

ESC Congress News



PARIS

ESC CONGRESS 2011

30 AUGUST

Further information reported from the SHIFT trial

Ivabradine's significant effect on cardiac remodelling in HF

CLINICAL TRIAL UPDATE

By Janet Fricker
ESC Congress News

IVABRADINE reverses cardiac remodelling in patients with heart failure and left systolic dysfunction, according to data from the SHIFT trial presented in the Clinical Trial Update session yesterday. This latest echocardiographic report from the SHIFT investigators, published simultaneously in the *European Heart Journal*, shows that heart rate reduction with ivabradine led to marked reductions in ventricular volumes and significant improvement in left ventricular ejection fractions.

Study presenter Jean-Claude Tardif, from the University of Montreal, Quebec, Canada, said the results suggest that ivabradine modifies disease progression in patients with HF receiving background therapy. He added that the results will have important clinical implications, since cardiac remodelling is a central feature of heart failure progression.

Initial results from the SHIFT (Systolic Heart failure treatment with the If inhibitor ivabradine) trial, first presented at ESC Congress 2010, showed that treatment with ivabradine, when added to standard therapy in patients with chronic HF and elevated heart rates, led to an 18% reduction in the endpoint of CV death/HF hospitalisation ($P < 0.0001$) and significantly reduced the risk of cardiovascular death and hospital admission.

Cardiac remodelling is central to the pathophysiology of HF and an established prognostic factor. The therapeutic effects of beta-blockade, ACE inhibition and cardiac resynchronisation therapy have all been linked to cardiac remodelling, thereby making it a relevant target for novel HF therapies.

In the SHIFT trial 6500 patients with moderate to severe chronic heart failure and documented LV systolic dysfunction (LVEF $< 35\%$) receiving background therapy for HF (including a beta-blocker) were randomised to ivabradine (5 mg bid) or placebo. Now, for the current remodelling sub-study 611 patients (304 on ivabradine and 307 placebo) were assessed by echocardiography. The primary endpoint was the change in left ventricular end-systolic volume index (LVESVI) between baseline and eight months.

Results showed that at eight months there was a LVESVI change of 13 mL in the

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Jean-Claude Tardif presenting results from the SHIFT study yesterday.

Non-inferiority of everolimus stent found in large-scale trial

By Helen Saul
ESC Congress news

The everolimus eluting stent (EES) was shown to be non-inferior to the sirolimus stent (SES) with respect to target-lesion revascularisation and angiographic in-segment late loss at eight to 12 months, according to the RESET trial reported in yesterday's Hot Line session.

Although SES is no longer widely used, said study presenter Professor Takeshi Kimura (pictured right) from Kyoto University Hospital in Japan, it represents the most extensively studied first generation drug eluting stent (DES), and should therefore be regarded as a benchmark for all current and future generation DES.

The Randomised Evaluation of Sirolimus-eluting versus Everolimus-eluting stent Trial (RESET) trial, randomised 3197 patients between February and July 2010 to either EES (n=1567) or SES (n=1600). An angiographic sub-study



evaluating in-segment late lumen loss and angiographic restenosis was performed at eight months in 571 patients.

Subjects were enrolled from 100 Japanese centres, and this all-comers study constitutes the largest trial comparing EES with SES to date.

Results for target lesion revascularisation procedures at one year were 65 (4.3%) in the EES group and 76 (5.0) in the SES group (P non-inferiority < 0.0001). Furthermore, the cumulative distribution curves for

Continued on page 2

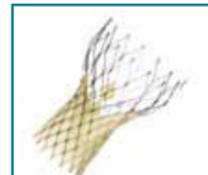
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Please visit the stand of the European Heart for Children humanitarian project. Fifty children, most with congenital heart disease, have now had life-saving surgery thanks to your support for this deserving charity

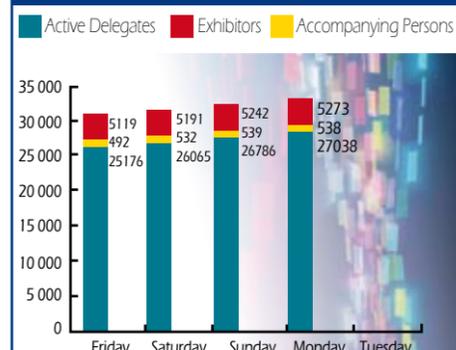


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ATTENDANCE



CABG preferred over PCI in triple vessel registry study



Patients with triple vessel disease benefit more from CABG than from PCI, according to results from a Hot Line presentation yesterday; PCI was associated with a significantly higher risk of a composite of all-cause death, MI and stroke.

The results from the CREDO-Kyoto PCI/CABG Registry Cohort-2

study confirm ESC guidelines for myocardial revascularisation that, except where patients have a low SYNTAX score, CABG should be the preferred option.

Presenting the data, Dr Hiroki Shiomi (pictured above) from the Kyoto University Hospital in Japan, said: "The use of PCI in patients with high SYNTAX scores should be discouraged, unless their operative risk is particularly high."

The Japanese registry comprised the largest ever study population of triple vessel disease patients with SYNTAX score assessment. It was a physician-initiated non-company sponsored registry study, which, between January 2005 and December 2007, enrolled more than 15,000 consecutive patients having a first coronary revascularisation; 2981 patients with triple vessel disease were included in the new analysis.

At three years, PCI was associated with a higher risk than CABG in the primary endpoint, a composite of all-cause death, MI and stroke (HR 1.47; 95% CI 1.13-1.92, $p=0.04$). Risk of MI in the PCI group was more than double that of CABG patients (HR 2.39; 95% CI 1.31-4.36, $p=0.004$). Risk of cardiac death or stroke was not significantly different between the two groups.

In contrast with the SYNTAX study, CREDO found that, even among patients with a low SYNTAX score, PCI was still associated with a significantly higher risk of the composite endpoint. One potential explanation for this, Dr Shiomi said, is the different characteristics of the study group; for example, that patients in CREDO were 70 years-old on average, compared to 65 years in the SYNTAX group.

