News from the 2006 Congress of the European Society of Cardiology and the XVth World Congress of Cardiology

The 2006 Congress of the European Society of Cardiology joined with the World Heart Federation's XVth World Congress of Cardiology this year and was held in Barcelona, Spain, from 2nd–6th September 2006. The joint meeting was dominated by one subject – new concerns about increased mortality and myocardial infarction with drug-eluting stents. We report on this and other highlights from this year's meeting.

Mortality/MI concerns with drug-eluting stents

Three new studies presented at the meeting added to previous concerns about increased rates of stent thrombosis with drug-eluting stents translating into increases in mortality and myocardial infarction (MI) risk.

Two of the studies are meta-analyses of all the randomised trial data of the Cypher® (sirolimus) and Taxus® (paclitaxel) stents. They were reported one after the other, at the same HotLine presentation, by Drs Edoardo Camenzind (University Hospital Geneva, Switzerland) and Alain Nordmann (University Hospital Basel, Switzerland).

One meta-analysis found an increased incidence of death and MI with the Cypher® stent and a trend towards increased death/MI with the Taxus® stent, while the other found no differences in cardiac mortality with either stent but did show an increase in non-cardiac mortality with the Cypher® stent.

Designated discussant of the two meta-analyses, Professor Salim Yusuf (McMaster University, Hamilton, Canada) said these data raised concerns. "I do not believe these trials are convincing but they are disconcerting given that we have no data that percutaneous coronary intervention (PCI) improves outcomes in stable angina," he commented.

While Professor Yusuf agrees that PCI and drug-eluting stents play a key role in the treatment of unstable angina and acute coronary syndromes, he said it was time to "stop and re-evaluate" the use of drug-eluting stents and PCI, in general, for stable angina.

"As clinicians we seem to have lost our clinical judgment let alone our ability to view data and evidence. The whole field of angioplasty has been led astray by a preoccupation with restenosis for which study after study has shown has no prognostic value," he said.

The data

The Camenzind meta-analysis was based on two separate analyses of the sirolimus and paclitaxel data. In the first, the investigators examined death and Q-wave MI in the published or presented papers, pooling them by time of follow-up. They found that the incidence of death/MI was 30-40% higher with the Cypher® stent than with bare-metal stent controls. The Taxus® stent showed a smaller non-significant increase of about 5%.

In their second analysis, all of the randomised trials involving each stent were stratified by last follow up data. Results showed a significant increase in serious adverse events in patients receiving the Cypher® stent (6.3% compared to 3.9% in the bare-metal stent group) and a much smaller non-significant increase in the Taxus® group (2.6% versus 2.3%).

We conclude that death and Q-wave MI as the clinical presentation of stent thrombosis have a higher incidence in first generation drug-eluting stents as compared to bare-metal controls," Dr Camenzind stated. "Excess events appear to occur with both types of stents, although the magnitude seems to be higher with sirolimus".

The second meta-analysis, by Nordmann *et al.*, combined data from 17 randomised controlled trials of the Cypher® and Taxus® stents. They found that total mortality trended towards a benefit of drug-eluting stents at one year but by two years this had reversed and showed a trend towards an increase with drug-eluting stents.

There was no statistically significant difference in cardiac morality between drug-eluting stents and bare-metal stents but there was a suggestion of increased non-cardiac mortality (specifically deaths from cancer, stroke or lung disease) with the Cypher® stent.

Dr Nordmann concluded that "long-term follow-up and assessment of cause-specific deaths in patients receiving drug-eluting stents are mandatory to determine safety of patients receiving these devices".

Third study focuses on stent thrombosis

A third study presented at the Barcelona meeting added to the concerns raised by the meta-analyses. This study, reported by Dr Peter Wenaweser (Thorax Center, Rotterdam, The Netherlands) focused on the incidence of stent thrombosis in four registries of patients receiving drug-eluting stents – the SIR-TAX and Post-SIRTAX registries in Bern, Switzerland, and the RESEARCH and T-SEARCH registries in Rotterdam, The Netherlands. Clopidogrel was given for three to six months in the Bern registries, and for three to 12 months in the Rotterdam studies.

In total, 152 stent throm-

boses occurred in 8,146 patients. The stent thromboses showed an almost linear increase over time, occurring in 1.2% of patients at 30 days, 1.7% at one year, 2.3% at two years, and 2.9% at three years.

