyer-Westendorf J *et al. Blood* 2014;124:955–62. **6.** IMS Health MIDAS, Database: Monthly Sales June 2015. **7.** Calculation based on IMS Health MIDAS, Database: Monthly Sales June 2015. **8.** Xarelto® (rivaroxaban) Product Information, 9 November 2015.

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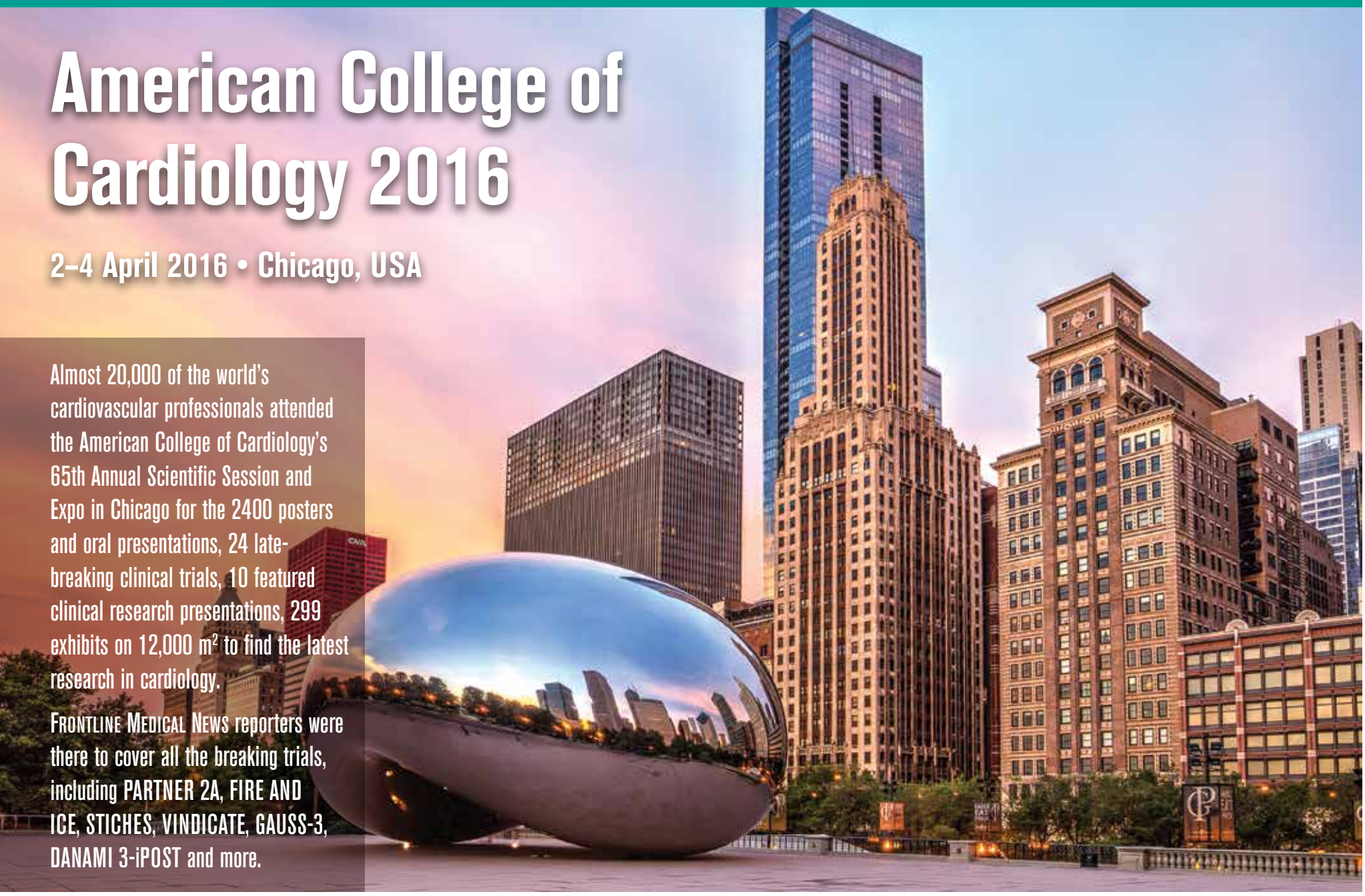
CONFERENCE COVERAGE

American College of Cardiology 2016

2–4 April 2016 • Chicago, USA



Almost 20,000 of the world's cardiovascular professionals attended the American College of Cardiology's 65th Annual Scientific Session and Expo in Chicago for the 2400 posters and oral presentations, 24 late-breaking clinical trials, 10 featured clinical research presentations, 299 exhibits on 12,000 m^2 to find the latest research in cardiology.

Frontline Medical News reporters were there to cover all the breaking trials, including PARTNER 2A, FIRE AND ICE, STICHES, VINDICATE, GAUSS-3, DANAMI 3-iPOST and more.

Early antiarrhythmic drugs boost survival in shock-refractory cardiac arrest

BY BRUCE JANCIN

Paramedic-administered amiodarone or lidocaine during resuscitation of patients with shock-refractory ventricular fibrillation or ventricular tachycardia of out-of-hospital cardiac arrest significantly improves survival, according to the findings of the largest-ever clinical trial of out-of-hospital cardiac arrest.

However, the survival advantage was limited to bystander-witnessed arrest. The reason for this difference in the Amiodarone, Lignocaine or Placebo Study (ALPS) is that observed arrest is a good surrogate for earlier recognition and treatment of an out-of-hospital cardiac arrest (OHCA), Dr Peter J. Kudenchuk explained in presenting the study findings at the annual meeting of the American College of Cardiology.

"The message from this trial is that, if you give these drugs to everyone across the board with out-of-hospital shock-refractory VF/VT cardiac arrest, you'll help those who can be helped and you won't hurt those who are beyond help," said Dr Kudenchuk, professor of medicine at the University of Washington, Seattle.

ALPS was a randomised, blinded, placebo-controlled clinical trial of 3026 patients with shock-refractory VF/VT OHCA at 10 US and Canadian sites participating in the Resuscitation Outcomes Consortium. Subjects were randomised to paramedic-administered treatment with prefilled syringes of amiodarone, lignocaine, or placebo. Time to treatment averaged 19 minutes from the initial call made to emergency services.

The primary endpoint in ALPS was survival to hospital discharge. Rates were 24.4% in the amiodarone group, 23.7% with lidocaine, and 21% with placebo. Differences in survival rates between the antiarrhythmic drug and placebo groups approached but did not achieve statistical significance.

Survival to hospital discharge in the 1934 participants with bystander-witnessed arrest was a prespecified secondary endpoint. That outcome was achieved in 27.7% of the amiodarone group and 27.8% who got lidocaine, compared with 22.7% of placebo-treated patients. Those differences were statistically significant and clinically meaningful, Dr Kudenchuk asserted.

"Though these differences – an absolute 5% improvement over placebo – may seem small, were we to implement this as policy, upwards of 1800 more lives could potentially be saved each year in the United States alone," said Dr Kudenchuk, an electrophysiologist and cardiologist.

Bystander-witnessed OHCA was 2.3-fold more common than unwitnessed arrest. In the unwitnessed arrest subgroup there was no hint of benefit for either amiodarone or lignocaine.

"Many patients with unwitnessed arrest have already sustained mortal ischaemic damage by the time they're found," he observed. "If you go into a morgue and give the best drug in the world, you're not going to save anybody."

Moreover, among the roughly 5% of patients whose OHCA was witnessed by EMS personnel, survival to hospital discharge was a whopping absolute 22% greater with antiarrhythmic drug therapy than with placebo.

"Taken together, these findings suggest that treatment sooner after heart collapse may be a critical determinant of drug effect," Dr Kudenchuk continued.

He said the ALPS findings are generalisable to all communities across North America where the local EMS system follows the Resuscitation Outcomes Consortium philosophy that early defibrillation and good CPR are the cornerstones of effective management of OHCA, without which no treatment can be effective.

Current use of these drugs across the United States is not standardised. "It is really a free-for-all," according to Dr Kudenchuk. "Some agencies strictly use lignocaine, others may use amiodarone. Some use both. And some use neither. I think in part that's because current guideline recommendations give these drugs a class IIb recommendation – meaning they're optional – because up until this point there have been no data to support their effectiveness in changing outcome."

In his view, the ALPS data clearly warrant upgrading the strength of the recommendation for antiarrhythmic drug therapy in the next iteration of the guidelines. Although he is on the guideline committee, Dr Kudenchuk added, he cannot predict what the committee as a whole will decide.

ALPS will not lead to a change in practice such that paramedic-administered antiarrhythmic agents are given only to patients with witnessed arrest, Dr Kudenchuk said. It's not practical for rescue personnel in the midst of the fray to try to figure out whether an OHCA was witnessed or not. Plus, there's an ethical issue involved.

"If we'd wanted to hit the headlines with a major trial with a positive outcome we would have selected only people with witnessed cardiac arrest from the get-go to do this trial, since we guessed that's where the money was going to be. The reality is you can't treat people that way. Everyone has to have a chance," he said.

Asked which antiarrhythmic drug the next edition of the resuscitation guidelines should recommend preferentially, he said ALPS wasn't powered to distinguish between amiodarone and lignocaine. "If I were writing the guidelines, I would simply say either or both happens to be okay."

An important footnote is that ALPS utilised a new, US Food and Drug Administration–approved formulation of amiodarone, known as Nexterone, designed to reduce hypotensive effects. Had investigators employed the more familiar version of the drug, the safety results wouldn't have been as good.

Out-of-hospital cardiac arrest accounts for roughly 350,000 deaths per year in the United States

Simultaneously with Dr Kudenchuk's presentation of the ALPS findings at ACC 16 in Chicago, the results were published online (*N Engl J Med* 2016 Apr 4; doi: 10.1056/NEJMoa1514204).

