Clinical experience with renal denervation for proven resistant hypertension

‘Interventional Cardiovascular Medicine’: is there a new speciality on the horizon?
Hybrid approaches to multivessel coronary artery disease
“Should interventionists be afraid of ISCHEMIA?”
Pre-hospital management of AMI

Supported by an unrestricted educational grant from Medtronic, Inc
Dear colleagues,

Welcome to the fifth issue of Confluence: concepts and opinions in interventional cardiovascular medicine. We have made some key changes to both the scope and content of this issue of the journal to make it, we hope, even more topical and relevant to your daily practice. The change in title reflects a shift in scope to focus on topics of interest to the entire multidisciplinary ‘Heart Team’. By addressing issues as diverse as the role of drug eluting balloons in peripheral cardiovascular disease, renal denervation as a new treatment for resistant hypertension, and novel approaches to the pre-hospital management of acute myocardial infarction, we hope there will be something to attract your attention.

With this change of scope in mind, we are fortunate enough to welcome two esteemed colleagues to the Confluence Editorial Board: Professor Isabelle Durand-Zaleski, France, joins us as a specialist in reimbursement and Professor Luis Ruilope, Spain, is an expert in the management of hypertension.

In terms of content, we have introduced a new type of article, our so-called ‘Hot topics’. These short news articles focus on controversial or cutting-edge topics identified by our Editorial Board. In this issue, we provide an update on the latest research on the use of drug eluting balloons in the peripheral and coronary field, overview some of the strategies that have been implemented to improve pre-hospital management of acute myocardial infarction, and present the latest findings of two pivotal studies: the Swedish Coronary Angiography and Angioplasty Registry exploring the risk of stent thrombosis with drug eluting stents, and the Resolute Integrity study in patients with diabetes. We hope you will find these articles stimulating, no matter what your speciality.

Another change is an increase in the number of our articles based on interviews with key thought leaders in the field of interventional cardiovascular medicine. These articles have provoked much interest in previous issues and have provided an invaluable insight into the opinions of these thought leaders on issues of particular importance to the Confluence readership. We have included an interview with Professor Eeckhout about the change in the way interventional cardiology is practiced. He describes the much awaited publication of Percutaneous

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Contents

Hot topic
SCAAR reveals lower risk of stent thrombosis and restenosis with unrestricted use of ‘new-generation’ drug-eluting stents in clinical practice

Expert opinion
Clinical experience with renal denervation for proven resistant hypertension

Interview
The Great Debate
Left main in 2011: CABG or PCI?

Hot topic
Pre-hospital management of acute myocardial infarction (AMI): strategies to improve diagnosis and allow for early reperfusion

Expert opinion
Hybrid approach to multivessel coronary artery disease: is minimally invasive left internal mammary artery to left anterior descending artery and drug-eluting stents in other vessels a viable solution?
Interventional Cardiovascular Medicine’, highlighting how this book aims to capture best practice in cardiovascular medicine. We also spoke with Professor Hochman, the Study Chair of the ISCHEMIA Trial, and asked her how this trial might impact clinical practice. Finally, we caught up with two of the discussants of ‘The Great Debate’, Professors Taggart and Ėrglis. We questioned them about the outcomes of this fascinating debate, which discussed left main coronary artery bypass graft versus percutaneous coronary intervention at the recent ESC and EACTS meetings, and at EuroPCR.

Our ‘Expert opinion’ forum continues to provide professional insight and opinion on controversial issues in the field of interventional cardiovascular medicine. The first of the three articles delivers an overview of the use of percutaneous renal sympathetic denervation as an alternative interventional treatment option for patients with resistant arterial hypertension. Drawing on their extensive experience with this approach, Dr Nef and his colleagues provide details on the renal denervation procedure and summarize the clinical evidence base for this technique. The second article examines the hybrid approach to multivessel coronary artery disease, asking whether minimally invasive left internal mammary artery to left anterior descending artery and drug-eluting stents in other vessels is a viable solution. Dr Repossini provides an insightful perspective on this controversial subject. The final article examines some of the challenges surrounding stent design. In this article, Dr Haworth and his colleagues provide a thoughtful assessment of longitudinal stent distortion in clinical practice and present a rationale for considering longitudinal strength when designing stents.

As a whole, our updated scope and look reflects our commitment to continuing to provide a journal that acts as a forum for the exchange of opinions and ideas, and the discussion of controversial topics. We hope that you will find this issue thought provoking and relevant to your everyday practice. As always, your opinions are important to us, so please do let us know your feedback on this issue, and the journal in general, by emailing us at confluence@axon-com.com. We would be delighted to receive proposals from you on topics to cover in future issues.

Christian Hamm
The Course is just around the corner!

Prepare your programme with the new and improved search engine, print your e-badge and confirm your room in two easy clicks on europcr.com...

Ready? See you in Paris!
SCAAR reveals lower risk of stent thrombosis and restenosis with unrestricted use of ‘new-generation’ drug-eluting stents in clinical practice

Data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR), an observational study from a large real-world population (n=94,384), has demonstrated that percutaneous coronary intervention (PCI) with new-generation drug-eluting stents (DES) is associated with a 38% lower risk of clinically meaningful restenosis, a 43% lower risk of stent thrombosis, and a 23% lower risk of death compared with older-generation DES. In 1,800 patients, Xience V has been shown to have reduced levels for all death, non-fatal myocardial infarction (MI), TVR compared to an old-generation stent (Taxus Liberté) at one year (56/827 [6%] vs 82/903 [9%] respectively; \(P=0.02\)). Recently, in 2,292 adult patients with chronic, stable coronary artery disease or acute coronary syndromes, the Resolute stent has been shown to be non-inferior to the Xience V stent for cardiac death, target vessel MI, and ischaemia-driven target lesion revascularization at 1 year. However, long-term and comparative clinical data for these stents are limited. The findings of the SCAAR registry help to shed light on the long-term benefits of these new stent designs.

As well as demonstrating new-generation DES (e.g., Endeavor Resolute; Xience V; Promos, Boston Scientific) are associated with a 23% lower risk of death at 2 years compared with older-generation DES (e.g., Cypher, Cordis Corp; Taxus, Boston Scientific; Endeavor, Medtronic, Inc.), these data, published in the European Heart Journal, represent the first time any mortality reduction has been shown between both new and old-generation DES, and BMS (e.g., Multilink, Abbott; Driver, Medtronic, Inc.; Chrono, CID) – either in randomized trials or from previous reports from SCAAR. The risk of death was 45% lower with new-generation DES and 28% lower with older-generation DES, when compared with BMS (1.9%, 3.4% and 6.8% mortality respectively). The authors note that that this phenomenon has not been observed in previous randomized studies and that unrecorded differences in baseline characteristics may have influenced this figure. However, they also note that the large study size could provide sufficient power to detect these differences.

Whilst these data demonstrate the advantages of new-generation DES, the authors acknowledge that further work is required to understand how the findings might impact on the clinical management of patients, especially those with a high-risk profile for stent thrombosis and restenosis.

REFERENCES:
Clinical experience with renal denervation for proven resistant hypertension

Introduction
Arterial hypertension represents a major risk factor for cardiovascular morbidity. The incidence of arterial hypertension in Europe is about 45%, although the number of unreported cases is thought to be even higher. Despite optimal medical treatment, 5–15% of patients have therapy resistant arterial hypertension. Hypertension is classified as resistant if there is an insufficient reduction in systolic and diastolic blood pressure, despite the intake of at least three antihypertensive drugs of different classes (including a diuretic), at maximum permissible doses alongside lifestyle changes. Importantly, secondary hypertension must be excluded.

