

## Surgeons under threat

According to Marko Turina of the University Hospital Zurich, cardiac surgeons are facing a future of more difficult ethical decisions, fund shortages and intense public scrutiny.

At the European Association for Cardio-Thoracic Surgery (EACTS) and European Society of Thoracic Surgeons (ESTS) joint meeting, Professor Marko Turina spoke on the role of the cardiac surgeon in the future environment. His stated aim was to outline the magnitude of the problems faced by cardiac surgeons.

Cardiovascular diseases remain the leading cause of death in developed countries, in spite of tremendous medical progress. In the European Union, cardiovascular diseases still comprise a large proportion of deaths, somewhere between 36–40% and they are also the leading cause of hospitalisation. However, cardiology has taken away a very large proportion of coronary artery bypass graft (CABG) patients from surgery. "CABG is going to reduce, it has been reduced already now," announced Turina.

"If you look at the UK cardiac surgery registry, in recent years there has been a considerable reduction in the number of coronary artery bypass grafting procedures, while congenital surgery and advanced surgery have remained reasonably constant. There is no doubt that we will be faced with less coronary patients – not only will there be less cases but they will be more complex," said Turina.

"In my country, Switzerland, we have seen a tremendous increase in the number of percutaneous procedures," continued Turina. This interesting change is also observed in Bruce Keogh's *First European Adult Cardiac Surgical Database Report*, which was launched at the EACTS/ESTS joint meeting.

Previously, coronary artery bypass grafting made up a substantial proportion of total cardiac surgery



Marko Turina

activity in developed countries. Now, according to Turina, at the bottom of the scale, in France and Switzerland, this has fallen to about 42–43%. It is only in so-called less developed nations, such as Turkey, that CABG still comprises a large proportion of cardiac surgery. "In

highly developed nations there is going to be less and less coronary surgery," admitted Turina.

"The reason is clear," he said, "stents are taking away many of our patients. Three-vessel disease used to be considered a classical surgical indication but these patients are being diverted to cardiology, based on various prospective randomised studies.

"At the risk of appearing old-fashioned, I must say that I am very reluctant to accept at bareface the results that are being shown now by these studies," Turina said.

"If you put together all the patients from these trials, of 91,000 patients screened only 4.9% of those patients were enrolled. Therefore, the prospective randomised trials represent only a very small proportion of present practice."

### Ageing patients

The second most important development affecting surgeons today is that their patients are becoming older and sicker. In the European Union, there

has been a tremendous increase in life expectancy over the last 40 years. This is driving cardiac surgeons' attention to older and more comorbid patients.

Turina said: "The problem we will be faced with in the next years is the change in the demography. The projection for Switzerland for 2025 shows that the people aged above 65 years of age will comprise 35% of the population. Compared with Turkey, a young nation, which in 2025 will still have only a very small proportion of the population above the age of 65."

Bruce Keogh, in the *First European Adult Cardiac Surgical Database Report*, has observed a substantial increase in the age of CABG patients in recent years. In the substantial database of over 100,000 patients from 1997–2003 there can be seen an increase in average patient age of almost four years from just over 65 to 69 years of age.

"The problem we are faced with is the true nature of atherosclerosis, substantial atheroscleroma in the aortic arch, which makes these patients so difficult to operate on and so prone to neurological complications," explained Turina.

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## TAXUS IV results

IN THE TAXUS IV trial, at nine months, target vessel revascularisation rate (the primary endpoint) in the TAXUS group was 4.7% compared with 12% in the bare metal stent group. TAXUS IV, a randomised, double-blind pivotal trial, is designed to assess the safety and efficacy of a paclitaxel-eluting coronary stent system in reducing restenosis in *de novo* lesions 10–28mm in length and 2.5–3.75mm in diameter. The study enrolled 1,326 patients at 73 sites in the US assessing the safety and efficacy of a Boston Scientific's slow-release formulation paclitaxel-eluting stent.