He reported having no financial conflicts regarding the ALPS study, which was funded by the US National Heart, Lung, and Blood Institute, the Canadian Institutes of Health Research, the American Heart Association, the US Army, and Defense Research and Development Canada.

Continued from page 1.

TAVR matches surgery in intermediate-risk patients

that treated patients should have a STS risk score of at least 8%, the labelling also gives the heart teams that perform TAVR the latitude to treat patients with risk scores below 8% when the heart teams identify other patient factors that confer high risk such as frailty or comorbidities. US and European TAVR registries have documented that many patients with STS risk scores below 8% have undergone TAVR since these systems received regulatory approval. The new results from PARTNER 2A may change that by leading to revised labelling that cuts the STS risk-score threshold.

"These findings might lead to a labelling change that would avoid a lot of the patient-evaluation gymnastics that have been used to justify" TAVR treatment, noted Dr Smith. New labelling like this "would sanction what is already going on" in terms of which patients undergo TAVR.

Others who heard these results at the meeting agreed they were an important milestone in TAVR development and its expanding use.

The new results "make a huge difference," commented Dr David R. Holmes Jr., an interventional cardiologist and professor at the Mayo Clinic in Rochester, Minnesota. "We base many of our guidelines on the results from randomised, controlled trials. It's true that there are reports of lower-risk patients undergoing TAVR, but we now have results from a well-designed trial with well-controlled and adjudicated endpoints that documents the safety and efficacy of TAVR in intermediate-risk patients," Dr Holmes said in an interview.

"The results will have a very important influence on the choice between TAVR and surgery," commented Dr Duane S. Pinto, an interventional cardiologist at Beth Israel Deaconess Medical Center in Boston. "It validates the strategy" of using TAVR in patients with a risk score of 4–8%. "TAVR has already been used in these patients, but these results validate this, especially when used in a transfemoral approach," Dr Pinto said in an interview.

One aspect of PARTNER 2A that received a lot of discussion at the meeting was whether enrolled patients could appropriately be characterised as "intermediate" in their risk level. Although their average STS risk score of 5.8% fell squarely within the target range specified for the study, they averaged 82 years old, and other clinical features at baseline suggested a higher risk population. The published report of the PARTNER 2A results that appeared online concurrent with Dr Smith's report at the meeting (*New Engl J Med* 2016;doi:10.1056/NEJMoa1514616) acknowledged that STS risk scores of 4–8% place the enrolled patients into the upper 20% for risk of all US patients who undergo surgical aortic-valve replacement.

"I would characterise the enrolled patients as 'less high risk' rather than intermediate risk," said Dr Pinto.

But as Dr Smith explained "even if the enrolled patients are not 'intermediate' risk they are at a different risk level" than were the patients enrolled in the prior TAVR randomised trials.

In the PARTNER 1 high-risk trial, the overall 1-year rate of all-cause mortality was 24% and 27% in the TAVR and surgical arms of the study, respectively. In the CoreValve trial these rates were 14% with TAVR and 19% with surgery. In PARTNER 2A 1-year all-cause mortality was 12% with TAVR and 13% with surgery.

> These findings might lead to a labelling change that would avoid a lot of the patient-evaluation gymnastics that have been used to justify TAVR treatment. New labelling like this would sanction what is already going on in terms of which patients undergo TAVR.

Two other notable findings of PARTNER 2A were the superior outcomes of patients who underwent TAVR using a transfemoral approach, and the improved outcomes that all TAVR patients had compared with surgical valve replacement for several secondary outcomes.

The rate of the study's primary outcome, all-cause death or disabling stroke after 2 years, was cut by a relative 21% in the 77% of TAVR patients who underwent a transfemoral procedure, compared with the surgery patients, a difference that was of borderline statistical significance. In contrast, the entire group of TAVR patients, including those treated via nontransfemoral routes, had an 11% relative reduction of the primary endpoint, compared with surgery, a difference that was not statistically significant but did easily meet the study's prespecified definition of noninferority. Dr Smith and others were especially encouraged by these findings as PARTNER 2A used the older Sapien XT TAVR system that is not often used today in US practice. When US patients undergo TAVR with a balloon-expandable valve they most often receive treatment with the S3 system, much smaller than XT and hence much more likely to be used with a transfemoral approach.

Other secondary outcomes included life-threatening or disabling bleeding events, which after 2 years had occurred in 17% of the TAVR patients and 47% of those who underwent surgery; atrial fibrillation, which occurred in 11% of the TAVR patients and 27% of those undergoing surgery; and acute kidney injury which occurred in 4% of TAVR patients and 6% of the surgery patients. With 2-year follow-up, the rate of disabling strokes was 6% in both arms of the study.

PARTNER 2A was sponsored by Edwards Lifesciences, the company that markets the Sapien TAVR systems. Dr Smith has received travel grants from Edwards. Dr Holmes had no disclosures, Dr Pinto has been a consultant to Medtronic.

VIEW ON THE NEWS

A game changer for intermediate-risk patients

Registries of patients who have undergone transcatheter aortic-valve replacement in Europe and the United States show that this procedure has already been frequently used in selected patients with Society of Thoracic Surgeons operative-risk scores of 4–8%. Even though regulatory approval specifies using the procedure in high-risk patients with risk scores of at least 8%, the labelling leaves the decision of which patients are at high risk up to local heart teams, and factors other than the risk score play into a patient's overall risk assessment including frailty and comorbidities.

Despite the prior experience using TAVR in patients with STS risk scores of 4–8% the results of PARTNER 2A are a game changer because they come from a prospective, randomised, controlled trial.

The PARTNER 2A results are also notable because this is the second randomised trial (in addition to the CoreValve high-risk trial) with results that show or suggest that transcatheter aortic-valve replacement (TAVR) produces better outcomes than surgery, especially in patients who undergo TAVR via a transfemoral approach. Other notable advantages of TAVR over surgery seen in PARTNER 2A include substantial reductions in disabling or life-threatening bleeding events and in new-onset atrial fibrillation, a statistically significant reduction in acute kidney injury, and no significant difference in the incidence of disabling strokes. In the past, we expected stroke rates to be higher with TAVR, but in PARTNER 2A, with neurologists adjudicating the strokes, we saw no difference in the TAVR and surgical stroke rates, a finding that was probably unexpected for many people.

The patients enrolled in PARTNER 2A were clearly at lower risk for all-cause mortality than the patients enrolled in the earlier TAVR trials. The operative risk score is just one of several ways to estimate patient risk. The data collected in PARTNER 2A provide a robust resource for finding new, additional ways to assess patients who are at intermediate risk and to match patients seen during routine practice to those who entered this trial.

Dr Ajay J. Kirtane is an interventional cardiologist and director of the coronary catheterisation laboratory at New York–Presbyterian/Columbia University in New York. He was a coinvestigator on prior Sapien TAVR studies but did not participate in PARTNER 2. His institution has received research support from Edwards and from Boston Scientific. He made these comments in an interview.

Self-expanding TAVR bests surgery based on 3-year stroke and death risks

BY JENNIE SMITH

Patients with severe aortic stenosis that puts them at increased risk for surgery continue to do better at 3 years after receiving a self-expanding transcatheter aortic valve replacement than do similar patients who have an open surgical valve replacement, according to new results from a randomised trial presented at the annual meeting of the American College of Cardiology.

Two-year follow-up results from the same trial cohort, the CoreValve US Pivotal High Risk Trial, showed superior survival and stroke outcomes for TAVR compared with open surgery (*J Am Coll Cardiol* 2015;66[2]:113–21). The difference in outcomes was thought to stem mainly from fewer postprocedural complications and faster recovery in the TAVR group.

> While the findings show sustained 3-year clinical benefit of self-expanding TAVR over SAVR in patients with aortic stenosis at increased risk for surgery, longer studies are needed to determine whether the crimping and re-crimping of the transcatheter valve would have an impact on long-term bioprosthesis durability.

The new study, presented at the meeting and simultaneously published online April 3 in the *Journal of the American College of Cardiology* (doi: 10.1016/j.jacc.2016.03.506) aimed to determine whether the previously seen benefits extended into the third year and whether these were accompanied by differences in valve haemodynamics.

Dr G. Michael Deeb, Herbert Sloan Collegiate Professor of Cardiac Surgery at the University of Michigan, Ann Arbor, and his colleagues evaluated three-year clinical and echocardiographic outcomes from the 391 patients who underwent TAVR and 359 who had SAVR. At baseline all patients had severe aortic stenosis and were considered to be at increased risk for SAVR, with an estimated 30-day mortality risk 15% or greater and a combined 30-day surgical mortality and major morbidity risk less than 50%.

At 3 years follow-up in the treated groups, combined all-cause mortality or stroke was significantly lower at 37% in TAVR patients as compared to nearly 47% in SAVR patients. All-cause mortality was 33% with TAVR and 39% with SAVR, a difference that did not reach statistical significance. Stroke rates were nearly 13% with TAVR and 19% with SAVR; major adverse cardiovascular or cerebrovascular events were 40% with TAVR and 48% for SAVR. Both were significant differences.

While mean aortic valve gradient measures were more favourable – 7.62 ± 3.57 mmHg with TAVR and 11.40 ± 6.81 mmHg with SAVR – regurgitation was significantly higher at nearly 7% with TAVR and no regurgitation with SAVR. Valve thrombosis and valve structural deterioration were not observed in either group.

While the findings show sustained 3-year clinical benefit of self-expanding TAVR over SAVR in patients with aortic stenosis at increased risk for surgery, longer studies are needed to determine whether the crimping and re-crimping of the transcatheter valve would have an impact on long-term bioprosthesis durability.

The study was funded by the device manufacturer Medtronic, and 21 of its 28 authors disclosed financial relationships with Medtronic and/or other manufacturers; one is a Medtronic employee. Dr Deeb disclosed serving as an unpaid advisor to Medtronic.