The persistence of hypertension is partly regulated by the renal sympathetic nervous system. Renal sympathetic efferent and afferent nerves (Th–10L1) within and surrounding the wall of the renal arteries are decisive for arterial hypertension. The afferent sympathetic system is activated by rising adenosine levels and affects regulation of the neuro-humoral axis by the central nervous system. In contrast, renin release, juxtaglomerular function and renal blood flow are regulated by the efferent sympathetic nervous system. In addition, sympathetic activity modulates glucose metabolism and insulin sensitivity. Modulation of the sympathetic system has been examined using a radical surgical method involving thoracic, abdominal and pelvic sympathetic nerve denervation in a trial of 50 patients. Although successful in lowering blood pressure, this method was associated with high peri-operative morbidity, vertiginous, and bowel, bladder and erectile dysfunction.

Percutaneous renal sympathetic denervation represents an alternative interventional treatment option for patients with resistant arterial hypertension. This treatment involves modulation of the sympathetic nervous system by selective denervation through radiofrequency (RF) ablation. Prior to the procedure it is essential to exclude arterial hypertension due to a secondary origin. The most prevalent origins of secondary hypertension are stenosis of the renal arteries, primary hyperaldosteronism and obstructive sleep syndrome. Therefore, imaging of the renal arteries, to exclude haemodynamic stenosis or abnormal anatomy, should be performed. In addition, hormonal diagnostics are necessary to detect primary hyperaldosteronism, pheochromocytoma and Cushing syndrome. An ambulatory blood pressure measurement is also recommended to rule out pseudo-resistance.

Procedure for renal denervation
Percutaneous sympathetic renal denervation is performed by a transfemoral approach using a 6F sheath via the femoral artery. The catheter is introduced into the arterial system and advanced to the renal arteries. A specific Symplicity Catheter (Symplicity Catheter System, Ardian, Medtronic, Inc. USA) is used for the procedure, which includes an electrode on the catheter tip for ablation (fig.1). The catheter is connected to a radiofrequency generator. In terms of anatomical conditions, the renal artery should have a diameter of at least 4 mm to tolerate the temperature rise and avoid spasm. In addition, the artery should have a length of at least 20 mm to the first significant bifurcation in order to allow several ablations to be

fig. 1
The Symplicity Catheter, including an electrode on the catheter tip for energy delivery. (Symplicity Catheter System, Ardian, Medtronic, Inc. USA)
performed. The first RF ablation point should be placed proximal to the first bifurcation of the renal arteries. The catheter is retracted by approximately 5 mm and the single ablation points are set in a circumferential formation. In total, depending on the anatomical conditions, RF ablation is performed 4–6 times within each renal artery, in anterior, superior, posterior and inferior positions across the full circumference (fig. 2). The power delivery is controlled by a connected generator and limited to a maximum of 8 watts and to a temperature of 40–70°C. Energy delivery time is limited to two minutes. Systemic anticoagulation is necessary during the procedure; antiplatelet treatment (acetylsalicylic acid [100 mg]) is required for a total of three months following intervention. A 24-hour ambulatory blood pressure measurement should be performed to measure treatment efficacy.

**Experience from clinical trials**

**Effects on blood pressure**

The effectiveness and feasibility of catheter-based sympathetic renal denervation has been shown in international multicentre studies. These studies enrolled patients with a systolic blood pressure >160 mmHg (>150 mmHg for patients with type 2 diabetes mellitus) despite taking at least three antihypertensive drugs (including diuretics) at maximum tolerable doses. 

At 12 months following renal denervation, results showed a notable reduction in systolic blood pressure, with an average reduction of 27 (± 12) mmHg (fig. 3), with no serious complications having occurred. Post-procedural renal imaging showed no evidence of renal artery stenosis, aneurismal dilatation or damage in these patients. In addition, no changes in renal function were measured, supporting the safety of this procedure, potentially including those patients with moderately reduced renal function. Sympathetic outflow increased in patients with essential hypertension, suggesting that renal denervation selectively reduces efferent sympathetic activity. This was confirmed by a reduction of the noradrenaline levels in the spillover measurement. Hence, both renal blood flow and renin plasma levels are decreased.

Given the regrowth of sympathetic nerve fibres, long-term data on the persistence of the blood pressure lowering effect are of particular interest. Results showed that the blood pressure reduction was sustained for an observation period of 24 months (fig. 4), suggesting that effects of nerve fibre regrowth are not clinically relevant. Furthermore, no major complications, including stenosis, aneurysm and cholesterol emboli, were reported during a post-interventional time period of two years. However, a progression of a pre-interventional existing stenosis was observed in one patient.

The therapeutic response, defined as a systolic blood pressure reduction of >10 mmHg, after renal denervation, was 84–92%. Intake of central sympatholytic medications, low heart rate, and an increased systolic blood pressure before renal denervation were shown to be predictors for a significant blood pressure reduction; predictors for non-responders are yet to be evaluated.

From our own observations, the efficacy in blood pressure reductions after treatment could be broadly assigned into three groups. One group (20–25%) showed a prompt blood pressure reduction within the first few days following denervation. This reduction was maintained at a lower level in follow-up measurements. The second group (65%) did not show any significant changes in blood pressure during the early period after treatment, but did show a notable reduction in blood pressure after 3–6 months. Finally, consistent with data from other trials, some patients did not show a significant reduction in blood pressure either during the early period, or after three or six months.

**Effects on glucose metabolism**

Resistant arterial hypertension is associated with comorbid metabolic anomalies, as a result of insulin resistance and dysregulation of the glucose metabolism caused by sympathetic overactivity. Findings demonstrated that lower levels of sympathetic activity alongside reduced
blood pressure following renal denervation was associated with a positive effect on glucose metabolism, such as insulin production.\textsuperscript{11}

\textbf{Effects on renal function}

To date, renal denervation studies have excluded patients with progressive chronic kidney disease (estimated glomerular filtration rate [eGFR] <45 ml/min/1.73 m\textsuperscript{2}) due to potential kidney damage after ablation.\textsuperscript{13} However, from own experience there is a trend for increased eGFR following renal denervation, although it is unclear whether this was due to the reduction in blood pressure or a direct effect of the reduced sympathetic nervous activity in the kidneys. Cholesterol emboli or thermal damage were not observed or were not described in previous studies.\textsuperscript{13} Severe resistant hypertension is common in end-stage renal disease and a high degree of sympathetic nervous activation is observed in such patients.\textsuperscript{16} In some patients with post-transplantation hypertension, bilateral nephrectomy is done to manage the severe hypertension present.\textsuperscript{17} This population may experience considerable benefit from catheter-based renal denervation procedures.

\textbf{Effects on sleep apnoea}

Obstructive sleep apnoea syndrome is associated with cardiovascular risk factors, such as resistant hypertension, insulin resistance and metabolic syndrome, as well as with cardiovascular diseases. It was considered that obstructive sleep apnoea syndrome could be both a reason for, as well a consequence of, increased sympathetic activity.\textsuperscript{18} Obstructive sleep apnoea syndrome is common in those with resistant hypertension having been described in up to 80\% of these patients.\textsuperscript{19-21} A recent study showed a relationship between reduced blood pressure levels and improvements in sleep apnoea.\textsuperscript{18} Whilst the association and mechanism of the interaction between catheter-based blood pressure reduction and improvement in sleep apnoea has yet to be evaluated, it has been suggested that the reduced fluid retention after renal denervation may play a major role in this process.\textsuperscript{18} Given the link between sympathetic nervous activity and insulin resistance, blood pressure and sleep apnoea, it is apparent that renal denervation could offer a clinical benefit in some patients with these disorders.\textsuperscript{18}

\textbf{Effect on the cardiorespiratory response}

It was recently demonstrated that a reduction in peak systolic blood pressure occurs during exercise following renal denervation.\textsuperscript{20} Moreover, the heart rate recovery was improved compared with baseline. Dysregulation of blood pressure or heart rate did not occur at the cost of blood pressure adaption. Despite a slight improvement of the maximum work rate, the oxygen consumption (VO\textsubscript{2} peak) was not significantly altered. Furthermore, there were no changes regarding the minute ventilation or ventilatory efficiency after renal denervation.\textsuperscript{22}

\textbf{Conclusion}

Renal denervation, through selective ablation of the renal sympathetic efferent and afferent nervous system, represents a new treatment option for patients with resistant arterial hypertension. In addition to the reduction in blood
pressure, the reduced sympathetic activity also has a positive effect on glucose metabolism, including increased insulin production, as well as on sleep apnoea. Persistence of the reduction in blood pressure was demonstrated by sustained effects over an observation period of 24 months. No major complications, including stenosis, aneurysm of the renal arteries and cholesterol emboli, were described. However, for a small proportion of patients (8–16%), no effects were achieved with this new therapy option. However, recent data presented at the 2012 American College of Cardiology Annual Meeting demonstrate that in patients followed for 36 months (n=24), there was a 100% response rate, as defined by an office blood pressure reduction ≥10 mmHg. Similar results were seen at 3 years even amongst non-responders at 1 month (n=8), with 100% of these patients also achieving ≥10 mmHg reduction in blood pressure.\textsuperscript{21} Predicting parameters for non-responders have yet to be described and it is still unclear which parameters or biomarkers can identify patients who will benefit from renal denervation. A better understanding of these issues requires further clinical trials in a large number of patients.