TAXUS IV reported an in-segment (stented vessel segment plus 5mm beyond each end of the stent) binary restenosis rate of 7.9% in the TAXUS group compared with 26.6% in the control group ( $P < 0.0001$ ). Binary restenosis being defined as 50% or greater vessel reocclusion. The study reported an in-stent binary restenosis rate of 5.5% in the TAXUS group compared with 24.4% in the control group ( $P < 0.0001$ ). In addition, the study found significant improvements in the more sensitive, quantitative angiographic measurements (in-segment, in-stent and at the edges), such as in-segment percent diameter stenosis (26.3% in the TAXUS group versus 39.8% in the control group;  $P < 0.0001$ ), in-segment minimum lumen diameter (2.03mm in the TAXUS group versus

1.68mm in the control group;  $P < 0.0001$ ) and in-segment late lumen loss (0.23mm in the TAXUS group versus 0.61mm in the control group;  $P < 0.0001$ ).

"The TAXUS stent system represents a major advance in the treatment of coronary artery disease," said Gregg Stone, the study's Principal Investigator and Vice Chairman of The Cardiovascular Research Foundation at the Lenox Hill Heart and Vascular Institute. "The extremely low restenosis rates at nine months with the paclitaxel-eluting TAXUS stent system – in concert with its proven safety profile, flexibility and deliverability – represent a new benchmark for the interventional treatment of patients with atherosclerosis. Remarkably, the outcomes were similar across the spectrum of patients studied in the trial, including those with diabetes, small vessels and long lesions."

For further details on TAXUS IV results and discussion see reports from TCT2003 inside.



Gregg Stone



Peter Walton and Bruce Keogh

## First European Adult Cardiac Surgical Database Report

AT THE European Association for Cardio-Thoracic Surgery (EACTS) and European Society of Thoracic Surgeons (ESTS) joint meeting in Vienna, the *First European Adult Cardiac Surgical Database Report* was launched. This report, produced by the EACTS Database Committee and Dendrite Clinical Systems, overviews performance parameters of cardiac surgery throughout Europe.

The *First European Adult Cardiac*

*Surgical Database Report* will increase knowledge about the status of cardiac surgery throughout Europe and, therefore, the representation of cardiac surgery and the specialty's ability to negotiate important aspects will be strengthened.

There is a need to understand the nature, variations and inequalities of cardiac surgical care across Europe to help surgeons negotiate with healthcare providers, acquire appropriate resources and develop their practices. The starting point for this is the collection of surgical data from across Europe.

The EACTS Council and Database Committee have taken the view that there is strength in a unified pan-European approach, where responsibility is co-ordinated by the surgical community through the EACTS and the national societies.

There is a growing recognition that in

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## ESC

## ON-TIME

RESULTS FROM the Ongoing Tirofiban in Myocardial Infarction Evaluation (ON-TIME) were presented by Arnoud van't Hof of Zwolle, the Netherlands. ON-TIME is a randomised multicentre trial of myocardial revascularisation with percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) treated with tirofiban before PCI.

One group of patients was randomised to the early administration of tirofiban, started during transportation to the catheterisation laboratory, and one group received placebo during transportation to the cath-lab and started tirofiban late, after the first angiogram.

The primary endpoint of the study (the angiographic normal coronary flow (TIMI 3) at the initial angiogram) was not significantly different between the two groups (19% in the early group versus 15% in the late group,  $P=0.22$ ). However, patients treated early had significantly less totally occluded vessels (TIMI 0: 44% versus 59%,  $P=0.0013$ ). Also patients in the early arm had a significantly higher rate of TIMI 2 or TIMI 3 (patency compared with the late arm (43% vs. 34% respectively,  $P=0.04$ ).

## GRACIA-2

The GRupo de Análisis de la Cardiopatía Isquémica Aguda (GRACIA) 2 trial, funded jointly by Guidant and Eli Lilly, was presented by Francisco Fernandez-Avilés of Spain. GRACIA is the Spanish equivalent of the acute ischaemic heart disease study group.

The hypothesis of the GRACIA-2 trial is that the combination of immediate thrombolysis plus early complementary angioplasty (facilitated angioplasty) is as widely applicable as thrombolysis and as effective as primary angioplasty.

With the advent of improved drugs and stents, a trial was necessary to reevaluate the potential benefits of an early interventional approach shortly after thrombolysis.