Coronary bypass shows compelling advantages in ischaemic cardiomyopathy

BY BRUCE JANCIN

Coronary artery bypass grafting plus guideline-directed medical therapy resulted in significantly lower all-cause mortality than did optimal medical therapy alone at 10 years of follow-up in the Surgical Treatment for Ischaemic Heart Failure Extension Study (STICHES), Dr Eric J. Velazquez reported at the annual meeting of the American College of Cardiology.

"We believe these results have the immediate clinical implications that the presence of severe left ventricular dysfunction should prompt an evaluation for the extent and severity of angiographic CAD, and that among patients with ischaemic cardiomyopathy, CABG should be strongly considered in order to improve long-term survival," declared Dr Velazquez, professor of medicine in the division of cardiology at Duke University, Durham, North Carolina.

STICHES included 1212 patients in 22 countries, all with heart failure and an ejection fraction of 35% or less along with CAD deemed suitable for surgical revascularisation. They were randomised to CABG plus guideline-directed medical therapy or to the medical therapy alone. The 98% successful follow-up rate over the course of 10 years in this trial drew audience praise as a herculean effort.

At a median 9.8 years of follow-up, all-cause mortality – the primary study endpoint – had occurred in 58.9% of the CABG group and 66.1% of medically managed patients. That translates to a 16% relative risk reduction and an absolute 8% difference in favour of CABG. The median survival extension conferred by CABG was 1.4 years. The number of patients needed to treat with CABG in order to prevent one death from any cause was 14.

The CABG group also did significantly better in terms of secondary endpoints. The cardiovascular mortality rate was 40.5% in the CABG group versus 49.3% with medical therapy, for a 21% relative risk reduction favouring CABG and a number needed to treat of 11. The composite endpoint of all-cause mortality or cardiovascular hospitalisation occurred in 76.6% of the CABG group and 87% of the medically treated patients.

In an earlier analysis based upon 56 months of follow-up, there was a trend favouring CABG in terms of all-cause mortality, but it didn't reach statistical significance (*N Engl J Med* 2011;364:1607–16). With an additional 5 years of prospective follow-up, however, the divergence in outcome between the two study arms increased sufficiently that the difference achieved statistical significance. But the more impressive study finding, in Dr Velazquez's view, was the durability of the CABG benefits out to 10 years.

Discussant Dr Jeroean J. Bax of Leiden (the Netherlands) University commented that while the solid advantage in outcomes displayed by the CABG group was noteworthy, he finds it sobering that even though the STICHES participants averaged only 60 years of age at entry, the majority were dead at 10 years' follow-up. What, he asked, is the likely mechanism for the very high mortality seen in this population?

"My take-home after many years working with our team is that I believe these patients have very low reserve, and they are at risk any time they take a hit. I don't believe just one mechanism is involved. In our previous analysis of the 5-year follow-up data, we showed the results can't be explained solely by viability, ischaemia, or functional recovery. I think the issue of arrhythmia reduction and substrate reduction is important. But for me, it's a combination of many factors. Any additional hit for this high-risk population is not well tolerated; that's what leads to death," Dr Velazquez replied.

> **We believe these results have the immediate clinical implications that the presence of severe left ventricular dysfunction should prompt an evaluation for the extent and severity of angiographic CAD, and that among patients with ischaemic cardiomyopathy, CABG should be strongly considered in order to improve long-term survival.**

Asked how he thinks multivessel percutaneous coronary intervention would perform as an alternative to CABG in patients with ischaemic cardiomyopathy, Dr Velazquez responded that he has no idea because it hasn't been studied.

"I can picture reasons for and against PCI providing benefits similar to CABG," he added.

Simultaneous with Dr Velazquez's presentation at ACC 16, the STICHES results were published online (*N Engl J Med* 2016 April 3. doi:10.1056/NEJMoa1602001).

In an accompanying editorial, Dr Robert A. Guyton and Dr Andrew L. Smith of Emory University in Atlanta asserted that these strong results from STICHES make a compelling case that CABG for patients with ischaemic cardiomyopathy should be upgraded in the ACC/AHA heart failure management guidelines from its current status as a class IIb recommendation that "might be considered" to class IIa, indicating it is "probably beneficial" (*N Engl J Med* 2016 April 3. doi:10.1056/NEJMe1603615).

STICHES was funded by the US National Institutes of Health. The study presenter reported having no financial conflicts regarding the study.

Novel drug fails to prevent contrast-induced nephropathy

BY BRUCE JANCIN

CMX-2043, a novel agent intended for prevention of contrast-induced nephropathy, failed in the phase II, double-blind, placebo-controlled CARIN clinical trial presented at the annual meeting of the American College of Cardiology.

The drug had also shown promise in small preliminary studies for the prevention of periprocedural myocardial infarction in patients undergoing coronary stenting. There again, however, CMX-2043 – a derivative of alpha lipoic acid with antioxidant and cell membrane-stabilising properties – proved ineffective in the 361-patient, 31-centre phase II trial, reported Dr Deepak L. Bhatt, professor of medicine at Harvard Medical School and executive director of interventional cardiovascular programs at Brigham and Women's Hospital, both in Boston.

All participants in CARIN had baseline severe impairment of kidney function or mild to moderate renal impairment plus another risk factor, such as diabetes or age greater than 75 years. One hour prior to coronary angiography, they received various doses of CMX-2043 or placebo.

Unfortunately, no difference between the four treatment arms was present in terms of the primary study endpoint: the incidence of acute kidney injury as defined by at least a 0.3 mg/dL rise in serum creatinine from baseline on day 4. No dose response to CMX-2043 was evident, nor did the investigational agent have any impact on the risk of major adverse cardiovascular events.

Immediately prior to Dr Bhatt's presentation, Dr Michelle L. O'Donoghue of Brigham and Women's Hospital presented the equally negative results of the LATITUDE-TIMI 60 trial, a phase III trial of the investigational mitogen-activated protein kinase inhibitor losmapimod, a drug developed to improve outcomes in patients with an acute coronary syndrome.

"It's a bit distressing" to witness back to back presentations of clinical trials that proved resoundingly negative despite very strong-looking preliminary data, commented discussant Dr Anthony N. DeMaria, professor of medicine at the University of California, San Diego. What's going on here? he asked.

"I think it's a fundamental truth that a lot of things that look good in preclinical work, even when backed up by a lot of solid science, don't pan out in human studies," Dr Bhatt replied. "That's a challenge, and probably in no other arena more so than in tackling inflammation and antioxidant therapy.

> I think it's a fundamental truth that a lot of things that look good in preclinical work, even when backed up by a lot of solid science, don't pan out in human studies.

"There's a graveyard of compounds that have not worked, and now we've perhaps added another one," Dr Bhatt continued. "But it doesn't mean that scientific inquiry isn't important, because I think eventually we'll have drugs for these problems, whether it's reperfusion injury or contrast-induced nephropathy. It'll probably just take a lot more time and effort."

The one solace regarding the CARIN trial, in Dr Bhatt's view, is that it highlighted the advantages of what is known as an adaptive trial design. Instead of jumping from positive early-phase results straight to a definitive 10,000-patient phase III clinical trial, investigators were able to obtain answers regarding the drug's ability to prevent two major problems in patients undergoing coronary angiography – contrast-induced nephropathy and major adverse cardiac events – by means of a single 361-patient trial that was comparatively inexpensive.

Acute kidney injury secondary to exposure to contrast agents remains a significant problem, with an incidence of 20–25% in high-risk patients. Numerous proposed prophylactic agents have ultimately proved not useful, including sodium bicarbonate, N-acetylcysteine, and intravenous fenoldopam.

Indeed, the only preventive measures of proven effectiveness are hydration with saline for 12 hours preangioplasty, and limiting the volume of contrast agent used. In real-world clinical practice, however, it's often impractical to administer the optimal 12 hours of saline because of hospital pressure to get patients out quickly, Dr Bhatt observed.

"There remains an important unmet clinical need to find agents that reduce the occurrence of contrast nephropathy," he stressed.

Ischemix funded the CARIN trial. Dr Bhatt reported receiving a research grant from the company that was directed to Brigham and Women's Hospital.

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FIRE AND ICE trial called a win for cryoablation of AF

BY BRUCE JANCIN

The largest-ever randomised trial of catheter ablation of atrial fibrillation has ended in a draw between radiofrequency and cryoballoon ablation in safety and efficacy – and that actually represents a win for cryoablation, a simpler and far more easily mastered procedure, Dr Karl-Heinz Kuck said at the annual meeting of the American College of Cardiology.

"We can teach physicians how to do cryoablation much more easily. That will allow more patients with atrial fibrillation to get access to catheter ablation, which is what we really need," according to Dr Kuck, principal investigator in the poetically named FIRE AND ICE trial and head of cardiology at St. Georg Hospital in Hamburg (Germany).

FIRE AND ICE included 769 patients in eight European countries. The participants, all of whom had antiarrhythmic drug–refractory paroxysmal atrial fibrillation (AF), were randomised to radiofrequency ablation – the long-time standard – or to cryoablation, a newer technology. Radiofrequency ablation was guided by three-dimensional electroanatomic mapping, while cryoablation utilised fluoroscopic guidance.

The primary efficacy endpoint was the 1-year rate of clinical failure, defined as an occurrence of AF, atrial flutter, or atrial tachycardia lasting for at least 30 seconds, or repeat ablation or the use of antiarrhythmic drugs following a 90-day postprocedural blanking period. The clinical failure rate was 34.6% in the cryoballoon group and similar at 35.9% in the radiofrequency group.

Serious treatment-related adverse events occurred in 10.2% of the cryoballoon group and 12.8% of the radiofrequency group, a nonsignificant difference. No procedural deaths occurred in the study.