Long-term results from other studies

Several other presentations at the Barcelona meeting reported long-term results from individual studies of drug-eluting stents, including the RAVEL, TAXUS II and BASKET studies. But none of these trials were really large enough individually to shed further light on the incidence of late-stent thrombosis.

RAVEL not reassuring

Reporting five years of follow-up in the RAVEL study of the Cypher® stent, Professor Patrick Serruys (Thorax Center, Rotterdam, The Netherlands) noted that no stent thrombosis was seen in this trial. While target lesion revascularisations were still reduced in the Cypher® group compared with the bare-metal stent at five years, there was a trend towards an increase in death/MI in the drug-eluting stent group (p=0.09). Commenting on this, Professor Serruys said that although this difference was not statistically significant and the study was not powered to investigate this specific outcome, this observation should be investigated prospectively in sufficiently powered studies.

Discussant of this presentation, Dr Bernard De Bruyne (Cardiovascular Center, Aalst, Belgium), said that: "Unless this finding is refuted by subsequent studies, the suspicion will be that sirolimus improves the artery, but harms the patient."

TAXUS II data maintained at four years

Four-year results of the TAXUS-II study, however, were more reassuring, showing no additional cases of stent thrombosis from three to four years with both slow- and moderate-release formulations of the paclitaxel stent. The study also reported a low overall cardiac death rate of 1.6%, which showed no statistical difference when compared to the bare-metal control overall cardiac death rate of 1.5%. Overall MI was 4.7% in the slow-release formulation and 5.3% in the moderate-release formulation of the pactlitaxel stent compared to 6.7% in the combined control.

BASKET

Dr Christoph Kaiser (University Hospital Basel, Switzerland) presented 18-month results from the BASKET study in which patients received either a Cypher®, Taxus® or bare-metal stent. As expected, non-infarct-related target vessel revascularisation was lower in the two drug-eluting stent groups but there were no significant differences in death/MI seen between the three groups (table 1).

In a post-hoc analysis, Dr Kaiser reported that patients with bypass graft stenoses or small stents appeared to do better with drug-eluting stents, whereas in patients without bypass grafts, or with stents 3 mm in diameter or larger, patients with bare-metal stents did just as well.

"Patients needing stenting of larger native vessels have no significant benefit and possibly even harm so drug-eluting stents may be best used only in small vessels and bypass grafts," Dr Kaiser said. "These findings challenge the notion that today every patient should receive drug-eluting stents," he added.

Table 1. BASKET: 18-month outcomes

End point (%)	BMS	DES	P
Death/MI	7.5	8.4	0.63
Non-infarct target vessel revascularisation	11.6	7.5	0.05
Overall major adverse cardiac events (death/ MI/ target vessel revascularisation)	18.9	15.8	0.26

Key: BMS = bare-metal stent; DES = drug-eluting stent; MI = myocardial infarction

Current usage too high?

Summarising the findings presented on drug-eluting stents at the end of the meeting, Dr Sigmund Silber (Dr Müller Hospital, Munich, Germany) said that they were still effective in reducing the need for repeat revascularisations, but that because of a "reasonable concern about the safety of first generation drug-eluting stents, current usage that exceeds 80% of procedures in some countries is not justified".

● MHRA statement

Since the congress, the Medicines and Healthcare products Regulatory Agency (MHRA) has issued a statement saying that it is aware of the heightened concern over the risk of late stent thrombases associated with DES.

It reads: "MHRA has been actively monitoring the performance of coronary stents, including drug-eluting stents and continues to do so. MHRA investigates all adverse incident reports received from both stent manufacturers and clinicians. Our evaluation of these reports to date does not indicate that drug-eluting stents are less safe than non drug-eluting coronary stents. The assessment of the safety of drug-eluting coronary stents is a complex issue. There are different short- and long-term advantages and disadvantages depending on stent type and the whole picture needs to be taken into account. MHRA will continue to assess the safety of drug-eluting coronary stents in consultation with clinical professionals and the relevant manufacturers as more information on their long term performance becomes available. It is therefore important that clinicians continue to report all stent related adverse events to our Adverse Incident Centre."

● An editorial 'Late clinical events after drug-eluting stents: is there a problem?' by Dr Martyn Thomas can be found on pages 313–16 of this issue.

IDEA: all Asian populations do not have same obesity profile

A new study has shown that Asian populations should not be considered as one in terms of obesity and cardiovascular risk, and that while Indians and Pakistanis have similar rates of abdominal obesity to western Europeans, those from East and South-East Asia have lower rates.