With this aim, the 15 Spanish and Portuguese GRACIA centres compared the progress at six weeks and six months of 212 patients with heart attacks who agreed to participate in the trial and to be assigned to two different strategies:

- 1) Optimal primary angioplasty within 180 minutes of symptoms onset; or
- 2) Facilitated intervention, consisting of performing immediate administration of the easily applicable thrombolytic tenecteplase followed by cardiac catheterisation and the reparation of all severely diseased coronary arteries by means of the implantation of a stent within 3–12 hours of symptoms onset. Patients not suitable for stent implantation underwent coronary open-heart bypass surgery or intensive drug therapy.

Delay from the onset of symptoms and the first medical contact was similar in both groups of patients and there were no differences between groups with respect to baseline demographics and clinical characteristics including age, gender, previous medical history, cardiovascular risk factors, type of infarction. Both groups were also similar with respect to the culprit artery. However, in the group of patients assigned to facilitated intervention a higher percentage of completely reopened culprit artery was found (70% versus 40%) as a result of previous thrombolysis.

Fernandez-Avilés concluded by saying the results of the GRACIA-2 trial indicate that, nowadays, in patients with heart attack, the strategy of performing cardiac catheterisation and appropriate intervention within 3–12 hours of facilitation with tenecteplase seems to be as feasible and safe as primary angioplasty.

He also said that these data suggest that the efficacy of primary angioplasty and facilitated intervention in preserving cardiac muscle and improving prognosis is equivalent. If this equivalency is confirmed in further larger trials, the proportion of patients with heart attacks who can benefit from early coronary stent-angioplasty will increase dramatically.



Francisco Fernandez-Avilés and Joachim Schofer

## ESC Hotline II

The Hotline II session of the European Society of Cardiology Congress included results from the E-SIRIUS and DELIVER II studies.

Frans Van de Werf of Gasthuisberg University Hospital, Leuven, Belgium, looked at the pros and cons of the trial. He commented that GRACIA-2 is very similar to the CAPTIM trial, which showed the benefit of thrombolysis when given early. He asked the question: Why is there a mortality reduction when early thrombolysis is given? He suggested cardiogenic shock and time to randomisation as possible factors. Van de Werf concluded by saying GRACIA-2 is a carefully designed pilot study which supports combined pharmacological and mechanical approach. However, results from larger trials, such as ASSENT 4, ADVANCE MI and FINESSE, which together will comprise more than 13,000 patients, are needed to confirm the GRACIA 2 findings.

## DECOPI

Gabriel Steg of the Hôpital Bichat, Paris, France, presented results from the Desobstruction Coronaire en Post-Infarctus (DECOPI) trial, which sought to determine whether reopening the closed artery after an acute myocardial infarction is useful. This trial was funded jointly by Guidant and CNAM.

Acute myocardial infarction is typically caused by abrupt blockage of a coronary artery. Timely reopening of the artery by thrombolysis or by angioplasty may salvage myocardium, preserve myocardial function and reduce mortality. However, for this treatment to be effective it must be implemented within the

first 12 hours after the onset of symptoms and patients often seek medical attention too late. When patients are seen later, there is controversy whether or not it is beneficial to reopen the closed vessel by angioplasty. On one hand, it is hoped that reopening the vessel, even late, may preserve the function of the heart, reduce the risk of arrhythmia and provide a rescue channel for blood to flow in the event that another coronary artery develops a blockage. On the other hand, it is too late to salvage myocardium and there are risks and costs to the procedure of angioplasty.

The DECOPI trial compared angioplasty to conventional medical therapy in patients with a complete occlusion of a large coronary artery two to 15 days after an acute myocardial infarction. 212 patients were enrolled in 34 hospitals (33 in France, one in Belgium) between 1998 and 2001 and randomly assigned to angioplasty of the closed infarct artery or medical therapy.

After an average of 34 months of follow-up, the comparison between the two strategies shows no significant difference in the occurrence of cardiovascular death, myocardial infarction or ventricular arrhythmia. (8.7% in the medical group, 7.3% in the PCI group,  $P=0.64$ ).

At six-months angiographic follow-up, patency of the infarct artery was significantly lower in the medical arm (39.7%) than in the angioplasty arm (82.7%). Investigators reported that 47% of the angioplasty patients

Gabriel Steg, Sigmund Silber and Eberhard Grube



developed restenosis. At six months, angiographic left ventricular ejection fraction was superior by approximately 3.5% in the angioplasty arm ( $P=0.025$ ).