There were, however, several significant procedural differences. Procedure time averaged 124 minutes in the cryoablation group, nearly 20 minutes less than the 142 minutes for radiofrequency ablation. However, the 17-minute fluoroscopy time in the radiofrequency group was 5 minutes shorter than for cryoablation.

Dr Kuck said the study underestimates the true procedural differences because FIRE AND ICE was carried out by extremely experienced operators. In routine clinical practice involving non-elite operators, it's not unusual for radiofrequency ablation fluoroscopy times to be two or even three times longer than the 17 minutes seen in the study. Plus, FIRE AND ICE was conducted when the procedure entailed two applications of the cryoballoon. Now only one application is recommended, cutting an additional 12 minutes off the total procedure time, he added.

Radiofrequency ablation takes longer because it entails creating a series of point-to-point lesions in a circle to isolate the pulmonary veins. With cryoablation, the balloon is moved into position, inflated, and a 3-minute-freeze is administered to create a circle of necrotic tissue in a single-step procedure.

Discussant Dr Hugh G. Calkins praised the FIRE AND ICE investigators' use of a rigorous definition of recurrence that required as little as a 30-second episode of atrial arrhythmia.

"That's a very high bar, so I think the results are very impressive," said Dr Calkins, professor of medicine and of paediatrics and director of the cardiac arrhythmia service at Johns Hopkins University, Baltimore.

He commented that "this study is a clear reminder that 90% success rates just don't happen in this field," despite what some practitioners have claimed.

Asked how he predicts the study results will influence the field of AF ablation, Dr Kuck replied that he foresees much wider adoption of cryoablation and a stronger endorsement of the technology in updated guideline recommendations.

"I personally believe this will be the most important development in our field in the next several years," he added.

The electrophysiologist noted that even though current guidelines give a class Ia recommendation to catheter ablation of paroxysmal AF that's refractory to at least one antiarrhythmic drug, at present only 4% of such patients actually undergo the procedure.

"Having just 4% of patients with AF undergo catheter ablation cannot be what we are looking for as physicians," Dr Kuck said. "I believe if we want to roll out catheter ablation for AF, we need simple and safe tools. This trial elegantly shows that with a simpler device that allows single-shot isolation of the pulmonary veins, we can get the same safety and efficacy as with radiofrequency ablation. I often tell people that radiofrequency ablation of atrial fibrillation is the most challenging procedure in all cardiology. We do this procedure from the groin in a moving heart. It's a very complex technology."

His dream, he continued, is that cryoablation will eventually enable patients with atrial fibrillation to be managed the same way electrophysiologists treat patients with Wolff-Parkinson-White syndrome; with the first episode, the patient goes to the electrophysiology catheterisation lab for an ablation procedure.

"I think there's a great message here: The cryoballoon will move catheter ablation from a niche procedure performed in specialised centres by the few guys in the world who can do it really well out into the broader world. To do that you need a tool that is safe, simple, and can be handled by the average doctor," Dr Kuck said.

Discussant Dr Anthony DeMaria commented that it would be premature at this point to start thinking about cryoablation as a first approach to new-onset AF, given the roughly 35% clinical failure rate at 1 year seen in FIRE AND ICE. That rate doubtless would have been even higher had patients been equipped with implantable loop recorders, added Dr DeMaria, professor of medicine at the University of California, San Diego.

Dr Kuck conceded that the high recurrence rate is one of the great unsolved limitations of catheter ablation of AF.

"We don't know how to get the pulmonary veins permanently isolated," he said. "We can create acute lesions, but over time what we've seen is recovery of tissue and then reconduction by the pulmonary veins. I believe that 20% of the 40% recurrence rate is due to reconduction from the pulmonary veins, and the rest is probably due to triggers coming from other sites."

The FIRE AND ICE trial was funded in part by Medtronic, which markets the Arctic Front Advance cryoablation catheter used in the study. Dr Kuck reported serving on a speakers' bureau for Medtronic and acting as a consultant to Biosense Webster, Edwards, and St. Jude.

Simultaneous with Dr Kuck's presentation at ACC 16, the results of FIRE AND ICE were published online (*N Engl J Med* 2016 Apr 4. doi: 10.1056/NEJMoa1602014).

VIEW VIDEO

Fire and Ice – which catheter ablation approach is best in AF?

BY BRUCE JANCIN

The largest-ever randomised trial of catheter ablation for atrial fibrillation ended in a draw, but there may be a clear winner for some patients.

Safety and 1-year efficacy of radiofrequency ablation and cryoballoon ablation were roughly 65% in both treatment arms of the 769-patient Fire and Ice trial.

However, in an interview at the annual meeting of the American College of Cardiology, principal investigator Dr Karl-Heinz Kuck of Asklepios Klinik St. Georg, Hamburg, Germany, explains why the results are actually a victory for cryoablation.

Scan this QR code with your phone to view an interview with Dr Karl-Heinz Kuck.

DANAMI 3-DEFER: No benefit with delayed stenting for STEMI

BY SHARON WORCESTER

Delaying stent implantation in patients with ST-segment elevation myocardial infarction failed to reduce the rate of mortality, heart failure, myocardial infarction, or repeat revascularisation, compared with conventional percutaneous intervention in the randomised, controlled DANAMI 3-DEFER trial.

Among 1215 patients with ST-segment elevation MI (STEMI) who were randomised to receive either standard primary percutaneous coronary intervention (PCI) with immediate stent implantation or deferred stent implantation 48 hours after the index procedure, the rate of the primary composite endpoint of all-cause mortality, hospital admission for heart failure, recurrent infarction, or any unplanned revascularisation of the target vessel within 2 years was 18% in the immediate treatment group and 17% in the deferred stent implantation group, a nonsignificant difference, Dr Henning Kelbæk reported at the annual meeting of the American College of Cardiology.

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Procedure-related myocardial infarction, bleeding requiring transfusion or surgery, contrast-induced nephropathy, or stroke occurred in 5% and 4% of patients in the groups, respectively, he said.

Although some might be relieved to know there won't be a need for doing a second procedure, the findings are a disappointment in that preliminary findings suggested a benefit when stenting is delayed for several hours to several days after angioplasty, said Dr Kelbæk of Roskilde Hospital (Denmark).

The thinking was that medication given during the delay might help diminish residual blood clots, thereby reducing the risk of distal embolisation, which occurs in 7% of cases, and which can occur despite successful treatment of the culprit artery lesion by primary PCI with stent implantation, he explained, noting that slow- or no-flow occurs in 10% of cases.

It is possible that the study may not have been large enough to detect overall differences in the two treatment groups. It is also possible that patients at the highest risk for developing another arterial blockage could potentially benefit from a delay, especially given that a small but significant improvement in left ventricular function was detected 18 months after treatment among patients who underwent deferred stenting (left ventricular ejection fraction, 60% vs 57% in the immediate treatment group), but such patients were excluded from DANAMI 3-DEFER (the Third Danish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: Deferred stent implantation in connection with primary PCI), he said.

He added that he and his coinvestigators will "look carefully for possible 'hypothesis-generating' findings in subsets of patients – both those who might have benefited from the deferred-treatment strategy and, equally important, those in whom this strategy might have worsened their condition."

Patients were enrolled into DANAMI 3-DEFER during March 2011–February 2014 at four primary PCI centres in Denmark. All were adults with acute onset symptoms lasting 12 hours or less, and ST-segment elevation of 0.1 mV or more in at least 2 contiguous electrocardiographic leads, or newly developed left bundle branch block. Those in the deferred treatment group were only randomised to that group if stabilised flow could be obtained in the infarct-related artery. Median follow-up was 42 months.

The findings indicate that at this point, deferred stent implantation cannot be recommended as a routine procedure for STEMI patients treated with primary PCI, Dr Kelbæk concluded. The findings were published online simultaneously with the presentation (*Lancet* 2016 Apr 3. doi: 10.1016/S0140-6736[16]30072-1).

The DANAMI-3-DEFER trial was funded by the Danish Agency for Science, Technology and Innovation and Danish Council for Strategic Research. Dr Kelbæk reported having no disclosures.

High-dose vitamin D improves heart structure, function in chronic heart failure

BY JENNIE SMITH

High-dose oral vitamin D supplements taken for 1 year significantly improved cardiac structure and function in patients with chronic heart failure secondary to left ventricular systolic dysfunction, according to results from a new study.

However, the same study, led by Dr Klaus Witte of the University of Leeds (England), found that 6-minute walk distance – the study's primary outcome measure – was not improved after a year's supplementation with vitamin D.

It is unclear why vitamin D deficiency co-occurs in a majority of people with chronic heart failure (CHF) due to left ventricular systolic dysfunction (LVSD) or to what degree reversing it can improve outcomes. However, vitamin D deficiency is thought to interfere with calcium transport in cardiac cells, and may contribute to cardiac fibrosis and inflammation, leading to faster progression to heart failure following damage to cardiac muscle.

The new VINDICATE study randomised 223 patients with CHF due to LVSD and vitamin D deficiency to 1 year's treatment with 4000 IU of 25(OH) vitamin D3 daily, or placebo, Dr Witte and associates concluded at the annual meeting of the American College of Cardiology. The results were published online April 4 in *JACC* (doi: 10.1016/j.jacc.2016.03.508).

Of these patients, 163 completed follow-up at 12 months, and 6-minute walk distance (MWT) and echocardiography findings were recorded at baseline and follow-up.

Dr Witte and colleagues found significant evidence of improved function in the vitamin D–treated patients as measured by left ventricular ejection fraction +6.07% (95% confidence interval 3.20, 8.95; P < 0.0001); and a reversal of left ventricular remodelling (left ventricular end diastolic diameter –2.49 mm (95% CI –4.09, –0.90; P = 0.002) and left ventricular end systolic diameter –2.09 mm (95% CI –4.11; –0.06; P= 0.043).