Because of the inconsistencies between the studies, Dr Shiomi said that it is too early to recommend surgery in all low risk patients: "Our results certainly suggest that even in patients with a low SYNTAX score, the superiority of CABG was significant," he said. "However, in clinical practice, we would select on the basis of patient comorbidities and general health status."

Remote ICD follow-up proves safe alternative

By Helen Saul
ESC Congress news

THE REMOTE follow-up of patients with ICDs appears to be safe, and a large French trial found no significant difference in outcome between patients who were tele-monitored and those who had conventional check-ups in the clinic. However, the trial failed to confirm the non-inferiority of the new technology.

Presenting results from the Evaluation of tele-follow up, or EVATEL, trial at yesterday's Hot Line session, Professor Philippe Mabo from the University Hospital of Rennes, France, said: "The remote follow-up of patients implanted with an ICD seems to be a safe alternative to conventional in-office follow-up."

The EVATEL study included 1501 patients with ICDs from 30 centres in France. They were enrolled between 2008 and 2010 and each was followed for a year. The primary endpoint of the study was a composite of death from all causes, cardiovascular hospitalisation, and ineffective or inappropriate therapy delivered by the device.

Of the patients seen every three months at an implant centre, 28.5% met the primary endpoint, compared with 30.2% of those followed remotely. There were no statistically significant differences between the two groups in one year survival, or the time to the first primary endpoint. Remote patients received fewer inappropriate therapies than controls.

The rationale behind the study was that conventional follow-up appointments are carried out regularly every three months and the timing of an appointment is not linked to a clinical event or device malfunction. By contrast, new technologies by which information is transmitted by phone from the patient's home to the implant centre allow constant updates on the ICD's function, battery status or ineffectively delivered therapy. Physicians are alerted to problems as they occur.

The trial was set up with a strict non-inferiority margin of 5%, and could not conclude that remote monitoring is non-inferior to conventional check-ups. Despite this, Mabo said that remote monitoring is ready for widespread use, though more studies need to be done: "We have many questions to solve, including the problem of reimbursement for the medical community, at least in France."



Philippe Mabo: Study failed to confirm non-inferiority of remote ICD telemonitoring.

Reimbursement from the healthcare system will be needed."

● A second French study, ECOST (Effectiveness and Cost of ICD follow-up using remote monitoring), similarly examined the remote monitoring of ICDs. It found that remote monitoring was associated with a 72% reduction in the risk of hospitalisation for inappropriate shocks, compared to controls receiving conventional office-based care.

Professor Salem Kacet from the Regional University Hospital of Lille, France, said at yesterday's session: "ECOST is the first trial to show that daily home monitoring follow-up could reduce inappropriate shocks with a significant impact on battery longevity of ICDs."

He also acknowledged that more research is needed: "We have demonstrated that we improve the device management but I think it's another thing to demonstrate the superiority of remote monitoring to the disease management of the patient. It's the next step."

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Clinical Trial Update: SHIFT trial

ivabradine group compared with no change in the placebo group ($P<0.001$).

In an accompanying commentary published in the *EHJ*, Friedrich Fruhwald and Burkert Pieske from the Medical University Graz, Austria, wrote that, although neurohumoral blockers of the renin-angiotensin and sympathico-adrenergic systems improve ventricular geometry and survival, "there is now a further possibility to do so by adding ivabradine to these drugs". In contrast to cardiac resynchronisation, they add, treatment with ivabradine can be started by every heart failure physician without great expense. "However . . . it works only in patients with sinus rhythm and, realistically only in a third of them."

● An additional quality of life sub-study also performed in SHIFT trial patients and presented during yesterday's Clinical Trial Update session suggests that lowering heart rate with ivabradine is also associated with improvements in quality of life.

The study, performed by Inger Ekman from the University of Gothenburg in Sweden assessed 1944 patients (968 on ivabradine and 976 placebo) according to the Kansas City Cardiomyopathy Questionnaire (KCCQ) at baseline, four and 12 months.

Results at 12 months showed quality of life was better preserved in the ivabradine group than in the placebo group ($P=0.018$). Furthermore, the incidence of clinical events (cardiovascular death or hospital admission for HF) was inversely associated with quality of life scores.



Inger Ekman: Quality of life results from SHIFT trial

"The present analyses suggest that the ivabradine-associated reduction in the severity of HF, as reflected by reduced hospital admissions and improved NYHA functional class, also translates into a favourable impact on HQoL," said Ekman. In contrast, she added, treatment with beta-blockers associated with similar reductions in heart rate and heart failure mortality have not been associated with improvements in quality of life.

Continued from page 1

RESET trial

in-segment late loss were 0.03 mm for the SES stent versus 0.07 for the EES stent (P non-inferiority <0.0001) and in-stent late loss was 0.14 for the SES and 0.16 for the EES ($P=0.53$).

In a prespecified subgroup analysis no statistical difference was found for target lesion revascularisation between the two groups in diabetic patients, those over 75, and those having hemodialysis. The subgroup analysis, however, did show that in diabetic patients treated with insulin use of the EES was associated with significantly lower target lesion revascularisation ($P=0.03$); and a trend favouring the SES was found in patients with multivessel disease having PCI ($P=0.07$).

"One year clinical outcome after both EES and SES use was excellent, with low rates of target-lesion revascularisation and very low rates of stent thrombosis," said Kimura.

Longer-term follow-up, he added, was important to address whether EES could positively affect the late adverse events beyond one year reported after SES implantation, such as late restenosis and very late stent thrombosis. He said that, despite the all-comers trial design, the population enrolled in the study represented a relatively low-risk group of patients, resulting in lower event rates than anticipated. Future stent trials, he added, should now focus on more complex patients in whom CABG could be considered a reasonable alternative.

The management of CVD during pregnancy: still questions



By Christi Deaton
University of Manchester
Manchester, UK



and Helmut Baumgartner
University Hospital Munster
Münster, Germany

and in some cases include life-threatening conditions for mother and child. In Europe maternal heart disease has become the major cause of maternal death during pregnancy.