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The Great Debate
Left main in 2011: CABG or PCI?

‘The Great Debate’ gathered esteemed cardiologists and cardiac surgeons from around Europe at the EuroPCR congress in May 2011, ESC congress in August 2011 and EACTS annual meeting in October 2011 to discuss left main disease in 2011: CABG or PCI?

Confluence caught up with two of the discussants: Professor David Taggart, a cardiac surgeon from the UK, and Professor Andrejs Ērglis, a cardiologist from Latvia to find out more…

What did The Great Debate set out to discuss?

Professor David Taggart: In broad terms there are three potential treatments for left main coronary artery disease (LM-CAD). Optimal medical therapy forms the basis for the management of all patients with CAD, and for patients with mild disease, this is generally all they require. For patients with moderate or severe disease, additional management is required. The treatments available for these groups of patients are percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).

The choice between the use of PCI and CABG in patients with moderate or severe disease is controversial, with cardiologists tending to favour PCI, whilst surgeons prefer CABG. The Great Debate set out to investigate the arguments for and against each treatment, and to look for consensus on how best to manage these challenging patients.

Why is this a hot topic in cardiology?

DT: We can see that, for more than a decade, there has been quite a lot of controversy over what the best interventional treatment for CAD is depending on the pattern and severity of disease.

Professor Andrejs Ėrglis: In the past, discussions about which was the preferred technique were sometimes not very scientific. However, nowadays, I think dialogue is much improved as we have more data to inform the discussions between surgeons and interventionists.

DT: What has emerged over the last few years is increasing evidence that, for patients with moderate to severe disease, CABG offers a survival advantage over stenting. What has really fuelled
the debate are the 4-year outcomes of the SYNTAX trial, which showed that, for around 80% of patients with three vessel disease, CABG is the best treatment as it offers a marked survival advantage. But what SYNTAX also showed was that patients with left main disease, around one third of patients with so-called lower or intermediate SYNTAX scores, seemed to do as well if indeed not better with stents than with CABG. That is what has really fuelled the controversy.

AÆ: I think we are always mentioning the SYNTAX study in this context as it was the first study where surgeons and interventionists worked together (the ‘Heart Team’ concept; fig. 1). As a result, discussion between these disciplines is not so much as competitors, but as colleagues. Whilst SYNTAX raised controversial questions, it also encouraged new ways of working. However, the data are really clear: PCI is not the solution for all cardiovascular disease. We need surgery, and respect between surgeons and interventionists is vital because we need each other’s help. From competition between these disciplines, we are now moving to a much more complementary team.

DT: The key thing to understand about the debate is that it was focused only on patients with left main disease, so it did not include the vast majority (about 80%) of patients who have three vessel disease without left main disease. The reason the Debate focused on left main was due to the rather surprising results of two trials, SYNTAX and PRECOMBAT from Korea. The latter showed that patients with, as I have said, lower or intermediate SYNTAX scores seemed to do at least as well with PCI as CABG, if indeed not better.

Can you tell us about the format of the debate and explain who was involved?

DT: There were two groups of debaters; three surgeons and three cardiologists – all well-known internationally or in Europe. The debate was chaired by a surgeon, Gerhard Wimmer-Greinecker, who had to override his natural proclivity to support CABG!

AÆ: All of the panel were fantastic and intelligent discussants. There were really outstanding people involved. Gerhard Wimmer-Greinecker, one of the pioneers of robot surgery, was the chair. The surgeons included Lucia Torracca, a surgeon from Ancona, Italy. She was joined by Volkmar Falk, a surgeon working out of Zurich, and David Taggart, a well-known surgeon from Oxford, both of whom were authors of the recent ESC/EACTS guidelines on myocardial revascularization.3,4 With respect to the interventionists, there was Marie-Claude Morice, a renowned interventionist, David Hildick-Smith from the UK, and myself.

We had to do some preparation work before the discussion and this was a very valuable exercise. It is easy for people at debates such as these to say, ‘I like this, this and this’, but here every point of the discussion was very well structured as a result of our pre-work and this led to excellent dialogues. Of course we can agree or disagree, but every point was concluded with a message from both the interventionists and the surgeons, meaning the debate was focused and productive.

Can you tell us a little about the key points of the discussions?

DT: What the debate was really focussing on were those patients with left main disease. We didn’t discuss three vessel disease at all in the debate, because I think it is widely accepted that CABG is the definitive treatment for most of these patients. The debate focused on the one third of patients with left main who may do equally as well with PCI or CABG, or who may indeed be better served with stents than CABG if they have the so-called low severity patterns of left main disease.

AÆ: We discussed the data and evidence for each of the treatments, looking at efficacy and safety, current understanding, and guidelines.

DT: There was also debate around how strongly guidelines should be adhered to. Marie-Claude Morice, for example, the French cardiologist,
felt that guidelines were only a guide and you didn’t necessarily have to follow them whereas I argued exactly the opposite. The key issue we were trying to dissect is what is best for the patients, and in determining what is best for the patient, we have to look to the guidelines. The advantage of following guidelines is: 1) they are a very transparent way of seeing how a decision was reached in the individual patient; and 2) they are also independent of the intrinsic prejudices that either the surgeon or the cardiologist may have. My own view is very strong: if you carry out an intervention on a patient in everyday clinical practice that doesn’t follow guidelines, this intervention should not be paid for by anyone. There may be a legitimate reason why the guidelines do not apply in an individual patient, but then that should be picked up by the multidisciplinary heart team, so that it is obvious why you didn’t follow guidelines in that patient. However, most patients should be treated according to approved guidelines and, as I have said, if you take that strategy then everyone can see how decisions were made in individual patients, so that an external observer who is not involved in the care of a patient would still be able to see very clearly how the decision was reached. Now one of the things that cardiologists often say is ‘oh but we don’t have time to discuss every patient in a multidisciplinary or heart team’. My argument would be, ‘but you don’t have to – if you are following approved guidelines, you don’t need to discuss the patient; you simply follow the guidelines in most cases. The heart team approach is, however, very useful in cases where there may be a patient for whom, for whatever reason, you feel it is not appropriate to follow guidelines. If you look at the ESC Guidelines 2010, which were written by a combined group of surgeons and cardiologists, they made this point very clearly.