The researchers also drew blood at 3-month intervals to check for serum calcium concentration, renal function, and vitamin D levels. Treatment was well tolerated, and no patients suffered hypervitaminosis or required a dose adjustment.

"There was no effect of vitamin D supplementation on the primary endpoint of 6 MWT distance but there were statistically significant, and prognostically and clinically relevant improvements in the secondary outcomes of left ventricular ejection fraction, dimensions, and volumes, suggesting that vitamin D is leading to beneficial reverse remodelling," the investigators wrote in their analysis.

The study's failure to meet its primary endpoint despite significant results from its secondary endpoints led Dr Witte and colleagues to say that its design led to underpowering.

"Variability in the walk distance measure at baseline was much greater than predicted from our pilot study such that our sample size only had 7% post hoc power to detect a difference between the groups," meaning it was underpowered to detect a clinically relevant change in walk distance. The findings "have implications for future studies using 6-minute walk distance as an outcome measure," they wrote.

The investigators championed the addition of vitamin D3 to CHF treatment regimens.

As new therapies for CHF are "often expensive, increasingly technical, and frequently fail to meet the rigorous demands of large phase III clinical trials," Dr Witte and colleagues wrote, vitamin D "might be a cheap and safe additional option for CHF patients and may have beneficial effects on multiple features of the syndrome."

The UK's National Institute for Health Research supported the study, and none of its authors declared conflicts of interest.

Similarities seen in rate and rhythm control for postsurgical AF

BY BRUCE JANCIN

Rate and rhythm control proved equally effective for treatment of new-onset post–cardiac surgery atrial fibrillation in a randomised trial that was far and away the largest ever to examine the best way to address this common and costly arrhythmia, Dr A. Marc Gillinov said at the annual meeting of the American College of Cardiology.

Thus, either strategy is acceptable. That being said, rate control gets the edge as the initial treatment strategy because it avoids the considerable toxicities accompanying amiodarone for rhythm control, most of which arise only after patients have been discharged from the hospital. In contrast, when rate control doesn't work, it becomes evident while the patient is still in the hospital, according to Dr Gillinov, a cardiothoracic surgeon at the Cleveland Clinic.

Atrial fibrillation (AF) is the most common complication of cardiac surgery, with an incidence variously reported at 20–50%. It results in lengthier hospital stays, greater cost of care, and increased risks of mortality, stroke, heart failure, and infection. Postoperative AF adds an estimated US$1 billion per year to health care costs in the United States.

While current ACC/AHA/Heart Rhythm Society joint guidelines recommend rate control with a beta-blocker as first-line therapy for patients with this postoperative complication, with a class I, level-of-evidence A rating, upon closer inspection the evidence cited mainly involves extrapolation from studies looking at how to prevent postoperative AF. Because no persuasive evidence existed as to how best to treat this common and economically and medically costly condition, Dr Gillinov and his coinvestigators in the US National Institutes of Health–funded Cardiothoracic Surgical Trials Network carried out a randomised trial 10-fold larger than anything prior.

The 23-site study included 2109 patients enrolled prior to cardiac surgery, of whom 40% underwent isolated coronary artery bypass grafting (CABG) while the other 60% had valve surgery, either alone or with CABG. These proportions reflect current cardiac surgery treatment patterns nationally. Overall, 33% of the cardiac surgery patients experienced postoperative AF. The incidence was 28% in patients who underwent isolated CABG but rose with increasing surgical complexity to nearly 50% in patients who had combined CABG and valve operations. The average time to onset of postoperative AF was 2.4 days.

A total of 523 patients with postoperative AF were randomised to rate or rhythm control. Rate control most often entailed use of a beta-blocker, while amiodarone was prescribed for rhythm control.

The primary endpoint in the trial was a measure of health care resource utilisation: total days in hospital during a 60-day period starting from the time of randomisation. This endpoint was a draw: a median of 5.1 days with rate control and 5.0 days with rhythm control.

At hospital discharge, 89.9% of patients in the rate control group and 93.5% in the rhythm control group had a stable heart rhythm without AF. From discharge to 60 days, 84.2% of patients in the rate control group and a similar 86.9% of the rhythm control group remained free of AF.

Rates of serious adverse events were similar in the two groups: 24.8 per 100 patient-months in the rate control arm and 26.4 per 100 patient-months in the rhythm control arm. Three patients in the rate control arm died during the 60-day study period, and two died in the rhythm control group.

Of note, roughly one-quarter of patients in each study arm crossed over to the other arm. In the rate control group, this was typically due to drug ineffectiveness, while in the rhythm control arm the switch was most often made in response to amiodarone side effects.

Roughly 43% of patients in each group were placed on anticoagulation with warfarin for 60 days according to study protocol, which called for such action if a patient remained in AF 48 hours after randomisation.

There were five strokes, one case of transient ischaemic attack, and four noncerebral thromboembolisms. Also, 21 bleeding events occurred, 17 of which were classified as serious; 90% of the bleeding events happened in patients on warfarin.

"I found the results very striking and very reassuring," said discussant Hugh G. Calkins. "To me, the clinical message is clearly that rate control is the preference."

It was troubling, however, to see that 10 thromboembolic events occurred in 523 patients over the course of just 60 days. "Should we be anticoagulating these postsurgical atrial fibrillation patients a lot more frequently?" asked Dr Calkins, professor of medicine and of paediatrics and director of the cardiac arrhythmia service at Johns Hopkins University, Baltimore.

Dr Gillinov replied that he and his colleagues in the Cardiothoracic Surgical Trials Network consider that to be the key remaining question regarding postoperative AF. They are now planning a clinical trial aimed at finding the optimal balance between stroke protection via anticoagulation and bleeding risk.

The US National Institutes of Health and the Canadian Institutes of Health Research funded the work. Dr Gillinov reported serving as a consultant to five surgical device companies, none of which played any role in the study.

Simultaneously with Dr Gillinov's presentation at ACC 16, the study results were published in the *New England Journal of Medicine* (doi: 10.1056/NEJMoa1602002).

PCSK9 inhibitor overcomes muscle-related statin intolerance

BY MITCHEL L. ZOLER

Statin-associated muscle symptoms are real for roughly 40% of patients with a history of this adverse effect, and for such patients who are truly unable to tolerate a statin treatment, a PCSK9 inhibitor provided an effective and well-tolerated alternative in a randomised trial with more than 500 patients.

"Controversy has surrounded the issue of statin-associated muscle symptoms because of large differences in the incidence of this disorder in randomised trials and observational studies. The GAUSS-3 study results demonstrate that muscle-related intolerance is reproducible during blinded statin rechallenge in a substantial fraction, about 40%, of patients with a history of symptoms," Dr Steven E. Nissen said at the annual meeting of the American College of Cardiology. "Alternative approaches to reducing low-density lipoprotein cholesterol in these patients represents an important medical priority."

Statin intolerance has been a challenging diagnosis for physicians to confirm because no biomarker exists to definitively document it, which led to this study to test a more systematic and objective approach to confirm the diagnosis, explained Dr Nissen, chairman of the department of cardiology at the Cleveland Clinic. GAUSS-3 (Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3), run at 53 centres worldwide, included two distinct phases.

In the first phase, researchers enrolled 511 patients with elevated LDL cholesterol levels who had a history of an inability to tolerate treatment with atorvastatin plus at least one other statin or at least three statins of any type. Following a 4-week washout period with no lipid-lowering treatments, they randomised patients to 10 weeks of 20 mg atorvastatin daily or placebo, followed by crossover to the alternative treatment for an additional 10 weeks. The patients averaged 61 years old, with an average LDL cholesterol level of 5.49 mmol/L.

During this phase, 43% of the patients reported having intolerable muscle symptoms while on atorvastatin, but not on placebo. In addition, 27% reported intolerable muscle symptoms while on placebo but not on atorvastatin, demonstrating the high incidence of psychosomatic muscle symptoms experienced by many patients with this history, Dr Nissen noted. This placebo-controlled statin rechallenge provides a model for how clinicians can reliably confirm which patients experience statin-specific muscle symptoms.

"This gives physicians a strategy for managing these patients. This was the best strategy we could use to find out who really has intolerance," Dr Nissen said.

The second phase included 218 patients who had their muscle symptoms confirmed in the first phase plus a small number of patients with a history of muscle-related statin intolerance who skipped the first phase because their serum creatinine kinase level was greater than 10-times above the upper limit of normal. The researchers randomised these patients to treatment with either a monthly subcutaneous injection with 420 mg of evolocumab or 10 mg of oral ezetimibe given daily. To maintain blinding, all patients received simultaneous placebo treatment that mimicked the drug they were not assigned to receive. The patients enrolled in the second phase had an average entry LDL cholesterol level of about 5.7 mmol/L.

After 24 weeks on treatment, patients on ezetimibe had an average 17% reduction in their LDL cholesterol level, while those on evolocumab had an average reduction of 53%. An LDL cholesterol level of less than 2.59 mmol/L was achieved in 2% of the ezetimibe patients and in 64% of those on evolocumab. Muscle-related symptoms occurred in 29% of the ezetimibe patients and in 21% of those on evolocumab, but discontinuations because of muscle symptoms were limited to 1 patient on evolocumab and 5 patients on ezetimibe, Dr Nissen reported. Concurrent with his report at the meeting, an article with the results appeared online (*JAMA* 2016 Apr 3. doi: 10.1001/jama.2016.3608).

"These findings show that it pays to be patient" when dealing with patients who report statin-associated muscle symptoms as more than half of them were able to tolerate the daily 20 mg atorvastatin challenge for 10 weeks, commented Dr Frederick A. Masoudi, a cardiologist and professor of medicine at the University of Colorado at Denver, Aurora. The report also "gives us a better approach for dealing with patients who have this nonspecific reaction to statin treatment, which remains the mainstay of cholesterol-lowering treatment."