In addition, pregnancy can have a negative impact on the long-term course of heart disease. Therefore, careful screening for heart disease, appropriate risk assessment and counselling are crucial. The "general considerations" section of the guidelines provides a practical approach for this purpose. This section also includes background on physiological changes of pregnancy and their consequences, genetic aspects, considerations for interventions during pregnancy, mode of delivery and methods of contraception.

The guidelines emphasise that pregnant patients with cardiovascular disease are managed by interdisciplinary teams, with high-risk patients recommended for treatment in specialist centres. Diagnostic procedures and interventions should be performed by specialists with great expertise in the individual techniques and experience in treating pregnant patients. The guidelines also emphasise that registries and prospective studies are urgently needed to improve the state of knowledge.

A special section on drugs during pregnancy and breastfeeding includes a list of the most commonly used drugs in heart disease. Eight sections provide precise information for specific disease groups: congenital heart disease, aortic

disease, valvular heart disease, coronary artery disease, cardiomyopathies, arrhythmias, hypertensive disorders and venous thromboembolism.

Several issues will remain controversial. While there is agreement that severe pulmonary hypertension (as well as severe symptomatic left heart obstruction, severe impairment of systemic ventricular function, poor NYHA function class III/IV and severe dilation of the ascending aorta) is a contraindication for pregnancy, it is not clear when the risk becomes acceptable in the presence of less severe pulmonary hypertension. Unfortunately, conclusive data are still lacking and make precise recommendations impossible.

The recommendations for anticoagulation in pregnant patients with prosthetic heart valves will certainly be of interest. While there is agreement that oral

anticoagulation is the treatment of choice during the second and third trimesters, strategy during the first trimester remains controversial.

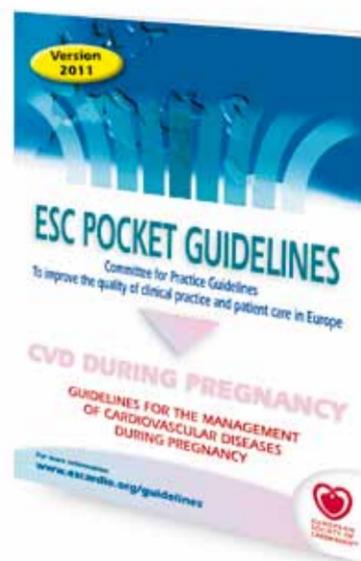
Careful weighing of risk and benefit for both mother and child appears to favour continuation of treatment, particularly when the drug dose is low. Most importantly, whenever oral anticoagulation is discontinued (either between week 6 and 12 or before delivery) adequate dose adjustment of heparin is critical.

THE NEW ESC Guidelines on the management of cardiovascular diseases during pregnancy will be introduced at a full session this morning.

Pregnancy in the presence of heart disease has always been a major concern and many uncertainties exist in daily clinical practice. An ESC expert consensus document was first published in 2003, and this new document updates the data and provides comprehensive guidelines for the pre-pregnancy counselling of women with heart disease and for the management of any cardiovascular disease during pregnancy and delivery, as well as postpartum.

Since prospective or randomised studies are the exception in this field, most recommendations correspond to the evidence level C. Nevertheless, the document provides – although mainly based on retrospective data and broad expert consensus – current best knowledge to guide physicians involved in the care of these patients.

Many women with pre-existing heart disorders tolerate pregnancy well. Nevertheless, complications are frequent



“

ESC Guidelines for the management of cardiovascular diseases during pregnancy
Tuesday 30 August 8:30 - 10:00, Oslo - Zone B, FP# 3703 to 3706

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Oral anticoagulation - New strategies toward optimized therapy



Programme

- 14.00 **WELCOME AND INTRODUCTION**
Professor José Luis Zamorano, Madrid, Spain
- 14.10 **ORAL ANTICOAGULATION IN ATRIAL FIBRILLATION – RECENT CHANGES AND OPEN QUESTIONS**
Professor A. John Camm, London, UK
- 14.25 **TARGET OR DOSE: ARE ALL THE NOVEL ORAL ANTICOAGULANTS THE SAME?**
Professor Jeffrey Weitz, Hamilton, Ontario, Canada
- 14.40 **FROM DOSE FINDING TO ENGAGE AF-TIMI 48 – WHY STUDY TWO DOSAGES OF EDOXABAN IN ATRIAL FIBRILLATION?**
Dr Robert Giugliano, Boston, USA
- 14.55 **FUTURE PERSPECTIVES IN ORAL ANTICOAGULATION FOR PATIENTS AND PHYSICIANS**
Professor Raffaele De Caterina, Chieti, Italy
- 15.10 **PANEL DISCUSSION**
All
- 15.25 **CLOSING**
Professor A. John Camm, London, UK

Satellite Symposium

TUESDAY, 30th AUGUST 2011

TIME: 14:00 – 15:30

ESC CONGRESS 2011

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France – Athens room, Zone F

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It's WISE to consider microvascular coronary dysfunction in women

By Janet Fricker
ESC Congress News

According to an editorial in the *European Heart Journal* in June, the female-specific pattern of ischemic heart disease is not easily recognised given the male pattern strategies now used for the detection and treatment of obstructive coronary artery disease. The editorial - titled "The Yentl syndrome is alive and well", after the 1983 film starring Barbara Streisand about a Jewish girl who dresses and lives like a man for the sake of her education - argued that women must present with "male pattern" obstructive disease to be appropriately diagnosed and treated.

The editorial was written by Noel Bairey Merz, a cardiologist from Cedars-Sinai Medical Center in Los Angeles, California, who has spent her career trying to unlock the female physiology of heart disease. And among her findings is that women are more prone than men to microvascular coronary dysfunction, a condition affecting the pre-capillary coronary arterioles, which branch from the epicardial coronary arteries, but occur before the capillaries. On Sunday, Bairey Merz told a symposium that cardiologists should consider microvascular coronary dysfunction (MCD) when investigating women for chest pain.