**AE:** We definitely need to follow guidelines; there is no question about that. However, we must remember guidelines really are guidelines. Guidelines tell us what is current best practice, but we should always be able to change guidelines. If you want to change guidelines, you must provide evidence as to why they need to change: this means that you can do something that is not included in guidelines in the setting of a clinical trial with a hypothesis to test. Without such testing, we can’t make progress. Until you prove something, you can’t change the guidelines. This is also the case if you look at efficacy and safety data. For example, interventionists might comment that surgery results in more strokes, whilst the surgeons say, ‘yes, but in the PCI group you have many more reinterventions’. The question is which is the more important: stroke or re-intervention? We also need to understand that the patients are not homogeneous and that the answer to this question may vary amongst different patient groups. We can improve both strategies and we can see from these discussions that we, as interventionists, need to decrease restenosis rates and re-intervention rates. That is why I think it was such an important discussion, and is also why there is a need for further studies investigating how we should develop our thinking about surgery versus PCI in a range of patients. Studies such as the Scandinavian Baltic British NOBLE study are therefore really important.

**DT:** The EXCEL trial is looking at patients with SYNTAX scores below 33, the very patients we debated in The Great Debate. SYNTAX was underpowered in that cohort of patients and therefore could not give a definitive answer to what the better therapy was in these patients. EXCEL started in September 2010 and I am delighted to say the first patient was enrolled in Oxford. SYNTAX showed that, for patients with scores of 33 and above, CABG is the best therapy for left main (which accounts for around two thirds of all patients). However, in the remaining one third of patients with left main and SYNTAX scores of less than 33, PCI seemed to do better than CABG. It is these patients that are now being recruited in the EXCEL trial. It is hoped the trial will recruit 2,600 randomized patients and have a registry of around 1,000 patients.

What were the key outcomes from the debate; was consensus reached between the two specialties?

**DT:** Both sides won. What we all agreed was that, for most patients with left main who have additional three vessel coronary disease, CABG is the best therapy. We also agreed that there is uncertainty in patients with less severe disease (SYNTAX scores <33).

**AE:** We need to treat more and more patients nowadays. If we look back ten years, we had patients with much more severe disease.
How will this impact clinical practice?

AE: I am really happy we had the opportunity to discuss left main. Originally, the guidelines did not encourage the use of PCI, whereas now it is a yellow (evidence class II). I hope that eventually PCI will be a class I primary indication for left main. The concept of the multidisciplinary team is really exciting; of course one physician can’t do everything, but with a team, we have a real-world model to help us realize optimal outcomes for patients. You don’t even need to be together physically: a virtual team can be especially helpful in developing guidelines. For example, if you look at antithrombotic therapy, there are guidelines for neurologists, guidelines for cardiologists and guidelines for oncologists. To achieve the best outcomes for patients we need to have one set of guidelines. Recognizing the benefit of multidisciplinary working is really important and this is one of the aspects I enjoyed most in these discussions.

How will patients benefit as a result of this meeting?

DT: Well, you know, I think the most important thing about this is that the decision-making process for interventions should be taken out of the hands of individual doctors. When an individual doctor makes a decision to treat a patient there are too many potential conflicts of interest in a whole range of areas, and therefore I firmly and very strongly believe that all patients should be treated according to guidelines as discussed previously.

AE: One of the key points from the debate was that discussions with patients and fellow physicians are really important. Some patients need to be treated immediately, however, with left main intervention, when the patient is on the table, it’s not really time to ask them ‘what do you want, PCI or CABG?’ A patient can’t understand the advantages and disadvantages of these two treatment strategies. To me, there is no question that the decision-making process should be taken out of the hands of individual doctors. When an individual doctor makes a decision to treat a patient there are too many potential conflicts of interest in a whole range of areas, and therefore I firmly and very strongly believe that all patients should be treated according to guidelines as discussed previously.

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AE: One of the key points from the debate was that discussions with patients and fellow physicians are really important. Some patients need to be treated immediately, however, with left main intervention, when the patient is on the table, it’s not really time to ask them ‘what do you want, PCI or CABG?’ A patient can’t understand how to make an informed decision if he or she is on the table! What we need is to provide, and I feel very strongly about this, is full information about the advantages and disadvantages of these two treatment strategies. To me, there is no question that this should be a priority.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not necessarily reflect those of the publisher, editor-in-chief, editorial board and supporting company. DT is an advisor to Abbott, Medtronic, XCI, Nicollaj. AE has received grant/research support from Abbott Vascular, and consulting fees/Honoraria from Boston Scientific, Cordis. AE.

REFERENCES:

table 1

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<th>Subset of CAD by anatomy</th>
<th>Favours CABG</th>
<th>Favours PCI</th>
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<tr>
<td>Left main (isolated or 1 VD, ostium/shaft)</td>
<td>IA</td>
<td>Ila B</td>
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<td>Left main (isolated or 1 VD, distal bifurcation)</td>
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<td>Left main + 2 VD or 3 VD, SYNTAX score ≥33</td>
<td>IA</td>
<td>III B</td>
</tr>
</tbody>
</table>

Adapted from Kohl et al. (2010) and Wijns (2010) in VD: vessel disease

Recommendation I A: Evidence from multiple randomized clinical trials or meta-analyses and/or general agreement that a given treatment or procedure is beneficial, useful and effective.

Recommendation Ila B: Conflicting evidence from a single randomized clinical trial or large non-randomized studies in favour of the usefulness/efficacy of the given treatment or procedure.

Recommendation Iib B: Conflicting evidence from a single randomized clinical trial or large non-randomized studies where usefulness/efficacy of the given treatment or procedure is poorly established.

Recommendation III B: Consensus of opinion of the experts and/or small studies, retrospective studies, registries that the given treatment or procedure is not useful/effective, and in some cases may be harmful.

Now we are catching patients much earlier in their disease and we can achieve more with optimal medical therapy. Also, the group of patients for whom surgery is suitable is unfortunately – or fortunately for the patients – becoming smaller, and with ever-improving surgical techniques, we are likely to see more hybrid operations requiring both specialties in the future.

DT: We didn’t really reach a consensus for how to manage patients who have left main, but without other significant CAD. While the surgeons said that they believed that CABG was still the gold standard and the interventional cardiologists said that they thought PCI was a better treatment, we didn’t really come to an agreement.

AE: We agreed physicians should follow the guidelines, and it’s important that PCI is no longer red [not to be used] in the ESC/EACTS guidelines; we cardiologists wanted to say that left main is not in itself a contraindication for PCI.

How will patients benefit as a result of this meeting?

DT: Well, you know, I think the most important thing about this is that the decision-making process for interventions should be taken out of the hands of individual doctors. When an individual doctor makes a decision to treat a patient there are too many potential conflicts of interest in a whole range of areas, and therefore I firmly and very strongly believe that all patients should be treated according to guidelines as discussed previously.

AE: One of the key points from the debate was that discussions with patients and fellow physicians are really important. Some patients need to be treated immediately, however, with left main intervention, when the patient is on the table, it’s not really time to ask them ‘what do you want, PCI or CABG?’ A patient can’t understand how to make an informed decision if he or she is on the table! What we need is to provide, and I feel very strongly about this, is full information about the advantages and disadvantages of these two treatment strategies. To me, there is no question that this should be a priority.
Pre-hospital management of acute myocardial infarction (AMI): strategies to improve diagnosis and allow for early reperfusion

Most deaths resulting from acute myocardial infarction (AMI) occur within an hour of its onset, with half occurring before hospital admission. An effective pre-hospital management system is therefore an important priority, a fact recognized in management guidelines from the European Society of Cardiology and the American Heart Association (AHA). In particular, acute-phase AMI patients require rapid diagnosis and early reperfusion to minimize infarct size and prevent complications.