Dr Nissen stressed that in his opinion, it is appropriate to use a PCSK9 inhibitor in this off-label way despite the controversial high cost for these drugs. "We have to do something for these patients who say that they cannot take a statin, but have multiple coronary disease risk factors and LDL cholesterol levels above 5.18 mmol/L. They are an accident waiting to happen. I am unwilling to leave patients with an LDL cholesterol of 5.18 mmol/L who can't take statins and just walk away."

GAUSS-3 was sponsored by Amgen, which markets evolocumab. Dr Nissen has received research grants from Amgen and several other drug companies. Dr Masoudi had no disclosures.

VIEW ON THE NEWS

Findings clarify muscle-related statin intolerance

Dr Nissen and his associates did a great job in this study of bringing much more clarity to the issue of muscle-related statin intolerance. Results from observational studies have suggested that this occurs in roughly 10–20% of patients who start treatment on a statin. The rate has often been much lower in randomised statin trials because statin-intolerant patients are often identified and excluded from participation during a run-in phase before the randomised phase begins.

The first phase of GAUSS-3 showed that significant and treatment-limiting myalgia in response to statin treatment is real, and affects about 40% of patients who have a history of reporting muscle pain while taking statins. This part of the study provides clinicians with an important message about how to determine whether a patient really has muscle-related statin intolerance, and also showed that controlled rechallenge with a statin can identify many patients who can tolerate a statin despite a history of intolerance.

The second phase of GAUSS-3 showed that most patients with a history of muscle-related statin intolerance could nicely tolerate treatment with an effective regimen of either ezetimibe or the PCSK9 inhibitor evolocumab. Evolocumab was especially effective, reducing patient levels of LDL cholesterol by more than 50%.

Currently, the US Food and Drug Administration-approved indications for treatment with PCSK9 inhibitors are limited to patients with familial hypercholesterolemia or with poorly-controlled LDL cholesterol levels and clinical atherosclerotic cardiovascular disease. That's because we still await reports of longer-term follow-up of studies designed to confirm the clinical benefits of lowering LDL cholesterol using a PCSK9 inhibitor. Results from these studies should be available within the next year.

Dr Roger Blumenthal is professor of medicine and director of the Ciccarone Center for the Prevention of Heart Disease at Johns Hopkins University in Baltimore. He had no disclosures. He made these comments in an interview.

VIEW VIDEO

Sapien 3 TAVR bests surgery in intermediate-risk patients

BY SHARON WORCESTER

Transcatheter aortic valve replacement (TAVR) using Sapien 3 – the latest-generation valve – is associated with low mortality, stroke, and paravalvular regurgitation rates at 1 year in intermediate-risk patients, and is superior to surgical valve replacement, according to findings from the SAPIEN 3 study.

The mortality rate at 1 year in the 1,077 patients in the observational study was 7.4% overall and 6.5% in a transfemoral access subgroup, the disabling stroke rate was 2.3%, the aortic valve reintervention rate was 0.6%, and the moderate/severe paravalvular regurgitation rate was 1.5%, Dr Vinod H. Thourani reported on behalf of the PARTNER trial investigators at the annual meeting of the American College of Cardiology. The findings were published simultaneously in *The Lancet* (2016 Apr 3. doi: 10.1016/So140-6736[19]30073-3).

A prespecified propensity score analysis comparing 963 SAPIEN 3 patients with 747 similar intermediate-risk patients from the PARTNER 2A trial who underwent surgical valve replacement showed that not only was Sapien 3 TAVR noninferior to surgery for the primary composite endpoint of mortality, strokes, and moderate or severe aortic regurgitation, it was also superior to surgery (pooled weighted proportion difference, –9.2% for each). The differences were highly statistically significant.

In fact, Sapien 3 TAVR "blew it out of the water" for both noninferiority and superiority vs surgery, Dr Thourani of Emory University, Atlanta said.

The propensity score incorporated 22 characteristics, and the analysis was conducted by blinded investigators. Even using the most conservative strategy for the analysis as approved by the US Food and Drug Administration, with the heaviest weighting against TAVR, Sapien 3 TAVR was superior to surgery for the primary composite endpoint, he noted.

Of note, while Sapien 3 TAVR was superior for the individual components of mortality and stroke from the composite endpoint, surgery was superior to Sapien 3 TAVR for the component of moderate or greater aortic regurgitation, he said.

However, the findings represent "strong evidence that in intermediate-risk patients with severe aortic stenosis, SAPIEN 3, compared to surgery, improves clinical outcomes and is the preferred therapy," he concluded.

In a video interview, he said that if approved by the US FDA, "this will become the impetus for [use in] a lower-risk population of patients. Currently we have the inoperative and high-risk patients, and this will open up the intermediate-risk patients for having transcatheter valve therapies, and I think it becomes exceedingly powerful."

Two ongoing industry-sponsored randomised trials in low-risk patients (those with a Society of Thoracic Surgeons score of less than 4) are underway, he noted.

Sapien 3 TAVR was previously shown to improve 30-day outcomes in intermediate-risk patients with severe aortic stenosis (*Eur Heart J* 2016 Mar 31. doi: 10.1093/eurheartj/ehw112), but longer-term data were lacking, and no comparisons with surgery in intermediate-risk patients were available.

For the current study, patients with a mean age of 82 years were evaluated at 51 centres in the United States and Canada during February-September 2014. Subjects had a median Society of Thoracic Surgeons score of 5.2% (range, 4-8) and 73% had New York Heart Association class III/IV heart failure. Almost 90% were treated via the transfemoral route, Dr Thourani said.

The Sapien 3 device is a balloon expandable valve that differs from prior-generation devices in that it has improved geometry of the trileaflet bovine pericardial valve, a longer cobalt alloy frame with more open outlet cells and denser inlet cells, a polyethylene terephthalate fabric skirt that provides an external circumferential seal to reduce paravalvular leak, four valve sizes, and lower-profile delivery catheters with more precise valve positioning inserted through 14 or 16 French sheaths for increased use of transfemoral access.

Discussant Dr David E. Kandzari, director of interventional cardiology and chief scientific officer at Piedmont Heart Institute, Atlanta, congratulated Dr Thourani and his colleagues on "a terrific trial and impactful result."

"There are, with regard to the Sapien 3 technology, many reasons to believe that this could be an advancement above existing predicate technologies," he said, specifically mentioning the improvements in the device, compared with prior generations, such as the modification to reduce paravalvular leak, which has been associated with worse outcomes for patients.

"In parallel, there were changes in practice, and one of them implemented in the context of SAPIEN 3 was the use of [computed tomography] imaging to help guide and inform the procedure itself," he said, adding that the results of the trial "really open the door for at least two very broad pathways."

First, they expand TAVR to intermediate-risk patients.

"Secondly, they lead the way even further with greater reassurance toward two large ongoing clinical trials in patients considered at low risk, as well," he said.

The remarkable outcomes in regard to mortality and stroke are "clinically meaningful and some of the best outcomes we've ever witnessed with transcatheter therapy," he said.

This study was funded by Edwards Lifesciences. Dr Thourani disclosed that he has received consulting fees and/or research grants from Edwards Lifesciences, St. Jude Medical, Abbott Medical, Boston Scientific, Claret Medical, DirectFlow, Medtronic, and Sorin. Dr Kandzari has received consultant fees and honoraria from Boston Scientific, The Medicines Company, and Medtronic.

Scan this QR code with your phone to view this interview.

ACEI: angiotensin-converting enzyme inhibitor; CV: cardiovascular; HF: heart failure; NYHA: New York Heart Association; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; RRR: relative risk reduction.

PBS Information: This product is not listed on the PBS.

See TGA approved Product Information before prescribing. TGA approved Product Information available on request. For the most up to date Product Information go to http://www.novartis.com.au/products_healthcare.html.