She told *ESC Congress News*: "Since the late 1950s, when coronary angiography was first developed, cardiologists have focused on the large epicardial coronaries that can be seen outside the heart muscle. They have been trained to think that as soon as they see coronary arteries that are not obstructed, the case is closed. This mind-set needs to be changed to consider the microvasculature." The major difficulty, she added, is that the pre-capillary coronary arterioles are very small (40-280 microns) such that their anatomy and function

are not evident on routine angiograms.

Much of our understanding of the physiological differences in women with CVD comes from the Women's Ischemic Syndrome Evaluation (WISE) study, sponsored by the National Heart and Lung Institute in the USA. In this study Bairey Merz and colleagues followed up 936 women referred for coronary angiography for suspected ischemia between 1996 and 2000. The results of angiograms, published in *JACC* in 2006, showed that only one-third of the subjects actually had obstructive blockages in their coronary arteries (in similar groups of men three-quarters would have had blockages); the remaining two-thirds had no blockages but more than half demonstrated low blood flow to the heart. It is from the data of the WISE study that investigators have estimated that around three million women in the USA suffer from ischemic heart disease in the absence of any obstructive CAD.

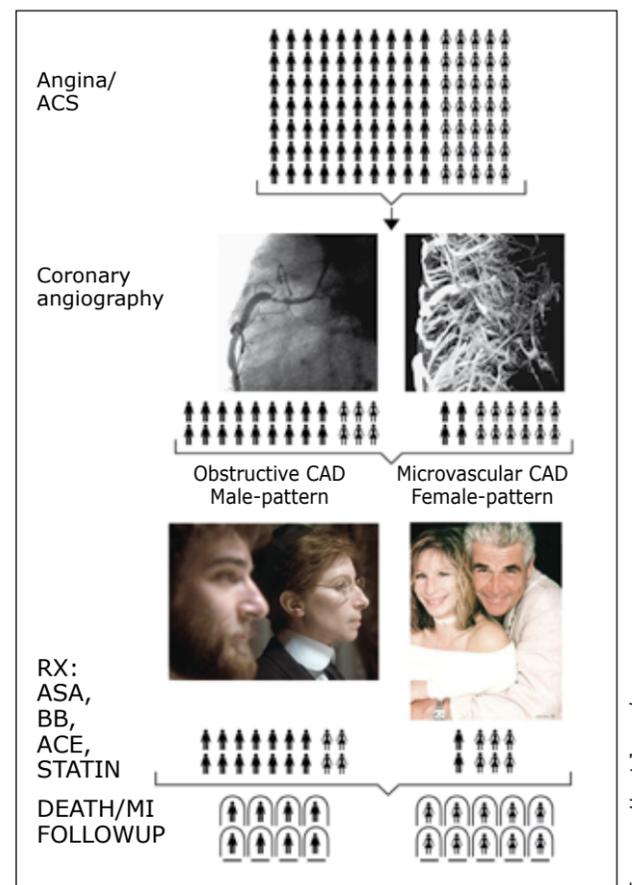
MCD is not caused by obstructive CAD, but is a condition where small vessels lose their ability to dilate and increase blood flow; the WISE study suggested dysfunction in up to four mechanistic pathways. Two of these pathways involve abnormalities of the vascular endothelial cells, which are unable to produce enough nitric oxide leading to suboptimal dilatation; the third is a non-endothelial auto-regulation of the micro vasculature, and the fourth abnormal smooth muscle contraction in the epicardial coronary arteries.

Symptoms are remarkably similar to atherosclerosis. "Which makes perfect sense," said Bairey Merz, "because, when myocardial tissue is starved of oxygen, symptoms will be the same whatever the cause. The main difference is that MCD patients can have prolonged episodes of chest pain at rest without evidence of myocardial infarction."

Risk factors include age, hypertension, cigarette smoking, dyslipidaemia, and visceral obesity. "Our WISE study suggests that there is also likely to be a genetic element involved," she said.

Far from being harmless, MCD points to long-term dangers. The WISE study found that 13% of the women who experienced angina symptoms without obstructive CAD had died within seven years. "This translates to a 2.5 % total risk of dying in any given year," explains Bairey Merz. While this is half that of obstructive CAD, it is still 2.5 times higher than in asymptomatic control subjects. Bairey Merz added that one quarter of the deaths are sudden cardiac death, one quarter acute MI, one quarter ischemic stroke and one quarter heart failure.

Such statistics, she said, highlight an urgent need to identify and treat women with MCD. To this end, cardiologists might routinely check coronary flow reserves in



Recent data suggest the Yentl syndrome is alive and well. In angina and ACS (top) relatively more men are chosen for coronary angiography, which reveals a majority of men with obstructive CAD (upper middle left) compared with women with MCD (upper middle right). Medical therapy follows according to male- and female-pattern disease. This produces undertreatment of at-risk women and men with female-pattern disease - and results in a higher death/MI rate in women than in men.

all patients with chest pain but no evidence of obstructive CAD. She recommends that these patients should be offered provocative coronary testing with a two-step diagnostic test where first adenosine is injected into the coronary arteries and blood flow measured, then acetylcholine is injected and blood flow measured. If either test shows decreased blood flow to the myocardium, a diagnosis of MCD may be made.

Women diagnosed with MCD, says Bairey Merz, require aggressive risk factor management, along with anti-anginal/anti-ischemic treatments such as beta blockers, ACE, exercise training, tricyclic antidepressants (used as a visceral analgesic) and ranolazine. Much to Bairey Merz's chagrin, ACC/AHA guidelines to date have awarded treatment of MCD Level II b evidence, although revised guidelines incorporating new data are under consideration.

The WISE study group is currently planning the WISE-ISCHEMIA trial to investigate whether mortality is influenced in women diagnosed with MCD and treated with anti-atherosclerotic and anti-anginal medications. "If we show a positive trial outcome," she said, "we should get guidelines for treatment of MCD raised to Level I evidence."