One of the key questions in pre-hospital management of AMI is how best to reduce time-to-treatment? Is it better to use a single emergency number that allows rapid transfer of the patient to the hospital, i.e. centralization, or to use emergency providers that diagnose and treat in the community, i.e. decentralization? Increasing evidence supports a strategy of early diagnosis based on pre-hospital assessments in the ambulance. Two recently reported registry studies suggest that early diagnosis based on pre-hospital assessment gives a more favourable clinical outcome as patients can be referred directly to a hospital that performs percutaneous coronary intervention (PCI). In line with this, the use of pre-hospital 12-lead ECG programmes by emergency medical services (EMS) may improve systems of care. The AHA issued a statement in 2008 recommending the acquisition and use of pre-hospital ECGs for the evaluation of patients with suspected acute coronary syndrome. In particular, a pre-hospital ECG may permit earlier administration of thrombolytic therapy if this reperfusion strategy is indicated (i.e. if primary PCI cannot be performed within two hours following first medical contact). Data from meta-analyses have shown that pre-hospital thrombolysis is significantly superior to in-hospital thrombolysis in terms of all-cause hospital mortality and time to thrombolysis, particularly if patients are treated within the first two hours following the onset of pain. Systems of care that have incorporated pre-hospital ECGs into a city-wide or region-wide strategy have demonstrated a significant reduction in door-to-balloon times and in-hospital mortality, usually by triaging patients in the pre-hospital setting, bypassing non-PCI-capable hospitals, and transporting patients directly to a designated centre capable of providing primary PCI when needed.

In reality, given the differences in the distances between medical centres and availability of PCI at these centres, across various regions and countries, a single model for pre-hospital management of AMI is unlikely to be effective. One of the key questions for generating country- and region-specific models should be whether a primary PCI can be performed within the two hour time goal. A well-functioning regional system of care based on pre-hospital diagnosis and triage, and fast transport to the most appropriate facility is key to treatment success. The use of standardized regional AMI treatment protocol programmes may help optimize pre-hospital management of AMI patients. In the Netherlands, recent findings from the guideline-based care programme, MISSION! showed optimal and uniformly distributed pre-hospital performance resulting in minimal time delays regardless of the area of residence. While the distance can delay patients’ arrival in hospital, the MISSION! protocol counterbalanced this by minimizing their time to reperfusion once admitted. Collaborative efforts among cardiologists, emergency department physicians, and EMS personnel are vital to achieving improved outcomes.

REFERENCES:

Hybrid approach to multivessel coronary artery disease: is minimally invasive left internal mammary artery to left anterior descending artery and drug-eluting stents in other vessels a viable solution?

Despite more than 40 years of intense scientific and clinical research, controversy still exists regarding the most appropriate therapy for patients with multivessel coronary artery disease (MV CAD). Both cardiac surgeons and interventional cardiologists feel they possess the ‘panacea’ to treat the disease: coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) with drug-eluting stents (DES), respectively. Recently, the SYNTAX trial has provided evidence supporting the superiority of CABG for patients with severe MV disease; surgery is associated with lower rates of major cardiac or cerebrovascular events at 12 months post-treatment compared with PCI. However, rates of death were similar for CABG and PCI over this time period.

While there appears to be a clinical benefit from CABG, surgical revascularization can impose a heavy burden in terms of invasiveness, bleeding, adverse neurological events, infection and pulmonary complications, especially in elderly or at-risk patients. Also, saphenous vein grafts (SVG) commonly used to treat non-left anterior descending (LAD) lesions during CABG are prone to occlusion. Routine post-operative angiography has revealed 6–12 month occlusion rates ranging from 13–21%. However, 95% of CABG procedures carried out in the US, recorded in the Society of Thoracic Surgeons (STS) registry, utilize an SVG. PCI, on the other hand, allows for the minimally invasive management of CAD, and as such can be associated with reduced costs and improved recovery periods. Compared with CABG, patients who undergo PCI are likely to require repeat revascularization. However, recently released data from the Swedish Coronary Angiography and Angioplasty Register (SCAAR) a very large, long-term observational study have shown that new-generation DES (n-DES) are associated with improved patient outcomes, compared with old-generation DES (o-DES) or bare metal stents (BMS). In the study, the rates of clinical restenosis at 1 and 2 years respectively, were 6.3% and 7.4% in the BMS group, 4.0% and 5.8% in the o-DES group, and 2.8% and 3.9% in the n-DES group.

Following the BARI trial, it is widely accepted that the survival advantage offered by CABG is related to the presence of a patent left internal mammary artery (LIMA) to LAD artery. Data presented from the SYNTAX trial revealed that the presence of a proximal LAD lesion (and only that!) strongly advocates a surgical revascularization (evidence level I vs II). Moreover, a minimally invasive direct CAB (MIDCAB; LIMA to LAD) technique has been performed, eliminating the need for sternal incision, aortic manipulation and cardiopulmonary bypass (CPB), while achieving the same patency rates as conventional surgery.

Hybrid coronary revascularization (HCR) intends to combine the advantages of both MIDCAB and PCI. Thus, HCR is a sternal-sparing, off-pump, minimally invasive, hand-sewn LIMA to LAD bypass graft through a 4–6 cm anterolateral minithoracotomy with PCI to non-LAD lesions, in order to achieve a functional complete revascularization. Uniting these two approaches could, in theory, provide the perfect revascularization: stents replace the need for the SVG, and MIDCAB provides a minimally invasive approach to reduce surgical morbidity.

Historically, HCR has been offered only to patients who have a high risk of complications during traditional CABG by median sternotomy. However, in the last few years, the use of HCR has increased in patients with MV CAD. This is primarily due to excellent clinical results from the latest generation of DES and to the desire of both patients and cardiologists for less invasive treatment options.

Despite the potential benefits of HCR, the technique has not been widely adopted. This can
be attributed to a number of factors including:

- A lack of co-operation between surgical and interventional groups
- The logistical difficulties surrounding the timing and sequencing of procedures
- The use of aggressive anticoagulation in surgical patients
- The resistance of the wider surgical community to adopt minimally invasive techniques

As a consequence of these issues, the status quo for the surgical treatment of MV CAD is to perform a sternotomy using a single LIMA and multiple SVG, under CPB. Despite recent guidelines, interventional cardiologists continue to treat MV CAD patients with multiple DES, with the aims of avoiding surgical risk and satisfying the patient’s desire for a less invasive treatment. As previously discussed, both of these approaches have notable drawbacks. The time has come to convince surgeons that they should stop fully revascularizing patients themselves and, at the same time, to convince interventional cardiologists that they can rely on surgery for an excellent method for revascularization of LAD lesions.

Some considerations on surgical revascularization in MV CAD

The same surgical strategy (one mammary artery and multiple SVG under CPB) has been used in CABG operations since the 1980s. Although the surgical population has changed dramatically over this time (becoming older and sicker), very few centres have changed their techniques accordingly. This is despite the development of several strategies for surgical revascularization to eliminate CPB, sternal incision, or both.

The development of stabilizer technology led to off-pump CAB (OPCAB) being proposed as a surgical solution to achieve complete revascularization. Initially, given the increased need for re-intervention associated with PCI, it seemed that the emergence of OPCAB would limit the use of HCR. However, only a few centres have adopted OPCAB as a routine strategy: 20% of CABG are now performed in this manner in the US and Europe. Expected advantages failed to be realized because of the need for a sternotomy approach, aortic manipulation and a troublesome approach to the posterolateral branches, causing suboptimal graft patency when compared with conventional on-pump CABG. In practice, this means that surgeons actually select patients for OPCAB based more on the coronary anatomy than with regard to risk factors. Moreover, occlusion rates of bypass grafts may be influenced by being placed on haemodynamically non-significant stenoses and surgeons are pushed to achieve complete anatomic revascularization, based only on angiographic evaluation (stenosis severity) without knowledge of the functional status of the lesion (fractional flow reserve evaluation).

The paradox of today’s OPCAB is that it offers patients an invasive procedure to place suboptimal SVG grafts with suboptimal patency rates, which are very similar to DES. This is despite the fact that the demonstrated survival benefit of CABG is largely attributable to the LIMA-LAD bypass which provides excellent long-term durability. Patency rate is similar in the off-pump and on-pump groups, and has the added advantage of being easily implanted and without requiring a sternal incision. Further, as OPCAB requires both a sternotomy and leg incisions, patients fail to recognize any reduction in invasiveness and continue to prefer repeated stenting procedures. Large series of MIDCAB have been reported in the literature and the extensive data confirms excellent angiographic and clinical results. To further reduce chest wall manipulation associated with open MIDCAB, and to improve post-op pain control, thoracoscopic and robotic techniques have been employed for LIMA mobilization and LIMA-LAD anastomosis. However, to date, few surgeons have mastered such techniques, meaning their widespread adoption has not yet occurred.