MINIMUM PRODUCT INFORMATION Entresto (sacubitril/valsartan) Indication: Treatment of chronic heart failure (NYHA Class II-IV) with reduced ejection fraction. **Contraindications:** Hypersensitivity to sacubitril, valsartan, or excipients. ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor. Angioedema related to previous ACE inhibitor or ARB therapy. Use with aliskiren in patients with Type 2 diabetes. Severe hepatic impairment, biliary cirrhosis and cholestasis. Pregnancy. **Precautions:** Dual blockade of the Renin-Angiotensin-Aldosterone System (RAAS): Do not administer with an ACE inhibitor due to the risk of angioedema. Do not initiate until 36 hours after taking the last dose of ACE inhibitor therapy. If treatment is stopped, ACE inhibitor therapy must not be initiated until 36 hours after the last dose. Caution is required while co-administering with direct renin inhibitors such as aliskiren. Do not administer with aliskiren in patients with Type 2 diabetes. Should not be co-administered with an ARB. Hypotension: May cause symptomatic hypotension, especially in patients ≥75 years old, patients with renal disease and in patients with systolic BP <112 mmHg. Use in patients with systolic BP <100 mmHg at the time of initiation is not recommended. Monitor BP when initiating therapy or during dose titration, Patients with an activated RAAS, such as volume- and/or salt-depleted patients (e.g., high doses of diuretics), are at greater risk. If hypotension occurs, dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g. hypovolaemia) should be considered. If hypotension persists, consider dose reduction or temporary discontinuation. Sodium and/or volume depletion should be corrected before starting treatment. Impaired renal function: May be associated with decreased renal function. In patients whose renal function depends upon the activity of the RAAS (e.g., severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Assess renal function before initiation and during treatment. Closely monitor serum creatinine, and down-titrate or interrupt in patients who develop a clinically significant decrease in renal function. May increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function. Patients with mild and moderate renal impairment are more at risk of developing hypotension. Patients with severe renal impairment may be at greatest risk of hypotension. Caution with severe renal impairment. Not recommended with end-stage renal disease. Hyperkalaemia: Should not be initiated if the serum potassium level is >5.4 mmol/l. Hyperkalaemia may occur. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption may be required. Medications known to raise potassium levels (e.g. potassium-sparing diuretics, potassium supplements) should be used with caution. If clinically significant hyperkalaemia occurs, measures such as reducing dietary potassium, or adjusting the dose of concomitant medications should be considered. In addition, if serum potassium level is >5.4 mmol/l, discontinuation should be considered. Angioedema: If angioedema occurs, immediately discontinue, and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms. Patients with a prior history of angioedema may be at higher risk, caution is recommended. Black patients may have increased susceptibility to develop angioedema. Patients with renal artery stenosis: Caution and monitoring of the renal function is recommended. Patients with NYHA functional classification IV: Caution should be exercised. Patients with hepatic impairment: Caution in patients with moderate hepatic impairment or with AST/ALT values more than twice the upper limit of the normal range, exposure may be increased and safety is not established. Do not use in patients with severe hepatic impairment, biliary cirrhosis or cholestasis. Caution in driving or operating machinery. Use in lactation: Not recommended. Females of child-bearing potential: Use contraception during treatment and for 1 week after their last dose. **Interactions:** Aliskiren in patients with Type 2 diabetes, ACE inhibitors/ARB. Caution with statins, sildenafil, lithium, potassium-sparing diuretics including mineral corticoid antagonists (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium, NSAIDs including selective COX-2 Inhibitors, frusemide, inhibitors of OATP1B1, OATP1B3, OAT3 (e.g. rifampin, cyclosporine) or MPR2 (e.g. ritonavir) and metformin. **Dosage and administration:** Target dose one oral tablet of 97 mg/ 103 mg twice daily. Starting dose is one tablet of 49 mg/ 51 mg twice daily. Starting dose of one tablet of 24 mg/ 26 mg taken twice daily is recommended for naive patients or those not currently taking an ACE inhibitor/ARB, patients with severe renal impairment, patients with moderate hepatic impairment, and in patients ≥ 75 years old. Also consider for patients who have risk factors for hypotension and patients with low systolic BP ≥100 to 110 mmHg. Double every 2-4 weeks to the target dose. **Side effects:** Very common (≥10%): Cardiac failure, hyperkalaemia, renal impairment and hypotension. Common (1 to <10%): Anaemia, angina pectoris, atrial fibrillation, cardiac failure chronic, cardiac failure congestive, ventricular tachycardia, constipation, diarrhoea, nausea, asthenia, cardiac death, fatigue, non-cardiac chest pain, oedema peripheral, bronchitis, influenza, nasopharyngitis, pneumonia, upper respiratory tract infection, urinary tract infection, diabetes mellitus, gout, hyperuricaemia, hypokalaemia, arthralgia, back pain, pain in extremity, dizziness, headache, syncope, insomnia, renal failure, chronic obstructive pulmonary disease, cough, dyspnoea and hypertension. (*ent200116m*).

References: 1. ENTRESTO® Product Information. TGA-approved Product Information. Novartis Pharmaceuticals Australia Pty. January 2016. **2.** McMurray JJ *et al. N Engl J Med* 2014;371:993–1004. **3.** Vardeny O *et al. JACC Heart Fail* 2014;2:663–70.

Novartis Pharmaceuticals Pty Limited. 54 Waterloo Road, Macquarie Park NSW 2113. Ph (02) 9805 3555. For medical enquiries please **contact 1800 671 203 (phone) or medinfo.phauno@novartis.com (email).** ENT0029. NOV4627/UC. Prepared February 2016.

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Stem cells show heart failure benefits in phase II trial

BY MITCHEL L. ZOLER

After rattling around in early-stage clinical studies for more than a decade, stem cell therapy for heart failure may have finally gained the efficacy evidence to send it to the next level: large-scale, phase III trials.

Patients with ischaemic cardiomyopathy and severe heart failure showed a statistically significant 37% relative reduction in their combined rate of death and cardiovascular hospitalisation during 1 year of follow-up after autologous stem cell injections to their left ventricular myocardium in a multicentre, fully blinded control, phase II trial with 109 North American patients.

The treatment used a technique in commercial development by Vericel that selectively expands ex vivo bone marrow cells taken from the heart failure patient. Clinicians inject 0.4 mL aliquots of the expanded cells – enriched for mesenchymal stem cells and M2 macrophages – via a transcatheter approach into the left ventricular myocardium using 12–17 injections per patient. The bone marrow preparation during ex vivo expansion is called ixmyelocel-T.

This treatment now needs testing in more patients, Dr Timothy D. Henry said at the annual meeting of the American College of Cardiology. "We need a new generation of cell trials in larger studies with completely double-blind, placebo controls using a more uniform preparation of cells," said Dr Henry.

"To the best of our knowledge, ixCELL-DCM is the largest randomised, double-blind clinical trial to date for cell therapy use in congestive heart failure," said Dr Henry and his associates in their report. The concept of stem cell therapy to replace damaged myocardium "has been very attractive, but most clinical trials to date have been small and unblinded, and used unselected bone marrow cells," explained Dr Henry, director of cardiology at the Cedars-Sinai Heart Institute in Los Angeles.

The ixCELL-DCM study ran at 31 sites in the United States and Canada. About 90% of patients had New York Heart Association class III disease, the average left ventricular ejection fraction was about 25%, patients on average would cover about 310 m during a 6-minute walk test, and the average serum level of NT-ProBNP was about 1,900 pg/L. Patients in the control arm all underwent the same bone marrow retrieval and transcatheter injection into the left ventricle, but the injections only contained carrier material without active cells.

The primary endpoint of death or a cardiovascular event, primarily hospitalisation, occurred at a rate of 110 events per 100 patient years during 1-year follow-up of 51 patients in the sham-treatment group. In the active-treatment arm, the endpoint occurred at a rate of 70 events per 100 patient years among 58 patients. The difference was primarily driven by a 3% death rate with cell therapy, compared with a 14% rate in the controls, and a 38% hospitalisation rate, compared with a 47% rate among controls.

> **Patients with ischaemic cardiomyopathy and severe heart failure showed a statistically significant 37% relative reduction in their combined rate of death and cardiovascular hospitalisation during 1 year of follow-up after autologous stem cell injections to their left ventricular myocardium in a multicentre, fully blinded control, phase II trial.**

The study results appeared online concurrent with Dr Henry's report (*Lancet* 2016 Apr 5. doi: 10.1016/S0140-6736[16]30137–4).

The results showed no significant differences between the active and sham groups for changes in left ventricular size, ejection fraction, and 6-minute walk distance.

"This trial was designed to look at events. It is not a cause for concern that we did not see effects on heart function," Dr Henry said. The current results were also generally consistent with results from two earlier, controlled, phase II studies with a total of 61 patients (*Circ Res* 2014 Sep 26;115[8]:730–7).

In the safety analysis, done in 114 patients, the rates of all adverse events and major adverse cardiovascular events were similar in the two arms. The rate of serious adverse events was significantly reduced in the patients treated with expanded bone marrow cells, compared with the controls.

The high rate of death and hospitalisation of patients with severe heart failure "is a very large, unmet need, so it's a natural to go to a larger trial," Dr Henry said. "The cell preparation was very safe and easy to do."

Another pressing research issue is to try to understand the mechanism by which the cell treatment improves clinical outcomes, with improved heart function or improved exercise capacity apparently excluded as mechanisms.

The trial was sponsored by Vericel, the company developing the ex vivo protocol for selective marrow cell expansion. Dr Henry has been a consultant to or received honoraria from Abbott Vascular, Baxter, Capricor, Cytori, Eli Lilly, and the Medicines Company, and he has received research grants from Aastrom, Baxter International, Mesoblast, and Vericel.

VIEW ON THE NEWS

Results merit phase III trial follow-up

The results reported by Dr Henry come from one of the first trials of stem cell or bone marrow treatment of failing hearts that used clinical outcomes as the primary endpoint. In contrast, prior studies focused on changes in functional characteristics of patients, such as 6-minute walk distance or left ventricular ejection fraction or size. What makes Dr Henry's study distinctive is that it showed benefit for a clinical outcome: the rate of death or cardiovascular hospitalisation.

Another distinct difference, compared with the vast majority of earlier trials, was the way the bone marrow was handled prior to placement in a heart. The bone marrow cells underwent a 12-day period of ex vivo treatment designed to expand the content of certain mesenchymal stem cells and macrophages.

The current study was also larger than most prior reported studies, with 114 randomised patients available for the safety analysis and 109 for the efficacy analysis. But by no means was this a large study; in fact, it is relatively small. Although it produced a statistically significant result for the primary endpoint, the efficacy needs expanded testing in larger numbers.

It's currently unclear how the expanded bone marrow cell injections improve clinical status and lead to reduced deaths and hospitalisation. The results show essentially no impact from the treatment on ejection fraction or 6-minute walk distance, raising the question of what alternative mechanisms link this treatment to improved clinical outcomes.

Until now, it has not been possible to move beyond early-stage trial designs for cell therapy of failing hearts. Now, for the first time, we have study results that suggest a phase III trial is indicated.

Dr John A. Jarcho is a deputy editor of the New England Journal of Medicine and a cardiologist at Brigham and Women's Hospital, both in Boston. He had no disclosures. He made these comments as a discussant of Dr Henry's report and in an interview.

Ticagrelor cuts post-MI events in diabetes patients

BY MITCHEL L. ZOLER

The benefit from dual-antiplatelet therapy in high-risk patients following a myocardial infarction was especially apparent in post-MI patients with diabetes in a prespecified secondary analysis from a multicentre trial of ticagrelor with more than 21,000 patients.