Noel Bairey Merz: "The WISE study found that 13% of the women who experienced angina symptoms without obstructive CAD had died within seven years. This translates to a 2.5 % total risk of dying in any given year."

... while women are still less optimally treated for STEMI

Despite an increasing focus on guidelines for the treatment of STEMI, as well as a shift of strategy from fibrinolysis to primary PCI, women continue to receive less guideline-adherent treatment than men, according to a Swedish registry analysis.

Dr Sofia Sederholm Lawesson and colleagues at the Department of Medical and Health Sciences of Linköping University in Sweden reviewed the treatment of all STEMI patients registered in the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions in 1998-2000 (n = 15,697) and 2004-2006 (n = 14,380) and assessed their treatment according to evidence-based guideline recommendations.

Results, which were presented in an abstract session on Sunday, showed

that the gender differences - with respect to treatment and outcome - seen in the first phase of treatment had not changed by the second phase. For example, 63.1% of women and 70.9% of men received reperfusion therapy during the 1998-2000 period, but there was still a marked gender difference in the 2004-2006 period, with 63.6% women and 75.3% men receiving reperfusion therapy.

"We assumed that with the shift towards primary PCI in the treatment of STEMI the gender differences would diminish," said Dr Sederholm Lawesson. "But we actually found the opposite. We were quite surprised."

Thus, while the overall use of coronary angiography, beta-blockers, ACE inhibitors/ARBs and statins all increased from the earlier to later periods, the gender differences in their use persisted.

The results also showed that the in-hospital female mortality rate was higher than the male rate in both time periods - although multivariate adjusted mortality rates at one year (and after adjustment for treatment) were not significantly different.

An explanation for the persisting gender differences has also proved elusive, despite multivariate and age adjustments to the data.

"The overall higher age of female STEMI patients will make a difference to treatment and outcome," said Dr Sederholm Lawesson, "but it couldn't explain all our results."

She also proposed as possible sources of bias - and thus an explanation for the results - the effects of a longer delay between symptoms and treatment for women and the greater risk of bleeding in women.



Sofia Sederholm Lawesson: "We assumed the gender differences would diminish . . . but we actually found the opposite. We were quite surprised."

The polypill: now enough data 'to advocate a full dose polycap in secondary prevention'

By Simon Brown
ESC Congress News

IN MAY this year results from the second randomised trial of a polypill were published in the journal *PLoS One*. The active compound was a four-drug combination (the "red heart pill") of aspirin 75 mg, lisinopril 10 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg, and results showed "sizeable reductions" in systolic blood pressure (of 9.9 mmHg) and LDL cholesterol levels (of 0.80 mmol/L) in the treatment arm over the 12-week study period. The investigators, known collectively as the Programme to Improve Life and Longevity (PILL) group, said the reductions were "expected to more than halve cardiovascular risk".

The results were similar to those of the phase II TIPS-1 study (of a five-in-one "polycap" containing thiazide 12.5 mg, atenolol 50 mg, ramipril 5 mg, simvastatin 20 mg, and aspirin 100 mg per day), which two years ago reported similar reductions in blood pressure and LDL cholesterol in subjects without cardiovascular disease and with one risk factor.

The latest PILL trial was performed in 378 people from seven countries (the majority in India, the Netherlands and UK) without indications for any of the ingredient drugs but a five-year Framingham risk value of 7.5%. But around one in 20 stopped the polypill because of side effects (mainly GI bleeding), and there was a significantly higher rate of such effects in the treatment group than in controls (58% vs 42%, $p=0.001$).

However, the authors themselves noted that the benefits, while apparently large,

were not as great as had previously been predicted and that side effects were not as rare. Thus, in view of the prevalence of side effects in the treatment group it was proposed that polypill therapy might best be targeted at those with a recognised risk of disease.

This question of who might benefit the most from a polypill is now a hot topic, and one due to be discussed this morning at a symposium aptly titled "Can the polypill save the world?". Presentations will consider primary and secondary prevention, as well as the "global" problem of CVD; in the context of the polypill, "the world" is not easily defined.

While the PILL investigators appear to be leaning towards secondary prevention, one of the speakers at the symposium, Dr Salim Yusuf from McMaster University in Ontario, Canada, who led the first TIPS study, believes there may be additional benefits of a polypill in primary prevention, especially in those at high or moderate risk.

Results of both the TIPS and PILL studies were based on doses that were half those used in the secondary prevention trials of most drugs. Therefore, said Yusuf, there was a need to assess the tolerability and safety of the polycap with the full daily dose of each medication; the TIPS-2 study, which Yusuf reports today, thus compared the low dose polycap (as in TIPS-1) with two capsules of the same preparation. Results show that the full dose was as well tolerated as the lower dose, but led to greater reductions in BP and LDL cholesterol.

"It is estimated," Yusuf said,



Dr Reddy's

"that the full dose will likely reduce the risk of CVD by 65-70%. So there is now adequate data to advocate a full dose polycap in secondary prevention."

Yusuf further told *ESC Congress News* that the concept of primary prevention in subjects with some degree of risk will now be thoroughly tested in the TIPS-3 trial in 5000 subjects over a five-year period beginning in November this year. "Only then," he said, "will we know that this approach is effective and

cost efficient." Notably, the active treatment in this trial does not contain aspirin (although aspirin will be tested simultaneously using a factorial design).

Efficacy and tolerability in secondary prevention, Yusuf adds, seem more straightforward, and dependent only on the equation that effects from the polypill equate with those of the individual agents - and the data on that, he says, are encouraging, although placebo controlled trials in secondary prevention are of course not possible or necessary.

It thus seems Yusuf's view that "the world" amenable to treatment with a polypill will be those people indicated for secondary prevention and for "high risk" primary prevention. Reaching that point, he notes, will depend not just on efficacy and side effects, but also on cost and regulatory acceptance.

"Regulatory approval of a polypill is the biggest bottleneck right now," said Yusuf. "The challenge is getting the regulators to accept the concept of a polypill. We're not expanding the patient population - they're the same people we'd target anyway to reduce blood pressure and cholesterol levels. So it's a substitution strategy. Clinically it will likely work and be safe in high-risk patients, but we'll need five years - until the studies in primary prevention are completed."