Indeed, in endoscopic-robotic MIDCAB there are more technical errors than in standard beating heart surgery. Therefore we arrive at a new paradox whereby, in order to minimize an already minimally invasive operation, they complicated an easy approach jeopardizing the patency of LIMA-LAD anastomosis (lesions in LIMA-LAD system: OPCAB (1%) vs endoscopic MIDCAB (4.8%).

Today, patients and referring cardiologists are asking for surgeons to adopt the gold standard operation that is the mammary artery on LAD, performed in a safe, effective and minimally invasive fashion, with an excellent success rate. As a surgeon involved in minimally invasive techniques, I think we must make MIDCAB accessible to all centres that carry out cardiac
surgery, because, as previously discussed, one of the main reasons HCR has not been widely adopted is that the majority of cardiac surgeons are yet to master the required techniques.

Some considerations about DES in MV CAD

Improvements in DES design, the eluting drugs, and delivery platforms have resulted in significantly reduced restenosis rates compared with o-DES and BMS. Although restenosis rates are quite low in large vessels with short uncomplicated lesions, complicated lesions can have re-occlusion rates as high as 60% when treated with PCI. However, restenosis does not necessarily pose a significant challenge to either cardiologists or patients, since an in-stent restenosis is still relatively easy to treat with a non-invasive repeated revascularization.

Incomplete revascularization in patients for whom PCI is not suitable, notably those with chronically occluded, small, calcified or tortuous vessels, or long atherosclerotic lesions, is a limitation considered acceptable in the cardiology environment. For interventional cardiology, the feasibility of PCI is related to the technical skilfulness of the operator. However, the long-term outcomes are often related to multiple, uncontrollable factors related to the pathophysiology of the atherosclerotic disease. Nevertheless, the recent results of the SYNTAX trial clearly demonstrated that a patient with MVD, including proximal LAD, should be treated with surgical revascularization, rather than multiple PCI. However, in clinical practice, proximal LAD lesions continue to be treated with PCI, even if most interventional cardiologists today show a more prudent attitude towards complex lesions, due to possible legal implications.

In my experience, close co-operation between an interventional cardiologist and a cardiac surgeon capable of performing safe and effective MIDCAB for LAD revascularization, can reduce the need for complex LAD PCI. The cardiologist can then treat the double vessel disease by PCI. In addition, the combined use of PCI and MIDCAB takes advantage of fractional flow reserve-guided evaluation of haemodynamically non-significant stenosis whose revascularization is not indicated. The invasiveness of a full sternotomy should be considered only if there are no other options available that will produce acceptable results.

Therefore, as noted by Delhaye et al., the benefits of choosing to perform a sternotomy for LAD revascularization alone are debatable.

Interestingly, PCI has recently emerged as an alternative for selected patients with left main (LM) disease. The procedure has been recently upgraded to a class IIb recommendation in guidelines and several observational analyses have demonstrated comparable short- and mid-term survival between CABG and PCI for LM stenosis, despite a higher incidence of repeat revascularization in patients treated with PCI.

The relatively large size of the LM coronary artery makes this vessel an attractive lesion to treat percutaneously in patients with focal disease. Of note, LM PCI (LM-circumflex [CFX] stenting) is performed more safely after recording a patent LIMA-LAD anastomosis, following MIDCAB surgery, and results for this procedure compare favourably with OPCAB outcomes. In isolated LM ostial stenting there should not be any residual stenosis and any graft (including LIMA–LAD) previously implanted is going to occlude due to competitive flow in the native arteries. Due to concerns about competitive flow to the LIMA after isolated ostial LM stenting, traditional OPCAB is currently my preferred approach for these patients.

In conclusion, the traditional surgical scepticism about increased repeat revascularization in any strategy involving PCI should be evaluated carefully. Indeed, this is critical when examining HCR. It is interesting to note that in the real world most candidates for a hybrid approach are not those patients who would otherwise get CABG, but who would instead be treated with MV PCI. These patients would, therefore, have a higher need for repeated revascularization without the opportunity to have received the proven long-term durability of a LIMA-LAD bypass. Hybrid candidates potentially have better short- and long-term survival and reduced incidence of adverse in-hospital events compared with OPCAB. This is combined with a lower requirement for repeat revascularization compared with multivessel PCI, since LIMA-LAD is the most suitable and effective treatment for proximal LAD disease. Thus, by successfully combining these positive features we provide the survival advantage of LIMA-LAD bypass with minimally invasive nature of PCI: a ‘best of both worlds’ strategy.
Considerations about patient selection and strategies for HCR

Selecting patients for HCR requires close co-operation between the cardiac surgeon and interventional cardiologist. It is essential to evaluate the suitability of the coronary anatomy for PCI, as well as specific characteristics for minimally invasive LIMA-LAD revascularization in prospective patients. Very small or long intra-myocardial LAD segments are technically challenging for the minimally invasive surgeon. It is also important to evaluate how aggressive PCI (non-LAD occluded vessels) should be, as the presence of a patent LIMA-LAD graft may change the safety for the interventional cardiologist. In general, the ideal candidate for HCR has a suitable LAD for MIDCAB with proximal lesions in the right coronary artery (RCA) and CFX artery. Exclusion criteria for patient selection are those with severe chronic obstructive pulmonary disease (forced vital capacity <60% of predicted value), severe pulmonary hypertension, severe obesity (relative) and actively ischaemic patients. In this last patient group (unstable patients with ST-segment-elevation myocardial infarction, or acute myocardial infarction), if the culprit lesion is on LAD an urgent MIDCAB can be very challenging or too risky to carry out.

The significant planning required for HCR and the use of aggressive anticoagulation in these patients have been suggested as limiting factors to the wider acceptance of HCR. Again, close co-operation between the surgeon and interventional cardiologist can ensure that both parties can have confidence in patient selection and can allay any fears. Indeed, a case-by-case tailored strategy for each patient is mandatory: any attempt to codify the optimal approach is likely to prove misleading and will probably result in failure. There are, however, three basic approaches to HCR, all with their potential advantages and disadvantages (fig. 1).25

Clearly, the order in which HCR is carried out is variable. However, in general, patients admitted with unstable angina attributable to a critical stenosis on the RCA or CFX are first treated with PCI, followed by MIDCAB. When LAD is considered the culprit this order is reversed (MIDCAB followed by PCI). Alternatively, some authors advocate a same-day combined surgical and PCI procedure performed in the operating theatre.4,26

I think that simultaneous MIDCAB and PCI, though psychologically appealing to the patients, requires both facilities and a level of organization that

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**fig. 1**

Alternative approaches to HCR:

- **PCI followed by MIDCAB:**
  - **Advantages:** minimizing the risk of ischaemia during MIDCAB, meaning conventional CABG remains as an option when suboptimal PCI results occur and after a primary PCI in non-LAD targets.
  - **Disadvantages:** lack of routine LIMA-LAD imaging, possible increased bleeding if MIDCAB is performed whilst the patient is receiving dual antiplatelet therapy, and a risk of stent thrombosis with discontinuation of antiplatelet inhibitors and the potential inflammation of MIDCAB.

- **MIDCAB followed by PCI:**
  - **Advantages:** availability of aggressive continuous antiplatelet therapy following PCI, routine angiography of LIMA-LAD and PCI of high-risk lesions with patent LIMA-LAD protection.
  - **Disadvantages:** MIDCAB is performed in the setting of residual coronary lesions and using conventional CABG as a fall back can lead to higher morbidity after a suboptimal or unsuccessful PCI.