Reporting the IDEA (International Day for the Evaluation of Abdominal Obesity) study, Dr Jean-Pierre Bassand (University of Besançon, France), said the results showed that one threshold for obesity in Asian populations may be inappropriate.

The IDEA study aimed to estimate the prevalence of abdominal obesity among Asian populations, as compared with Western Europe, to identify more accurately patients at risk of cardiovascular disease. Investigators measured the waist circumference of 30,000 individuals in three Asian regions – South Asia (India and Pakistan), East Asia (China, Korea and Taiwan) and South-East Asia (Indonesia, Malaysia, the Philippines, Singapore, Thailand and Vietnam) – and compared these with figures from a similar number of people in North West Europe. They also correlated the waist measurement with height, body weight, demographic data, the presence or absence of classical cardiovascular risk factors and existing cardiovascular disease.

They found that abdominal obesity is highly prevalent in Asia but still lower than in Europe (apart from South Asia, which had similar rates to Europe). However, the prevalence of cardiovascular disease was generally similar, or even higher, in Asian populations than in Europeans, suggesting that the impact of obesity may begin at different thresholds in Asian populations.

Enoxaparin a safe and effective alternative to UFH in PCI

New results presented in Barcelona provide further evidence that enoxaparin is a safe and effective alternative to unfractionated heparin (UFH) in ST segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI) after thrombolysis.

Professor Keith Fox, Duke of Edinburgh Professor of Cardiology at Edinburgh University's Centre for Cardiovascular Science, told the BJC: "These results are important because they should reassure interventionists performing PCI on STEMI patients that it is not necessary to switch from enoxaparin to unfractionated heparin beforehand and that the procedure can be performed safely in the presence of enoxaparin".

Professor Jennifer Adgey, Professor of Cardiology at Royal Victoria Hospital in Belfast, agreed: "These results show beyond doubt that enoxaparin is as safe as unfractionated heparin in STEMI patients undergoing PCI".

The EXTRACT TIMI-25 study had previously compared a new enoxaparin dosing regimen (lower doses for elderly and renally impaired patients) with unfractionated heparin in more than 20,000 STEMI patients being treated with thrombolysis. Overall results showed a reduction in death/MI and a net clinical benefit with enoxaparin despite an increase in major bleeding.

New results presented from the PCI-ExTRACT-TIMI 25 study, a prospectively planned subanalysis of the ExTRACT-TIMI 25 (Enoxaparin and Thrombosis Reperfusion for Acute Myocardial InfarCtion Treatment, Thrombosis In Myocardial Infarction – Study 26) trial, showed that death or non-fatal myocardial infarction (MI) occurred in 10.7% of enoxaparin-treated patients compared to 13.8% of the UFH patients (0.77 RR; p<0.001). This difference was driven by delayed onset and reduced recurrence of MI and was achieved without differences in bleeding complications (1.4% versus 1.6%, enoxaparin and UFH rates, respectively). There were also fewer strokes both before and after PCI among patients treated with enoxaparin compared with those who received UFH (0.3% versus 0.9%, RR 0.30, p=0.006).

A total of 20,479 subjects for whom fibrinolysis was planned were randomised to a strategy of enoxaparin throughout the index hospitalisation or UFH for 48 hours in a double-blind manner. The blinded study drug was continued in patients who underwent PCI. Out of 20,479 randomisations, 4,676 (22.8%) underwent subsequent PCI (2.8% rescue) at the discretion of the treating physicians; 47% were still blinded to the study drug. These patients were younger, had a lower TIMI risk score and a better adjunctive treatment.

Dr Michael Gibson of the TIMI Study Group at Harvard Medical School, Boston, US, said: "These results indicate that adding enoxaparin for anticoagulation supports a practice pattern in which PCI is performed at some time following fibrinolytic administration. As enoxaparin reduces the onset and occurrence of repeat heart attacks, the window of opportunity to perform PCI is larger than that with UFH."

Results from the STEEPLE trial, presented at last year's European Society of Cardiology meeting and published this month in the New England Journal of Medicine (September 7th), also showed that enoxaparin was a safe and effective alternative to UFH in elective PCI.

Everolimus-eluting stent better than paclitaxel-eluting stent for reducing six-month late loss

New six-month angiographic findings from the SPIRIT II study show a significant advantage of the second-generation cobalt-chromium everolimus-eluting stent, Xience Vision®, in preventing in-stent late loss compared with the Taxus® paclitaxel-eluting stent in patients with *de novo* native coronary lesions.