Salim Yusuf: "The full dose will likely reduce the risk of CVD by 65-70%."

Can the polypill save the world?

Tuesday 30 August 8:30 - 10:00, Lisbon - Zone D, FP# 3749 to 3752

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Agenda

- 14:00 Introduction and welcome
- 14:05 Know your enemy: Understanding the science of thrombus formation
- 14:25 Analysing the clinical intelligence: Choosing the right antiplatelet combination for the right patient
- 14:45 Strategies for treating high-risk ACS patients: Decisions from the front line
- 15:05 Discussion
- 15:25 Closing remarks

<< Aspirin

ADP receptor antagonist >>

GPIIb/IIIa inhibitor >>

TAVI: heading for mainstream and low-risk surgical patients?

By Janet Fricker
ESC Congress News

USE of transcatheter aortic valve implantation (TAVI) is heading for the mainstream and for low-risk surgical patients with aortic stenosis, according to the findings of two ESC abstracts to be discussed today.

A French registry study shows that few complications occur in younger and less sick patients implanted with the Edwards Sapien valve (abstract no 85810), while a German study showed no deterioration in echocardiographic functional measurements taken three years after implantation with the Medtronic CoreValve (abstract no 82314).

TAVI - first introduced by Alain Cribier in 2002 - is currently performed in patients with severe aortic stenosis considered at high risk for surgical valve replacement. Aortic stenosis is a disease in which a long latency is followed by rapid progression after the appearance of symptoms; more than half the patients die within two years.

It is estimated that over the age of 65 years 26% of the population has mild, moderate or severe aortic stenosis, with 2% having symptomatic disease needing treatment.

"With the current ageing population it's thought that over the next 15 years the number of patients with aortic stenosis will double," said Mathieu Godin from the University Hospital of Rouen, France, and first author of the French study. "This makes it increasingly important to have non-surgical techniques more widely available."

The TAVI procedure, which has been performed in around 40,000 patients worldwide, involves percutaneously placing a metallic stent frame containing valvular tissue within the damaged aortic valve, with access for retrograde implantation gained from the femoral artery, subclavian artery and ascending aorta or antegradely from the apex of the left ventricle.

Today, two different CE-mark TAVI devices are available - the Edwards Sapien valve and the Medtronic CoreValve. The former is a balloon expandable system with a bovine pericardium valve in a cobalt-nickel stent, available in three sizes; while the CoreValve is a self expandable system with a porcine pericardium valve in a nitinol stent available in two sizes (with a third expected). Many next generation valves are currently under development.

Publication of the PARTNER trial last year represented the coming of age for TAVI (NEJM : 2010; 363:1597-1607). In this study, from Columbia University Medical Center in New York, 358 patients with aortic stenosis who were not considered candidates for surgery were randomised to TAVI or the standard therapy of balloon aortic valvuloplasty.

Results at one year showed that the death rate from any cause was reduced by 45% among patients randomised to TAVI.

While TAVI is considered an alternative option to surgery in high-risk patients, long-term data on TAVI outcomes have been limited, making clinicians reluctant to carry out the procedure in patients in lower risk patients.

"One crucial test for TAVI will be the question of whether the durability of transcatheter valve prostheses is comparable to other biological prostheses," said Anke Opitz, first author of the German study.

In the French study Godin and colleagues investigated the outcomes of patients with low EuroSCOREs (a system developed to predict the operative mortality of coronary surgery) who nevertheless had other contraindications to thoracic surgery - such as thorax deformity, porcelain aorta (with calcification), and mediastinal radiotherapy. "These patients were often less sick and younger," said Godin, "making it interesting to assess results of TAVI in this population." So far, he added, most registries have only included patients at high risk of complications.

The investigators performed a retrospective study of 177 patients implanted with the Edwards prosthesis in Rouen between May 2006 and January 2011. The patients were divided into two groups according to their EuroSCOREs: high-risk patients were defined as having a predictive logistic EuroSCORE >20%, while low risk patients were defined as having a predictive logistic EuroSCORE <20%.

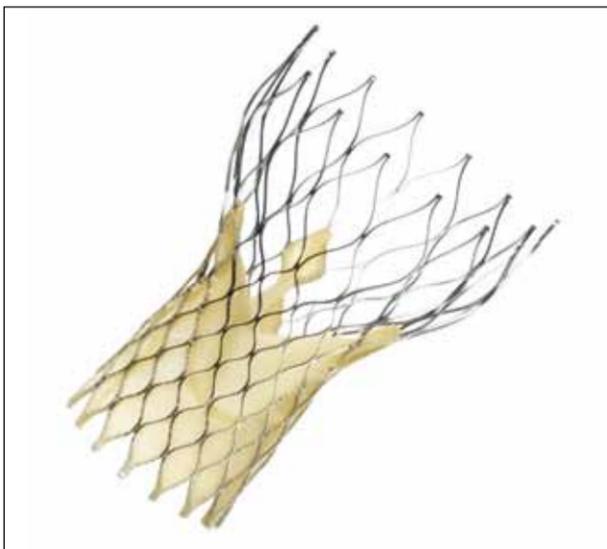
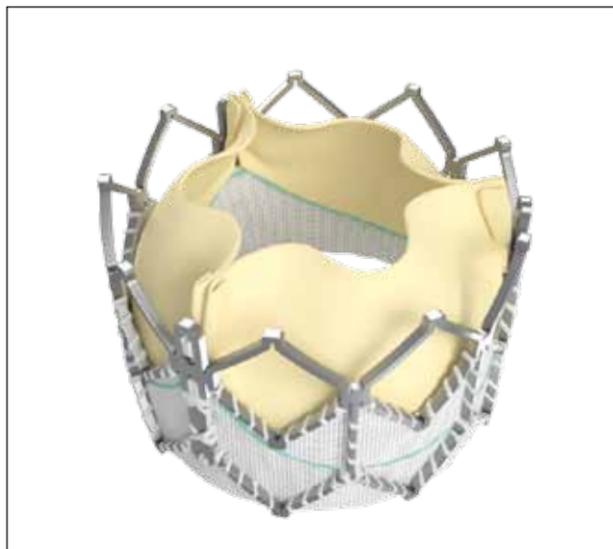
Results showed that procedural success was 100% in the low risk group, and 95.3% in the high risk group (p=0.1). Results also showed that at one month no deaths were observed in the low risk group and 11.1 % in the high risk group (P<0.04), and that at one year the mortality rate was 5% in the low risk group and 24.8% in the high risk group (P<0.01).