- **Simultaneous MIDCAB and PCI:**
  - **Advantages:** immediate angiography of LIMA-LAD and PCI of high risk lesions with documented patent LIMA-LAD and single-step complete revascularization.
  - **Disadvantages:** risk of possible bleeding with dual antiplatelet therapy at the time of surgery, a risk of stent thrombosis due to inflammatory response of surgery, and economic and logistical issues.
are only available in selected centres. However, the concept that HCR requires a ‘hybrid suite’ is misleading and risks being a further obstacle to the uptake of this strategy. Instead, very close co-operation and communication between interventional cardiologists and cardiac surgeons is of paramount importance in order to achieve success, as previously discussed.

Finally, in today’s economic climate, it is important to consider the costs of such procedures. At present, the total cost of the HCR probably exceeds the costs of CABG in most centres. Nevertheless, since HCR can reduce post-operative morbidity compared with results from conventional OPCAB,4 and patients return to work or normal activities quicker after hybrid procedures, such costs should be taken into consideration. Performing more procedures, further integrating skill sets and co-ordinating protocols is likely to drive efficiency and reduce costs.

Conclusions

Over the last decade, the volume of data supporting MIDCAB means that it can now be considered one of the standard revascularization techniques available to patients with CAD. As patients with CAD are becoming older, with high risk scores, a tailored case-by-case approach to revascularization will need to be adopted for each patient, combining conventional CABG, CPB, OPCAB, MV stenting and HCR. After careful evaluation of coronary anatomy and clinical conditions of each individual patient, the heart team should decide the ideal approach to improve the quality of life and prolong life expectancy.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not necessarily reflect those of the publisher, editor-in-chief, editorial board and supporting company. All have no relevant disclosures to declare.

REFERENCES:
Drug-eluting balloons: an update from their use in the peripheral and coronary field

The last few decades have witnessed considerable advances in intravascular interventions for the treatment of coronary and peripheral arterial disease, including the recent introduction of drug-eluting balloons (DEB). Data presented at the Transcatheter Cardiovascular Therapeutics (TCT) scientific symposium and American Heart Association (AHA) Scientific Sessions in November of last year add to the growing body of evidence that DEB show promise as a viable alternative to standalone balloon angioplasty and stent implantation for the treatment of coronary and peripheral arterial disease.

At the TCT scientific symposium, Professor Bruno Scheller (University Hospital, Saarland, Germany) reported 6-month results from the IN.PACT clinical trial programme and specifically from the IN.PACT CORO ISR trial, as well as providing an overview of the FreePac (Medtronic, Inc.) technology. The IN.PACT programme includes 15 trials and more than 2,000 patients and will assess the efficacy and safety of the IN.PACT devices (Medtronic, Inc.), which include one DEB for use in the coronary setting (Falcon) and three devices for use in the peripheral setting (Admiral, Amphirion and Pacific).

In his overview of the programme, Professor Scheller discussed the ongoing European IN.PACT SFA (superficial femoral artery) I trial, which compares the IN.PACT Admiral DEB with standard balloon angioplasty for treatment of de novo and restenotic lesions in the superficial femoral and proximal popliteal arteries.1 He also reviewed final data from the IN.PACT CORO ISR trial that is evaluating the IN.PACT Falcon DEB as a treatment for coronary in-stent restenosis. At 6 months, in-stent late lumen loss was 0.07 mm, suggesting minimal tissue growth inside treated vessels.1 Results from The Balloon Elution and Late Loss Optimization (BELLO) study were recently reported at the 2012 Joint Intervention Meeting, Rome, Italy. This assessed late lumen loss at six months in the small coronary vessels in 182 patients randomized to IN.PACT Falcon DEB or the Taxus stent (Boston Scientific). The IN.PACT Falcon DEB was shown to be significantly superior to the Taxus stent in preventing late lumen loss (P=0.001) however, major adverse cardiac events rates were similar between the two interventions in small vessels.

The BELLO data suggest a new indication for DEB not only for in-stent restenosis but also for de novo disease of small coronary arteries.2 Positive 1-year outcomes with DEBs were also reported in two abstracts at the TCT conference: one study in patients with femoropopliteal arterial disease using IN.PACT Admiral3 and the other in patients with diabetes with critical limb ischaemia in below-the-knee vessels using IN.PACT Amphirion.4 Other recently published data showed that the early restenosis rate of long-segment infrapopliteal disease is significantly lower after treatment with IN.PACT Amphirion compared with historical data using uncoated balloons.5 Two reports from the 2011 AHA Scientific Sessions support the use of DEB as a promising tool for the treatment of in-stent restenosis.6, 7 Zadura et al. retrospectively investigated the responses of 84 in-stent restenosis patients who underwent revascularization using SeQuent Please paclitaxel-eluting balloons (B Braun). After 6–9 months, 85/91 (93.4%) lesions showed no significant loss of gain. Repeat in-stent restenosis (>50% of vessel lumen) occurred in 6/91 lesions (6.6%) with only three patients with 70% and 80% in-stent restenoses requiring an additional procedure.4 In another study, the same research group followed 63 patients with de novo lesions being treated with paclitaxel DEB (Taxol, BMS; SeQuent Please) instead of a drug-eluting stent. After 6–9 months, 94.5% of patients experienced no significant restenosis. Four lesions showed repeated narrowing; however, only two patients required a subsequent targeted revascularization.7 Since patients receiving a DEB require a shorter anticoagulation period versus drug-eluting stents (4 weeks versus 1 year of dual antiplatelet therapy), these findings suggest that DEB may provide an attractive alternative to stents for patients with a high risk of bleeding complications, as well as in elderly or non-compliant patients.

Recently, Gutiérrez-Chico and colleagues have shown that sequential application of a DEB and a non-pre-mounted bare metal stent (BMS) for treatment of de novo coronary lesions results in efficient inhibition of neointimal hyperplasia.8 However, they reported that the order of application (DEB vs BMS first) had little influence.
on neointimal hyperplasia, except that better stent apposition was observed in patients treated with BMS first.3

Following its initial development and publication of two landmark trials,9, 10 numerous DEB technologies have been explored by various companies. Within the peripheral vasculature, DEBs are being evaluated for treatment of disease in the superficial femoral, popliteal and tibial-peroneal arteries. For coronary interventions, because DEB treat the artery without leaving a permanent implant, they provide an attractive treatment option for treating in-stent restenosis, bifurcation lesions and small arteries. The increasing availability of data with DEB support the current opinion that this novel therapeutic strategy is a viable alternative to standalone balloon angioplasty and stent implantation for the treatment of coronary and peripheral arterial disease. Further data are now required to establish the most appropriate role for DEB in the treatment of the numerous clinical problems managed by vascular interventions.

REFERENCES:
‘Interventional Cardiovascular Medicine’: is there a new speciality on the horizon?

Are we beginning to see a change in the way interventional cardiology is practiced? Professor Eric Eeckhout, Associate Professor of Cardiology, University of Lausanne Medical School, believes so.

What do you mean by interventional cardiovascular medicine; how is this different from interventional cardiology?

I have seen a shift in the arena of interventional cardiology from the early days of PCR. The field initially expanded into ballooning and stenting, and has continued to adopt new technology and treat novel indications. This extension of our traditional role has necessitated working with a range of different specialities. With peripheral intervention came radiologists, angiologists and vascular surgeons. Then, as we progressively expanded to include structural heart and valvular disease, where new technology has become available for the percutaneous treatment of valve pathology, we have, more recently, established a link with cardiovascular surgeons. As we have moved forward, the collaboration between cardiac surgeons, cardiovascular surgeons and cardiologists has become an established part of the management of heart patients (in Europe at least). Pure cardiovascular surgery is not, of course, covered by the concept of interventional cardiovascular medicine (the latter relies on a percutaneous approach). However, there is an ever-increasing level of co-operation between these specialities. I believe that new technology, such as that for the percutaneous treatment of heart failure or arterial hypertension, will continue to foster ever-closer working.