Steg concluded by saying that the overall event rate in the study population was low and there was no obvious clinical benefit to systematic angioplasty of the infarct related vessel. The results show limited benefit for routine PCI after an acute myocardial infarction from a limited sample. Steg commented that PCI is €1,000 more expensive and that there are also problems with PCI such as the restenosis rates of 47% at six months.

Eugene Braunwald from the US talked about the effect of late PCI post-MI, which has been looked at in various studies such as Total Occlusion Post-Myocardial Infarction Intervention Study (TOMIIS); Thrombolysis and Angioplasty in Myocardial Infarction-6 (TAMI-6). Although DECOPI had less than one-third of the planned number of patients, it is the largest single trial to date with 212 patients.

There seems to have been no effect on any one endpoint, but DECOPI does not kill the "open artery hypothesis" according to Braunwald because the trial was underpowered, it was a low-risk population and in the PCI arm only 82% achieved TIMI 3 flow.

Braunwald said there is a real need now to look at a high-risk population. He went on to mention the Open Artery Trial (Judith Hochman), which is NIH sponsored with 3,200 patients, 1,400 of which have been recruited. This trial is currently underway in the US, and the hope is that it will give more definitive answers in four to five years.

## E-SIRIUS

Joachim Schofer from Hamburg, Germany, presented the results of a European multicentre randomised, double-blind study of the Sirolimus-coated balloon-expandable stent in the treatment of patients with *de novo* native coronary artery lesions (E-SIRIUS)

E-SIRIUS was conducted at 35 hospitals all over Europe and enrolled a total of 352 patients, 175 of whom received the sirolimus-eluting stent, whereas the remaining 177 patients were treated with the uncoated, bare-metal stent.

42% of all patients receiving the bare metal stent exhibited restenosis, defined as a greater than 50% re-narrowing of the coronary artery lumen at the treatment site. In contrast, only 6% of patients treated with the coated stent showed restenosis. This corresponds to a relative reduction of 86% in the incidence of restenosis.

Consequently, the incidence within nine months of major adverse cardiac events (MACE) – which comprised deaths, myocardial infarctions and repeat interventions at the original treatment site – was also significantly reduced in patients treated with the coated stent (8% as opposed to 23% in control patients).

The outstanding finding was that not a single patient that had a drug-eluting stent had any restenosis at the stent margin.

In 26% of the E-SIRIUS patients, 45 of whom received the coated stent and 47 the bare-metal control stent, the investigators chose the direct stenting approach. Neither for the coated stent nor for the control group was there a statistically significant difference in the restenosis rates and the MACE rates between the direct stenting and the predilatation approach. Based on these data the investigators believe that direct stenting is as safe and as effective as predilatation plus stenting.

Sigmund Silber of the University of Munich, Germany, was the discussant for E-SIRIUS. He said that there was a 1.7 ratio of stent length to lesion length, which may explain why there was no edge effect. The results between direct stenting and predilatation were very similar and he said that the results for CYPHER are similar to those of TAXUS.

He highlighted some limitations in the

study including that:

- 1) This was not a randomised study;
- 2) Direct stenting is not the most important parameter – the most important parameter is the degree of decalcification of the lesion;
- 3) The primary endpoint was angiographic not clinical

#### DELIVER II

The DELIVER II trial is a prospective, non-randomised controlled trial in which 1,533 patients were included in 86 sites across Europe, the Middle East and Africa. Patients were followed for six months and a subset of 500 patients will have a long-term follow-up. Only patients with coronary lesions with a high risk of revascularisation were included.

The trial is designed to evaluate the ACHIEVE paclitaxel-eluting coronary stent system in the treatment of lesions at high risk for revascularisation due to restenosis. Preliminary results were presented by Eberhard Grube.

At six months, the target lesion revascularisation (TLR) rate in the overall population was 10.5%, and the hierarchical MACE rate (death, Q-wave MI, non-Q-wave MI and TLR) was 15.7%. Univariate analysis identified the following lesion risk factors as the ones contributing the most to TLR: small vessel (=2.75 mm), left anterior descending (LAD) artery, restenotic lesion and total stent length ( $P<0.05$ ). The following patient risk

factors were pointing to worsened prognosis: angina and number of diseased vessels. Multivariate analysis identified the following factors to be at higher risk of revascularisation: post-procedure minimum lumen diameter, LAD, restenotic lesion, total stent length and number of diseased vessels.