"While we were expecting a lower mortality among patients with low EuroSCOREs, the observed difference was much greater than anticipated," said Godin. "In fact, the mortality rate was comparable to results with conventional surgery. The results represent a first step towards a broader assessment of percutaneous techniques in populations at lower surgical risk. However, we must state that to date, surgery remains the gold standard treatment for this population."

In the German study Opitz and colleagues from the German Heart Centre in Munich performed an echocardiographic evaluation of 393 patients consecutively implanted with the Medtronic CoreValve between June 2007 and June 2011. Transthoracic echocardiography was performed preoperatively then at discharge and at 6, 12, 24 and 36 months, with readings taken to evaluate the transaortic valve mean and peak gradient (P mean, P max) and the effective orifice area (EOA).

Results showed that EOA increased significantly, but that pressure gradients decreased significantly (the higher the gradient, the higher the severity of the stenosis, p<0.0001 for all readings). In addition, there was no observable change in EOA or pressure gradients at 6, 12, 24 and 36 months.

"The results show that after three years follow-up patients treated with the CoreValve prosthesis demonstrated a sustained reduction in transaortic valve gradients and improvements in EOA," said Opitz. "And the good news is that we didn't have any unexpected early valve deterioration. He added that the next planned survey will be after five years."



Two different CE-mark TAVI devices are available - the Edwards Sapien valve (left) and the Medtronic CoreValve.

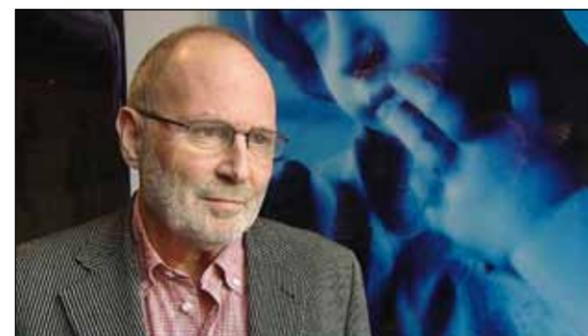
'Causative' link between AF and exercise in men

By Simon Brown
ESC Congress News

A NORWEGIAN population study whose original participants totalled almost 500,000 has found that the risk of atrial fibrillation in men rose with increasing levels of physical activity - although the same graded increase was not evident in women.

The study, presented on Sunday as a poster, merged three population surveys performed during 1974-2003 to provide a single cohort of men and women aged between 30 and 81 years at the start of the study and free of any known structural heart disease. An estimation of atrial fibrillation (AF) incidence during the study period (January 2004 to December 2009) was determined by a first prescription of flecainide.

During the study period 1183 men and 609 women were prescribed flecainide for the first time, and thus represented the presumed number of AF cases. Analysis showed that the incidence of AF increased in men in proportion to an increasing level of physical activity (as described in the original surveys), indicating a rising relative risk; this pattern persisted even when adjustments were made for height, age, BMI and education.



This same pattern, however, was not apparent among the women, where the relative risk attributed to activity remained non-significant. Investigator Professor Dag Thelle (pictured above), a cardiovascular epidemiologist, suggested that this neutral finding in women might be explained by an under-reporting of exposure (and that hard exercise among women was less common in the 1970s and 80s than today). Body size, he added, might be also be a factor. "The taller you are, the higher the incidence of atrial fibrillation," he said.

However, in men Thelle said the association between AF and physical activity was indeed "causative" and not merely statistical. "We excluded all individuals with pre-existing cardiovascular disease," he explained, "so the reported episodes are likely to be related to the activity, particularly at the higher levels."

He also stressed that this was a longitudinal population study, and thus applicable to ordinary people in everyday activities. "They're the ones who should be aware of the risk," he said. "We have lots of studies in endurance athletes, but not in the everyday population."

	Walking at least 4 hours/week	Light sports, heavy gardening	Hard exercise several times/wk
Men (n = 204, 897)			
Adjusted for	HR	HR	HR
Age	1.21	1.47	2.94
Age + BMI	1.21	1.46	2.92
Age + educn	1.20	1.42	2.75
Age + ht + ed + BMI	1.18	1.39	2.75
Women (n = 223, 622)			
Age + ht + ed + BMI	1.00	0.78	-

“

Poster session 6 : Transcatheter aortic valve implantation - clinical
Tuesday 30 August 14:00, Poster Zone C , Abstract 82 182, 84 857, FP# P4973, P4994

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The link between pre-eclampsia and long-term CVD

By Janet Fricker
ESC Congress News

PRE-ECLAMPSIA, a condition which affects 2-5% of all pregnancies, is characterised by new onset of hypertension (BP \geq 140/90) in the presence of abnormal proteinuria (24 hour proteinuria \geq 300mg/24 hours) and associated with significant maternal morbidity during pregnancy. Although the signs and symptoms disappear after delivery, a history of pre-eclampsia is increasingly recognised as an important risk factor for later CVD. Two abstracts presented at this ESC Congress provide new information about the condition: the first on how to better identify those who may be at risk of developing pre-eclampsia, and a second on the distinguishing cardiovascular features of young mothers who have previously had pre-eclampsia.

While the early diagnosis of pregnant women with pre-eclampsia would allow early referral for treatment, no validated and accepted risk scores are available. In the first study Dr Eduardo Perna and colleagues, from the Instituto de Cardiología and Hospital Llano in Corrientes, Argentina, set out to develop a practical user-friendly tool for estimating the risk of a pregnant woman developing pre-eclampsia.