The everolimus stent, which has already gained CE mark approval in Europe, replaces stainless steel as the base stent with an alloy that permits thinner, more flexible struts. The SPIRIT II trial, which was designed as a non-inferiority study, randomised 300 patients in a 2 to 1 ratio to the everolimus-eluting or paclitaxel-eluting stents. Presenting the results, Professor Patrick Serruys (Erasmus University Hospital, Rotterdam, The Netherlands) reported that the primary end point of the study, in-stent late loss measured at 180 days, turned out to be significantly lower in those treated with the everolimus-eluting stent (0.11 mm) compared to 0.036 mm in the paclitaxel stent. In-stent diameter stenosis was also less in patients treated with the Xience Vision® stent. There were no significant differences in clinical events (a composite end point of cardiac death, myocardial infarction and ischaemia-driven target lesion revascularisation) between the two stents.

Given the current controversy over late thrombotic events in patients receiving drug-eluting stents, the question inevitably arose as to whether late loss was an appropriate end point. Designated discussant of the SPIRIT II study, Dr Robert Harrington (Duke University Medical Center, Durham, US) explained that late loss had been shown to be a consistent measure of neointimal hyperplasia, which is the underpinning of restenosis in the stented population. But he noted that in autopsied patients with a drug-eluting stent, investigators have observed less neointimal hyperplasia and more fibrin deposition compared with those treated with a bare-metal stent, suggesting less healing, as well as less strut endothelialisation, which could cause long-term thrombosis issues. Professor Serruys added that it was a balance between neointimal hyperplasia and the quality of the endothelium. "This will, of course, be the topic of research and debate for the next few years," he said.

PEP-CHF: ACE inhibitors benefit symptoms of diastolic heart failure

Adding an angiotensin-converting enzyme (ACE) inhibitor to diuretics appeared to alleviate symptoms and boost exercise capacity in patients with heart failure and preserved left ventricular function but failed to show a significant effect on clinical outcomes in the Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study.

Presenting the results, Professor John Cleland (University of Hull) said the study provided support for ACE inhibitor therapy in a population for which few treatments are available. "This is the first study to show a clear effect of a treatment other than diuretics on symptoms in this patient group," he commented.

Table 1 One-year outcomes in PEP-CHF

End point	Perindopril n=424	Placebo n=426	P
All-cause mortality or unplanned heart failure hospitalisation	10.8%	15.3%	0.055
Unplanned heart failure hospitalisation	8.0%	12.4%	0.033
All-cause mortality	4.0%	4.5%	NS

The PEP-CHF trial included 850 elderly heart failure patients who had preserved left ventricular function and echocardiographic features suggesting possible diastolic dysfunction. They were randomised to perindopril (4 mg/day) or placebo.

Underpowered

Professor Cleland said the trial ended up being underpowered as patient enrolment was slow and did not reach its target of 1,000 patients. The number of clinical events was also lower than expected. Nevertheless, results showed a strong trend towards fewer deaths/heart failure hospitalisations in the perindopril group after one year, which did not quite reach significance.

Several subgroups, however, did reach significance, including patients aged 75 or younger, those with systolic hypertension, and those with a prior myocardial infarction. And significant improvements were observed compared to the placebo group in some secondary end points, including the proportion of patients in New York Heart Association functional class 1 and change in six-minute walk distance, after a mean follow-up of 26 months.

New findings from ASCOT: amlodipine-based regimen reduces onset of diabetes

New findings from ASCOT (the Anglo-Scandinavian Cardiac Outcomes Trial) show that the amlodipine-based antihypertensive regimen reduced the risk of new-onset diabetes by 34%, compared with the beta blocker-based regimen.

The ASCOT trial compared a regimen of atenolol plus bendroflumethiazide with one of amlodipine plus perindopril for control of hypertension in 19,257 patients. Of these, 14,120 did not have diabetes at the outset and 1,366 developed diabetes over the study period: 567 (8%) in the amlodipine arm and 799 (11.4%) in the atenolol arm.

This analysis was presented by Dr Ajay K Gupta (Imperial College London), who commented that these results were important as diabetes significantly increases the risk of myocardial infarction (MI) and stroke.

In the current analysis, risk predictors for new-onset diabetes were determined in order to develop a risk score to identify those at higher risk. Fasting plasma glucose was found to be the strongest risk factor for new-onset diabetes but body mass index, high density lipoprotein cholesterol and triglyceride levels were also important baseline predictors. When the population was divided into quartiles for risk based on these factors, the highest quartile had a risk of new diabetes almost 20 times higher than the lowest quartile. In each quartile, those in the atenolol-based arm had a higher risk for diabetes than those in the amlodipine-based arm. Dr Gupta concluded that: "The risk model developed is robust, has an excellent discriminative ability and could potentially play an important role in clinical practice."