According to Grube, DELIVER II indicates that patients receiving non-polymeric paclitaxel-eluting stents that have one or more of these risk factors should be followed up more extensively and care should be taken to avoid negative clinical consequences.

The discussant, Carlo Di Mario, said that although DELIVER II included real life challenging lesions, he felt that the endpoint of the trial was wrong. Di Mario is unconvinced of the value of the detection of predictors of TLR. He also highlighted that the study was not randomised.

#### ESTEEM

The Efficacy and Safety of the oral Thrombin inhibitor ximelagatran in combination with aspirin, in patients with recent Myocardial damage (ESTEEM) trial is a multicentre, placebo-controlled, double-blind study that compared the safety and efficacy of four doses of the direct oral thrombin inhibitor ximelagatran in combination with aspirin against placebo in the long-term treatment of patients who had recently been admitted for ST-segment elevation or non-ST-segment myocardial infarction (MI).

ESTEEM is a randomised, placebo-controlled, double-blind dose-guiding study that included 1,883 patients in 191 hospitals in 18 countries throughout 2001–2002. Within 14 days of a heart attack patients were randomised to six months treatment with tablets twice daily of either 24, 36, 48 or 60mg of ximelagatran or placebo. This treatment was added to the current standard treatment with aspirin and other drugs known to protect against new heart attacks.

ESTEEM showed that compared with placebo, ximelagatran reduces the risk of death, recurrent heart attack or attacks of severe chest pain from 16.3% to 12.7% during six months treatment ( $P=0.036$ ). This corresponds to a relative risk reduction of 24% – meaning that patients treated with ximelagatran are 24% less likely than those treated with placebo to suffer a recurrent heart attack, severe chest pain or death. This improvement was seen in comparison to placebo when given on top of the current standard treatment, aspirin. There was an even more pronounced reduction in the combination of death, heart attack and stroke from 11.1% to 7.4% corresponding to a relative risk reduction of 34%. There was no difference in efficacy between different doses of ximelagatran

“The results of this study are very exciting as they show the first proof of the efficacy of oral direct thrombin inhibition in this new

indication, and demonstrate that this new concept holds great promise for better protection against heart attack and stroke in patients at risk of further cardiovascular events”, said Lars Wallentin, Professor of Cardiology at Uppsala University Hospital, Sweden, who presented the ESTEEM study results at the ESC meeting.

Freek Verheugt, of Nijmegen, the Netherlands, commented that this study proves the concept of a novel oral anticoagulant therapy, although three issues remain.

- 1) There was no dose response efficacy but there is bleeding and liver enzyme abnormalities. If we trade in coumadin for ximelagatran – do we have to replace International Normalized Ratio (INR) blood test for Liver Function Test (LFT)?
- 2) The trial made no comparison to clopidogrel or coumadin.
- 3) What would have been the outcome if early intervention had been done?

Verheugt said that more studies with acute coronary syndromes (ACS) are needed. He continued by saying that there also needs to be a direct comparison with clopidogrel and coumadin. He emphasised that the liver safety issues need to be studied and said that he sees the future use of ximelagatran as early in ACS with or without reperfusion therapy, in patients undergoing PCI and patients with artificial heart valves.

## Carotid stenting: Ready for primetime?

THE STATE of carotid stenting was addressed in a main session during the European Society of Cardiology (ESC) Congress 2003. The session was opened by Martin Brown of the National Hospital for Neurology and Neurosurgery, London, UK, who spoke on the medical management of carotid disease and indications for revascularisation. He presented data that indicated there was no major difference in outcome based on odds ratio to risk (0.99 for carotid stenting vs. surgery) based on the available data. Brown concluded his talk by stating that carotid artery stenting (CAS) is nearly ready for primetime. The technology has improved greatly with smaller guidewires and better quality stents, and with the introduction of cerebral protection devices. The technique continues to evolve.