The study was a retrospective multiple regression analysis of 15,460 consecutive deliveries which took place between November 1998 and July 2008 at the Hospital Llano. Results revealed the following variables associated with pre-eclampsia: primipara (OR 2.3), maternal age \geq 35 years (OR 2), chronic hypertension (OR 2.3), multifetal gestation (OR 3.4), obesity (OR 2), inter-pregnancy period $>$ 3 years (OR 1.1), smoking (OR 2.1) and previous abortion (OR 1.3).

Using a classification and regression tree (CART) analysis to identify the best predictors of pre-eclampsia among the independent variables, the authors identified age $>$ 35 years, primiparity, obesity, multifetal gestation and smoking as the five key clinical predictors. "These risk factors are all present from the start of pregnancy, allowing women with them to be closely monitored for early detection," says Perna. The next step, he added, will be to prospectively validate the model in other centres.

In the second study (abstract 89442) Dr Paul Leeson and colleagues from University of Oxford, UK, studied the cardiovascular health of 74 young women who had

experienced pre-eclampsia five to ten years earlier and compared the findings with those in 47 women with normotensive pregnancies at the same time. In addition to conventional markers of cardiovascular risk, they used cardiovascular MR imaging, echocardiography and ultrasound to study in detail what was different about the cardiovascular system of both groups.

Results showed that women with pre-eclampsia (whose mean age was only 40 years) already had significantly higher peripheral systolic blood pressure ($p<0.001$) and diastolic blood pressure ($p=0.002$), as well as greater pulse wave velocity ($p=0.03$) and common carotid intima media thickness ($p=0.004$).

Additionally, the investigators found a graded association between the severity of the pre-eclampsia

and the degree of changes to the cardiovascular system. The authors believe that these vascular changes may provide useful intermediate endpoints to test future prevention strategies.

"At present the best advice for women who have had pre-eclampsia is to maintain a healthy lifestyle and have regular check-ups for CVD risk factors," says Leeson. His group is currently performing an intervention trial using statins in women five to ten years after pre-eclampsia to see whether they can reverse or slow progression of the identified vascular changes. "Our findings highlight the importance of taking a history of pre-eclampsia when determining CVD risk in all women," said Leeson, "and potentially identifying those who have the more severe, early onset pre-eclampsia for prevention advice."

Awards to six young investigators from the Pulmonary Circulation and Right Ventricular Function Working Group

Yesterday, the ESC Working Group Pulmonary Circulation and Right Ventricular Function made awards to six young investigators: four for the best abstracts on pulmonary hypertension and two for the best abstracts on venous thromboembolism, based on the marks awarded by the ESC abstract reviewers. Winners, pictured here with Working Group chairman Simon Gibbs are (left to right): Enri Leci (IT), Christopher J. Valerio (GB), Marieke Lankeit (DE), Anna M. Budaj-Fidecka (PL), Johannes M. Douwes (NL) and Barbara Girerd (FR).



A new option for your high-risk patients with aortic stenosis

In the landmark clinical study—The PARTNER Trial—Balloon-expandable transcatheter aortic valve implantation demonstrated a 20% absolute reduction in all-cause mortality versus standard treatment at one year.¹

Additionally, the reduction in mortality and rehospitalization versus standard treatment at one year was 40%.¹

For more information, visit edwards.com/EU

Reference: 1. Leon MB, Smith CR, Mack M, et al; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363(17):1597-1607.

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TO LEARN
MORE
AUG 30, 14:00-15:30
WARSAW - ZONE A

STANDARD TREATMENT

20%
REDUCTION IN ALL-CAUSE MORTALITY AT ONE YEAR¹

BALLOON-EXPANDABLE TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

How important is it to target blood pressure?



 Anouchska Autar
Medical student,
Rotterdam, The Netherlands

"It's really important because hypertension is a widespread condition that has so many different effects on the human body, including cardiac and neurological diseases and so on. It can be difficult to address alongside today's unhealthy lifestyles, but, if you could treat blood pressure to target, there would be many advantages both for society in terms of reduction of healthcare costs and also for individual patients in terms of mortality outcomes. We need to develop better, cost-effective and meaningful screening tests. The white coat effect, where patients experience elevated blood pressure in the clinical setting due to anxiety, can be a real issue."

"We need to make all possible efforts to reach therapeutic targets. It's crucial. The general population of hypertensive patients need to reach 140/90 and special populations like diabetes patients or those with chronic kidney disease or renal impairment should be lower. We are not doing a good enough job. We may give our patients weak recommendations, or just not be sufficiently involved to get them to modify their habits. Asymptomatic patients may be reluctant to take medication, and we must make all possible efforts to convince them about the severity of hypertensive disease. If it's not well controlled, it is a strong marker of a poor prognosis."



 Luis Alberto Guzman
Clinical cardiologist
Cordoba, Argentina



FACES IN THE CROWD

 Axel Frey
Interventional cardiologists
Munich, Germany



"In reality many patients are only diagnosed with hypertension after they've experienced an event, like an arrhythmia, shortness of breath or signs of heart failure. The fact that so many are slipping through the net makes me really concerned they'll suffer long term damage (such as heart failure and kidney disease). We need to improve identification strategies, such as flagging up people with a family history of hypertension (particularly in a first degree relative) to be followed up more intensively. We also need to teach young people to keep their weight down and reduce salt intakes to reduce the population risk of diabetes."

"The prevalence of people with hypertension in global communities is high, and the condition frequently goes underdiagnosed in people who feel healthy. Even once it's picked up, it's often undertreated. In Colombia, probably 20% of the population have levels above normal and would benefit from non-pharmacological measures at least - to avoid being overweight, sedentary, and smoking, and to follow dietary recommendations about reduction of salt intake. Many people, though, will also need pharmacological treatments on top of these measures. It's important to identify people who don't know they have hypertension."

 Manuel Urina Triana
Interventional cardiologist
Bogota, Colombia



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