Designated discussant of these results, Dr Jose Zamorano Gomez (Hospital Clinico San Carlos, Madrid, Spain) noted that a variety of factors have to be considered when choosing antihypertensive therapy for individual patients including whether the patient has heart failure, is post-MI, and has diabetes or renal failure. Now risk of new-onset diabetes also needs to be taken into account.

Commenting on the results, Professor Neil Poulter, a member of the Executive Committee of the ASCOT study, said: "These findings have critically important implications for many thousands of people. Hypertension already increases the risk of diabetes two to three times. Now we know that the commonly used combination of a beta blocker ± diuretic significantly increases the risk compared with a new combination, amlodipine ± perindopril. Physicians should think carefully before using the beta blocker based strategy to treat hypertension".

The ASCOT trial was stopped prematurely because of a mortality advantage in the amlodipine-based group. Based on the findings of the study, the UK National Institute for Health and Clinical Excellence (NICE), has recommended that beta blockers should no longer be the preferred initial therapy for hypertension, and that a calcium channel blocker or thiazide-type diuretic should be the first choice for initial therapy in hypertensive patients ages 55 or over, or in black patients of any age. "These data highlight the additional risk of new-onset diabetes with a beta blocker ± diuretic and provides support for this recommendation," Professor Poulter said.

PROactive: pioglitazone reduces recurrent stroke in patients with diabetes

Pioglitazone reduced the risk of stroke in patients with diabetes, but only among those with a prior history of stroke, in a new subgroup analysis of PROactive (PROspective pioglitAzone Clinical Trial in macroVascular Events) reported at the meeting.

Presenting the results, Professor Robert Wilcox (School of Medicine and Surgical Sciences, Nottingham) noted that recurrent stroke was reduced by 47% in patients with a prior history of stroke who received pioglitazone relative to those treated with placebo in the trial. However, pioglitazone had no effect in reducing the risk of first strokes, where the overall risk for stroke was much lower. "Whether longer-term therapy with pioglitazone would similarly benefit diabetic patients without prior stroke, or perhaps indeed non-diabetic patients with prior stroke, awaits further inquiry," Professor Wilcox said.

He explained that there was, to date, no conclusive evidence about the benefit of a glucose-lowering therapy in patients with diabetes on their incidence of stroke. In addition to glucose lowering, pioglitazone also reduces triglycerides and C-reactive protein, and increases high-density lipoprotein cholesterol, all of which may positively affect cardiovascular risk.

The main PROactive trial randomised 5,238 patients with type 2 diabetes who were considered at high risk for cardiovascular events to either pioglitazone (45 mg/day) or placebo given on top of standard medications. Results showed a non-significant 10% reduction in the primary end point, a compos-

ite of all-cause mortality, non-fatal myocardial infarction (MI), stroke, leg amputation, acute coronary syndrome, and cardiac or leg revascularisation. But there was a significant reduction in the secondary end point of death, MI and stroke. In the overall trial, there was a trend towards fewer strokes in the pioglitazone group, but this was not significant.

In the current subgroup analysis the occurrence of stroke was determined in patients with and without a prior history of stroke. Professor Wilcox reported that the risk of recurrent stroke was reduced among patients with a history of stroke for those treated with pioglitazone relative to those not treated, from 10% to about 5%.

Antiplatelet-anticoagulant combination looks good in elderly with AF

A regimen combining oral antiplatelet and anticoagulant agents reduced both clinical events and severe bleeding complications compared with anticoagulation alone in older patients with atrial fibrillation (AF) in a new analysis of NASPEAF (National Study for Prevention of Embolism in Atrial Fibrillation).

Presenting the findings, Dr Francisco Perez-Gomez (Hospital Clinico San Carlos, Madrid, Spain), said the better outcome in the combination group was probably due to a less intense level of anticoagulation used in those patients (average International Normalised Ratio [INR] was 2.1 in the combination group versus 2.5 in those taking only the anticoagulant).

The trial enrolled 714 patients with AF considered to be at intermediate thromboembolic risk, who were assigned to chronic therapy with triflusal (a cyclo-oxygenase inhibitor antiplatelet agent) or acenocumarol (a warfarin-like anticoagulant), or both drugs. In addition, 495 patients deemed to be at high thromboembolic risk were randomised to the anticoagulant with or without the antiplatelet agent. Results showed benefits for the combination therapy in both the intermediate- and high-risk groups.