An overview of the carotid stenting technique, and the pros, cons and pitfalls of various embolic protection devices was then given by Marco Roffi from Zurich, Switzerland.

#### Filters

Roffi highlighted some of the disadvantages of filters:

- 1 The larger crossing profile;
- 2 The fact that the crossing is unprotected;
- 3 Particles of <100microns may embolize.

Talking about troubleshooting with filters he looked at the problem of advancing the device through the lesion, the problem of advancing the device distal to the lesion, also how to manage no flow as well as failure to retrieve the filter.

#### Distal/proximal occlusion

Roffi said that with distal/proxi-

mal occlusion the advantages are that there is no unprotected crossing and there is more complete emboli capture. The disadvantages that he cited were poor visualisation, potential for cerebral ischaemia, more difficult handling and the fact that the devices are larger.

Roffi concluded by telling the ESC audience that they should work with the devices that they are most comfortable with and ideally tailor them to the patient.

Klaus Matthias, the founding father of carotid stenting, then took the podium to tackle the issue of what you should know before engaging the common carotid artery.

He emphasised that CAS is a preventive therapy and the feasibility and selection of devices should be based on the following:

- Is there normal access to the internal carotid artery (ICA)?
- Is the stenosis haemodynamically compensated?
- Is there additional brain pathology?
- What is the type of ICA pathology?
- Has there been good evaluation of plaque?

Ivan Casserly of the Cleveland Clinic gave an overview of the randomised controlled trials that have compared stenting versus surgery. He pointed out that carotid endarterectomy was first performed in 1954 and that it needed 40 years for level 1 evidence to become available with the publication in 1998 of the North American Symptomatic Carotid Endarterectomy Trial (NASCET), and the European Carotid Surgery Trial (ECST). Carotid artery stenting started in 1994. The first randomised controlled trial was CAVATAS in



Marco Roffi  
Ivan Casserly



Martin Brown



2001, the one-year data from SAPHIRE has just been published and data is expected from the CREST in 2005/6.

Casserly highlighted that in the NASCET trial one-third of patients were enrolled from the participating sites so that this was a healthy subset of patients with carotid disease. He compared the mortality rates in the trial, which were 1.4% to the non-trial rate (1.7%) and the mortality rate in low-volume

centres (2.5%).

Casserly concluded by pointing out how MI/death/stroke rates for Gary Roubin's carotid stenting series have dropped from 9.3% to 4.3% and highlighted that CAS results have improved with embolic protection devices and that there are now results from a randomised controlled trial (SAPHIRE) and registries such as ARCHeR, SHELTER and MAVERICK, which corroborate the findings.

## Euro Heart Survey on Diabetes and the Heart

THE FIRST DATA from the ongoing Euro Heart Survey on Diabetes and the Heart, which aims to cover 6,000–9,000 patients with coronary artery disease across Europe, were released during the European Society of Cardiology Congress 2003.

The preliminary data, which looked at 3,540 patients recruited from 95 centres and 25 countries, found that among consecutive acute patients admitted to coronary care units or cardiology wards, 69% had glucose intolerance and that among chronic patients (treated routinely in cardiology outpatients' clinics), 47% had glucose intolerance. This suggests that glucose intolerance among heart disease patients may be more widespread than previously thought.

Professor Lars Rydén, from the Karolinska Hospital, Stockholm, Sweden, said: “The results suggested that abnormal glucose tolerance is much higher than anticipated in patients with coronary artery disease. It may prove a useful tool when outlining the long-term management of patients with coronary artery disease.”

The Euro Heart Survey on Diabetes and the Heart started in April 2003 and its main objectives are to:

- Assess the prevalence of diabetes mellitus and impaired glucose tolerance in adult patients with coronary artery disease (newly or previously established, acute or stable, with or without heart failure);
- Verify the applicability of established guidelines, based on the outcome of major clinical trials, in this population through investigating clinical practice in the form of diagnostic and therapeutic strategies in patient management;
- Compare diagnostic and therapeutic strategies in patients with coronary artery disease in relation to glucose metabolism (diabetes, impaired glucose tolerance or no diabetes);
- Identify opportunities to improve patient management by improving established or developing new guidelines and their implementation.

According to Rydén the survey will be completed by “the end of this year and then follows data analysis”.