Among post-MI patients with diabetes, treatment with ticagrelor plus aspirin led to an absolute 1.5% reduction in the rate of cardiovascular death, MI, or stroke during a median 33-month follow-up, compared with an absolute 1.1% cut in patients without diabetes, Dr Deepak L. Bhatt said at the annual meeting of the American College of Cardiology. The relative risk reduction, compared with placebo was 16% in both the diabetes and no diabetes subgroups, statistically significant differences in both subgroups.

"Long-term treatment with ticagrelor reduced the composite of cardiovascular death, MI, or stroke in diabetic patients with a greater absolute risk reduction than in nondiabetic patients," said Dr Bhatt, professor of medicine at Harvard Medical School and executive director of Interventional Cardiovascular Programs at Brigham and Women's Hospital in Boston. Treatment with ticagrelor plus aspirin in post-MI patients with diabetes also led to an increased number of major bleeding episodes, compared with patients on aspirin alone, but no excess of intracerebral hemorrhages or fatal bleeds, he noted.

This finding of a significant benefit from ticagrelor in post-MI patients with diabetes confirms similar, prior findings with other antiplatelet drugs (including clopidogrel, prasugrel, and vorapaxar) and prior findings with ticagrelor, Dr Bhatt noted.

The new analysis used data collected in the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. The primary results from PEGASUS-TIMI 54 had shown that adding ticagrelor to aspirin treatment of high-risk post-MI patients, including those who both had or did not have diabetes, significantly cut the composite rate of cardiovascular death, MI, and stroke, compared with aspirin alone (*N Engl J Med* 2015 May 7;372[19]:1791-800). The study group included 6,806 patients with diabetes (type 2 diabetes in 99% of these patients), and 14,355 without diabetes. All patients had their MI 1-3 years before entering the study.

Dr Bhatt and his associates examined the incidence of the various clinical endpoints measured in the study among only the patients with diabetes divided into those who received any dosage of ticagrelor (60 mg b.i.d. or 90 mg b.i.d.) or placebo, and also among the patients without diabetes. In addition to the primary endpoint, the new analysis showed that the rate of cardiovascular death during follow-up was 3.9% in the diabetes patients on dual therapy and 5.0% among the diabetes patients on aspirin only, a 22% relative risk reduction with ticagrelor added that was statistically significant. In contrast, among patients without diabetes the rates of cardiovascular death between those on and not on ticagrelor only differed by 0.2%, a 9% relative risk reduction that was not statistically significant. The same pattern occurred for the endpoint of death from coronary artery disease.

Concurrent with Dr Bhatt's report, the results appeared in an article published online (*J Am Coll Cardiol* 2016 Apr; doi: 10.1016/S0735-1097[16]30023-7).

A new study, THEMIS, is examining the safety and efficacy of combined ticagrelor and aspirin treatment in a lower-risk group of patients with diabetes, those with coronary artery disease who have not had a prior MI. Those results may be available in 2018.

PEGASUS-TIMI 54 was sponsored by AstraZeneca, the company that markets ticagrelor. Dr Bhatt has been an advisor to Cardax and Regado Biosciences and has received research support from AstraZeneca and several other companies.

Pre-PCI beta-blockers offer no clinical benefit

BY SHARON WORCESTER

Early intravenous administration of the beta-blocker metoprolol before primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction (STEMI) was safe but did not reduce infarct size in the randomised, placebo-controlled Early-BAMI trial.

No difference was seen in infarct size, as measured by magnetic resonance imaging at 30 days, between 336 patients with STEMI who presented within 12 hours of symptom onset and were randomised to receive intravenous metoprolol (2 vials with 5 mg) before undergoing angioplasty, and 347 such patients who received placebo (left ventricular volume, 15.3% and 14.9%, respectively), Dr Vincent Roolvinkof Isala Hospital, Zwolle, the Netherlands, reported at the annual meeting of the American College of Cardiology.

No differences were seen between the groups for the secondary endpoints of blood flow from the left ventricle or levels of cardiac enzymes, Dr Roolvink noted.

Further, while significantly fewer cases of ventricular arrhythmia occurred in the metoprolol patients (3.6% vs 6.9%), this difference was not clinically significant, he said.

No significant differences were seen with respect to safety endpoints, including abnormally slow heart rate, low blood pressure, or cardiogenic shock.

The Early-BAMI subjects had a mean age of 62 years, and most (75%) were men. They were enrolled at centres throughout the Netherlands and Spain.

"In this nonrestricted STEMI population, early intravenous metoprolol before primary percutaneous intervention did not reduce infarct size," Dr Roolvink said, noting that the findings follow conflicting results from prior studies, with some suggesting that beta-blockers could reduce heart attack severity or improve blood flow from the left ventricle when given to STEMI patients prior to angioplasty.

However only one randomised trial took place in the primary percutaneous coronary intervention era, and that trial – METOCARD-CNIC (Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction) – involved only patients with STEMIs involving the anterior wall of the left ventricle (*J Am Coll Cardiol* 2014;63[22]:2356–62).

Early-BAMI (The Effect of Early Administration of Intravenous Beta Blockers in Patients with ST-elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention) was the first double blind, placebo-controlled international multicentre study to test this approach.

"Our results do not confirm the effect observed in the METOCARD-CNIC trial," Dr Roolvink said.

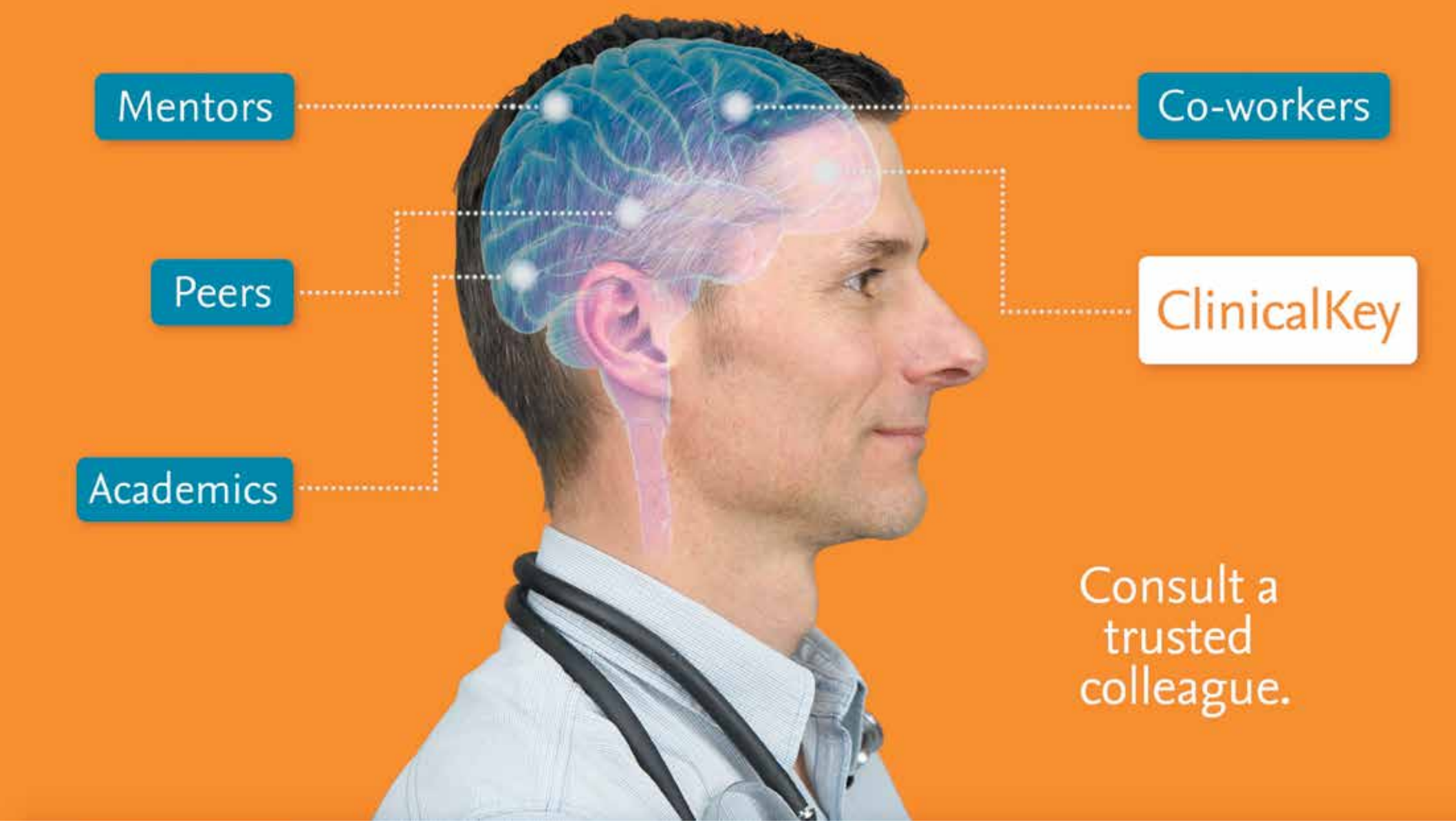
> **Additional large randomised trials are needed to clarify whether early beta-blocker treatment is of benefit before angioplasty in STEMI patients.**

He noted, however, that the current findings are limited by the fact that study subjects had lower than expected overall heart attack severity.

Additional large randomised trials are needed to clarify whether early beta-blocker treatment is of benefit before angioplasty in STEMI patients. The safety profile, low cost of beta-blocker administration, and the reduction of acute malignant arrhythmias among those receiving beta-blocker treatment in the current trial should encourage the performance of additional larger trials, he said.

The findings were simultaneously published online (*J Am Coll Cardiol* 2016 Apr 3. doi:10.1016/j.jacc.2016.03.522)

Early-BAMI was funded by the Dutch Heart Foundation and Medtronic. Dr Roolvink reported having no disclosures.



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