In the current post-hoc analysis of the trial, which involved the 967 patients who received either combination therapy or the anticoagulant alone, the benefit of combination therapy appeared concentrated in two high-risk subgroups—patients aged 75 years or older and those with a history of embolic events. The risk of major bleeding complications was increased in the older patients on anticoagulation only but not among those taking the combination therapy. In particular, intracranial bleeding occurred more frequently among those taking only the anticoagulant, contributing greatly to their higher mortality.

PRAGUE-2: five-year results show transfer strategy best for STEMI

Five-year results from the PRAGUE-2 trial show that the early benefit of transporting myocardial infarction (MI) patients for PCI (percutaneous coronary intervention) rather than giving thrombolysis locally appears to translate into lower mortality rates.

PRAGUE-2 randomised 850 MI patients to treatment with thrombolysis (streptokinase) at their local hospital or transport to a larger centre where PCI could be performed. The primary end point of 30-day mortality was lower in the PCI patients but this was not significant. However, the combined end point of death/MI/stroke was significantly reduced in the transfer group (see table 1).

Table 1: Five-year results in the PRAGUE-2 study

Outcome	Thrombolysis group (n=416)	Transfer PCI group (n=428)	P value
Death/MI/stroke/revascularisation	73.3%	58.5%	<0.0001
Death	43.3%	36.5%	0.0417

Key: PCI = percutaneous coronary intervention; MI = myocardial infarction

Dr Peter Widimsky (University Hospital Vinohrady, Prague, Czech Republic) noted that the new data show that this early benefit persisted, leading to a significant difference in mortality between the groups at five years.

Discussant Dr Anselm K Gitt (Herzzentrum, Ludwigshafen, Germany) said: "These findings show that primary PCI provides benefit in an acute setting and in long-term survival. We must endeavour to make this strategy available to all STEMI patients."

OASIS studies show fondaparinux superior in ACS patients

Combining the results of the OASIS-5 (Organisation to Assess Strategies for Ischaemic Syndromes) and OASIS-6 trials show that the factor Xa inhibitor, fondaparinux, is superior to unfractionated heparin (UFH) or enoxaparin across the whole spectrum of acute coronary syndrome (ACS) patients, except for those undergoing primary angioplasty, Dr Shamir Mehta (McMaster University, Hamilton, Canada) said. He reported a new analysis of the two trials together showing that fondaparinux reduced both the composite efficacy end point of death/myocardial infarction (MI)/stroke and rates of bleeding compared with UFH/enoxaparin in ACS and ST-elevation MI (STEMI) patients.

Table 1. OASIS-5 and OASIS-6 combined: 30-day main efficacy and bleeding outcomes for UFH/enoxaparin versus fondaparinux

End point	UFH/enoxaparin (n=13,242)	Fondaparinux (n=13,270)	HR	P value
Death/MI/stroke (%)	8.0	7.2	0.91	0.030
Major bleeding (%)	4.4	3.0	0.67	<0.00001

Key: UFH = unfractionated heparin; MI = myocardial infarction; HR = hazard ratio

OASIS-5 randomised 20,078 non-ST elevation ACS patients to fondaparinux or enoxaparin, and showed similar efficacy of the two drugs in reducing cardiac events but a significant reduction in bleeding with fondaparinux. OASIS-6 compared fondaparinux to usual care (UFH or placebo) in 12,092 STEMI patients who had received either thrombolysis, percutaneous coronary intervention (PCI) or no reperfusion therapy, and showed a significant reduction in death/re-MI with fondaparinux with no increase in bleeding.

In the combined analysis, Dr Mehta presented data comparing fondaparinux with both active comparators (UFH and enoxaparin) together, which showed a reduction in both cardiac events and bleeding with the factor Xa inhibitor (table 1).

Can be used safely in PCI

Addressing concerns about catheter thrombosis in patients undergoing PCI on fondaparinux, Dr Mehta presented new data from the two trials combined suggesting that this can be avoided if UFH is added at the time of the PCI procedure and that, under such conditions, fondaparinux still looked favourable compared with enoxaparin/UFH as the initial antithrombotic given in terms of bleeding risk in PCI patients. Of the 306 patients on fondaparinux who were also given UFH at the time of PCI, only one had a catheter thrombosis, and this patient did not get an optimal dose of UFH, he reported.

"A simple tailored strategy of using fondaparinux upstream followed by UFH in the cath lab if PCI is needed preserves the overall benefits of fondaparinux," he noted. But he added that he would not recommend using fondaparinux for primary PCI.

TROICA: no benefit of thrombolysis in cardiac arrest

The first large-scale trial of thrombolysis in cardiac arrest patients has not shown any benefit of such therapy in this indication. The addition of the thrombolytic, tenecteplase (TNK) to standard cardiopulmonary resuscitation (CPR) treatment did not increase survival in cardiac arrest patients in the TROICA (The Thrombolysis in Cardiac Arrest) trial.

Presenting the results, Dr Bernd Boettiger (University of Heidelberg, Germany) explained that out-of-hospital cardiac arrest can have a mortality as high as 95% but there is no specific treatment apart from standard CPR. As up to 70% of cases of cardiac arrest are believed to be caused by acute myocardial infarction or pulmonary embolism, it would seem reasonable to try using thrombolysis in such patients, and several small observational studies have indeed suggested a benefit of this approach, he said.

The TROICA trial involved 1,050 patients with a witnessed cardiac arrest of presumed cardiac origin who were randomised out of hospital to TNK or placebo. TNK was given by paramedics at the same time as CPR. Results showed no difference in any of the efficacy end points. There were no significant differences in symptomatic intracranial haemorrhage or major bleeds between the two groups.

But Dr Boettiger said he still believes there is a rationale for thrombolysis in cardiac arrest. He said the TROICA investigators would be looking carefully at their results to try to establish reasons why no benefit showed. Factors that will be investigated include the timing of thrombolysis, concomitant therapy (heparin), and possible interactions of thrombolysis with other processes going on during cardiac arrest. "All these things are speculative, but I'm not ready to give up on thrombolysis in cardiac arrest yet," he said.

Designated discussant of the study, Dr Frans van de Werf (University of Leuven, Belgium) suggested that in patients who have had prolonged CPR, there may be insufficient blood flow to get the thrombolytic to the heart.

EUROACTION shows nurse-led approach to adjusting lifestyle reduces cardiovascular risk factors

A nurse-led multidisciplinary team approach, coupled with the support and involvement of a patient's partner and family, brought about significant lifestyle improvements and risk factor reductions in patients with heart disease and those at high risk of developing heart disease in the EUROACTION programme.

The largest ever Europe-wide preventive cardiology project, EUROACTION involved eight countries and 24 hospital and general practice centres and addressed the cardiovascular health of more than 10,000 coronary and high-risk patients and their partners. EUROACTION nurses performed complete lifestyle and risk factor assessment of patients and partners and then supported them in making lifestyle changes. Advice was issued according to European preventive cardiology guidelines published in 2003.

Significant improvements with this approach were observed not only in EUROACTION patients but also in their partners, compared to usual care in other hospitals and general practices, across the key lifestyle and risk factors: diet (fruit and vegetable, saturated fat and oily fish intake), physical activity, central obesity, blood pressure, cholesterol and glucose. The administration of cardioprotective medication – antiplatelet therapy, beta blockers, angiotensin-converting enzyme (ACE) inhibitors and statins – was also improved.

Professor David Wood, Chairperson of EUROACTION, commented: "Prevention guidelines are very difficult to implement but the EUROACTION approach sets a new standard for preventive care across Europe which all hospitals and general practices can achieve. The principles of nurse-led multidisciplinary teams, family-based lifestyle intervention as well as total cardiovascular risk management are all central features of EUROACTION, which has demonstrated the potential to significantly improve the quality of patient care. Moreover, having run our prevention programme in busy hospitals and general practice settings, these results are directly applicable to everyday clinical practice".

Professor Michal Tendera, President of the ESC, said: "The European Society of Cardiology produces guidelines which set standards for best practice and measure the uptake of these through European-wide surveys. Now, for the first time, our society has demonstrated, through the EUROACTION project, that we can achieve these targets in a large majority of patients and to great effect. It is now up to us to follow the EUROACTION example and work to establish similar prevention programmes in every general hospital and general practice so that patients across Europe can receive the best possible care".

The EUROACTION study: a perspective from primary care

A number of surveys have highlighted the implementation gap between the evidence base for cardiopreventive interventions and their translation into routine clinical practice. Stimulated by the disappointing results of the EUROASPIRE studies[1] and widespread failure in many European countries to offer cardiac rehabilitation programmes to patients with coronary heart disease (CHD), the European Society of Cardiology (ESC) conceived the EUROACTION initiative. Final results, based on more than 10,000 people, demonstrate the effectiveness of a nurse-led, multidisciplinary team approach, which, coupled with the support and involvement of a patient's partner and family, yield significant lifestyle improvements and risk factor reductions in both CHD and high-risk primary prevention patients.

The project set out to demonstrate the feasibility and effectiveness of a nurse-led intervention programme designed to implement a range of lifestyle and therapeutic goals laid down by European preventive cardiology guidelines.[2] Cluster randomisation between the intervention programme and usual care took place across 24 hospital and general practice settings from eight European countries and the representative, non-specialist nature of the centres mean the results can be generalised to everyday practice.

In both the hospital (secondary prevention) and the general practice (high-risk primary prevention) arms of the study, patients and their partners attended a structured 16-week programme which included lifestyle education, goal setting and tracking (using a personal record card), sup-

'The study took place in busy, hard-working centres and should be reproducible in everyday practice'

Jonathan Morrell

porting documentation and workshops. Recruitment to, attendance at and completion of the programme were good. Lifestyle and therapeutic end points were assessed at 16 weeks in the hospital centres and at one year in primary care. An important feature of both arms of the study was the relationship between the study nurses and prescribing clinicians, prompting new prescriptions and drug titrations when necessary.

Significant lifestyle improvements made

In CHD patients, the EUROACTION programme demonstrated significant improvements in physical activity and fruit, vegetable and oily fish consumption and reductions in saturated fat intake and waist circumference. In addition, significant results were seen for the achievement of blood pressure targets and glycosylated haemoglobin (HbA_{1C}). In high-risk primary prevention patients, significant benefits were seen in physical activity and fruit and vegetable consumption, body mass index (BMI) and waist circumference and again for blood pressure and HbA_{1C} targets. In both arms, non-significant trends only were seen for total and low-density lipoprotein (LDL) cholesterol targets and smoking cessation.

Prompted by the study nurses, the use of drugs increased in both arms. In CHD patients, there were significant increases in anti-platelet agents, beta blockers and statins and in the use of diuretics, angiotensin-converting enzyme (ACE) inhibitors and statins in primary care.

The statistical assessment of the study was exacting. Subject numbers were lower than hoped and, together with allowing for result heterogeneity between centres, this meant that some of the end point trends were non-significant. Compared to EUROASPIRE 2, the results for CHD patients in usual care were surprisingly good. This could represent genuine improvement but could also reflect an involvement bias that underestimates the treatment effect in the intervention groups. In the hospital arm, a fifth of subjects received cardiac rehabilitation in usual care. In general practice, a quarter of subjects in usual care were assessed at baseline to facilitate comparison and this could also be confounding. Although 78% and 81% of intervention CHD patients, respectively, reached total and LDL cholesterol targets, the results were not significant because of the high levels of achievement in usual care (71% and 74%). The trends for smoking cessation (58% *vs.* 47% in CHD patients, 74% *vs.* 72% in primary prevention) are disappointing but further analysis confirms a significant between-groups increase in the number of attempts to quit.

Extensive and useful database

The EUROACTION database is extensive. Much will emerge about the process of the intervention, its specific details, psychosocial dynamics and acceptability and, most importantly, cost-effectiveness. Careful evaluation will emerge concerning staff and drug costs and ultimately, healthcare costs for cardiovascular event saving. Partners were also assessed for lifestyle and risk factor change.

EUROACTION is about effectiveness and translating evidence into practice. The study took place in busy, hard-working centres and should be reproducible in everyday practice. The results in CHD patients are particularly impressive and should stimulate a rethink about the delivery of secondary preventive care in Europe. In primary preventive care, despite positive improvements with the EUROACTION programme, management gaps are still apparent, with disappointing levels of major risk factor control.

EUROACTION succeeds in providing a comprehensive model of care that raises the standard of preventive cardiology for priority patients. The foundation of lifestyle advice within the programme, coupled with therapeutic target achievement and the empowerment and involvement of patients and their family, moves implementation another step closer to the expectations of the evidence base.

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References

1. EUROASPIRE 1 and 2 Group. Clinical reality of coronary prevention guidelines: a comparison of EUROASPIRE 1 and 2 in nine countries. *Lancet* 2001;**357**:995-1001.
2. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Executive summary: *Eur Heart J* 2003;**24**:1601-10 and *Eur J Cardiovasc Prevent and Rehabil* 2003;**10**:S1-S11.