The most recent guidelines on coronary revascularization are a perfect example of collaboration between cardiologists and cardiovascular surgeons. Such multidisciplinary working has also been applied in a clinical trial setting: the successful ‘Heart Team’ concept in the recent SYNTAX study is an often-cited example. Likewise, these principles are now being applied in clinical practice and hybrid facilities, where the two specialities work together on a patient who has a pathology that requires both skill sets.

A good example of this may be very complex percutaneous coronary intervention. In the case of hybrid coronary intervention, surgeons do part of the work and the cardiologists do part of the work, which means combining stenting and bypasses. However, such working still has a long way to go and it is not yet mentioned in guidelines, but I think a hybrid room is something that you may see more and more in the future.

I would say that the concept of interventional cardiovascular medicine covers the broad spectrum of treating cardiovascular pathology with a team of interventional cardiologists, cardiovascular surgeons, angiologists and radiologists. We also manage stroke intervention, so the concept really stands for a global, percutaneous team-based approach to the field of cardiovascular medicine.

What benefits will patients see?

Many patients would really benefit from having their management reviewed in the ‘Heart Team’ meeting where consensus can be reached as to the best option for the patient. The days where a single physician always decides the best approach for an individual patient are outdated. The management of stable patients with a cardiac pathology should always be discussed in a group setting, a multidisciplinary meeting where people present their opinions on what the best option is for the patient. The European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) revascularization guidelines also tell us that having a single person who says, ‘I know what is best for you’, is probably not the right way to go. The guidelines are very clear: when we have a stable patient you need a ‘Heart Team’ approach, and you need to get the patient down from the table and you need to discuss their case on an individual basis.
This is, of course, for the stable patient. With unstable patients, you don’t have time to lose and they need to get on a fast track for treatment. This can be a surgical treatment for an aneurysm that is bleeding or rupturing, or it can be a cardiac intervention for an acute myocardial infarction. Here, there is no time for discussion.

You are a co-editor of an upcoming book on this subject. Can you tell us a little about who has been involved in the development of the book?

This book, *Percutaneous Interventional Cardiovascular Medicine* (fig. 1), is the result of a joint endeavor between PCR and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and is due for official release during EuroPCR in May 2012. We hope the book will provide a comprehensive overview of the field of interventional cardiovascular medicine and will prove to be a useful reference for many years to come.

During the editing process, I have been lucky enough to work with a number of very well-respected physicians. We really wanted to represent our association, the PCR family and, of course, interventional cardiology across Europe. Together with Patrick Serruys, I am the editor-in-chief of the book. The other editors are William Wijns (the first President of EAPCI), who is covering the coronary and coronary structural valve field with input from Patrick; Alec Vahanian (previous Chairman of the Guidelines Committee of the ESC), who is covering the valvular field; and Marc van Sambeek (a member of the Board of PCR), who is covering peripheral vascular surgery. We have a number of other sub-editors that are helping to pull together the different sections in the book. These include people from across Europe who are involved in the EAPCI Board, as well as contributors from as far afield as America, New Zealand, Singapore and Brazil.

What topics does it cover and what makes it different from other cardiovascular textbooks?

The book will cover all aspects of interventional cardiovascular medicine across 94 chapters, including coronary, structural, valvular and vascular aspects of patient care. It has been designed to harness the joint resources and strengths of both EAPCI and PCR. We have tried to ensure that we have covered new technologies and indications to the best of our ability. We believe that this will make it the most comprehensive textbook available in the field of cardiovascular medicine and we hope that readers will recognize this as a real strength.

Right from the very beginning, we wanted to ensure the book was easy to digest. In many respects, some reference textbooks are so grey and uninviting: there is no colour and there is a lot of text. We were keen to ensure that this book was very accessible, without losing any of the detail. Therefore, for the reader who wants to skim through the book, there will be highlight boxes that will give them an overview of the important take-home messages for each of the chapters.

This text will also be highly innovative, with a very strong online companion version and an iPad app to support learning. This means that the textbook will be linked to a very strong multimedia library of video, audio and clinical cases, and it will be linked to the full gamut of PCR online resources. A good example of the benefits this can provide can be found in the chapter on pericardiocentesis. Although the procedure is well illustrated in the book, added value can be found on the website where readers will be shown how to puncture a pericardium when a patient is going into tamponade. An additional advantage of having an online version is that it enables us to keep the book up-to-date, because whilst the printed paper...
version will be reviewed on a regular basis, the online version will be updated very regularly as new data become available. The text will also include a number of personal perspectives as in the ESC cardiology textbook.

Given the book’s strong connection with PCR and EAPCI, we would like to position it as the reference book for training in this field. In the future, we will provide a database of multiple choice questions that may become very important for future accreditation or potential board exams.

Who are the target audiences for the book?
We have worked hard to produce a reference text for interventional practice as a whole. The contents of the book have been designed around the curriculum for interventional cardiologists developed by the ESC and EAPCI, so that means that, if you know everything in the book, you are a bright person! It is almost impossible to know everything covered in this book, so we see it as being useful for every level of experience. It is a reference for the veteran interventional cardiologist who wants to just check some information quickly and confirm that what he or she thinks about a particular issue is correct, right through to the book working as a training tool for the newly qualified interventional cardiologist. From young to old; it is a book for everybody.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not necessarily reflect those of the publisher, editor-in-chief, editorial board and supporting company. EE has no relevant disclosures to declare.

REFERENCES:
THE PCR-EAPCI TEXTBOOK

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Longitudinal stent distortion in clinical practice. How common is the problem and does stent design matter?

Introduction
Coronary stents represent the single most important advance in percutaneous coronary intervention (PCI) since the first angioplasty procedure by Andreas Gruentzig in 1977. The first generation designs were primitive:1

the Palmaz-Schatz stent, cut from a stainless steel tube, was stiff and could be difficult to deliver, whereas the Gianturco–Roubin stent, made from a coiled wire, was more flexible but provided limited lesion coverage and radial support. Examples of early stents can be seen in figure 1. A tendency for the struts of wire stents to distort, by either collapsing like a concertina or unravelling when deployment and balloon withdrawal was attempted in challenging lesions and vessels, was noted soon after their introduction.2, 3

However, the last 20 years has seen steady and impressive improvements in stent design, leading to better acute performance and long-term clinical outcomes.

Stent design
“…every human benefit and enjoyment, every virtue, and every prudent act, is founded on compromise…”

EDMUND BURKE (1729–1797)

The complex technical requirements that stents must fulfil has influenced their mechanical design. Over the last decade, drug-eluting stents (DES), which release various anti-proliferative agents, have allowed PCI to be undertaken in patients with more severe and extensive coronary disease, often in heavily calcified and tortuous vessels. This has driven the development of low profile, highly flexible stent/balloon systems to facilitate delivery to the lesion site. Such design has, in turn, required a trade-off in terms of reduced longitudinal strength.

Indeed, all coronary stent designs are a result of compromise (fig. 2), and a major challenge in stent design is achieving the optimal balance between different stent properties. Balloon expandable coronary stents must be able to be crimped down securely onto their delivery balloon. Once crimped, the stent and delivery balloon combination must have a low profile and be flexible to facilitate stent deliverability to the lesion site. This commonly entails traversing highly tortuous and calcified coronary arteries. During deployment, the stent struts must exert sufficient radial force on the vessel wall to overcome lesion resistance and vessel recoil. To achieve an optimal lumen diameter post-placement, the vessel wall must be uniformly and adequately scaffolded, with minimal tissue prolapse between stent struts. At the same time, side branch access between struts must also be possible, so that bifurcation disease can be treated. The deployed stent must conform to the vessel curvature adjacent to the lesion, to minimize vessel distortion at the stent edge. Radio-opacity is also important to aid positioning and appropriate delivery in the vessel, to guide post-dilation, and to assess optimal stent expansion. However, the stent lumen must also be readily visible upon radiographic imaging.

In some instances, however, maximizing one desirable feature, for example vessel wall coverage, can only be achieved by compromising another characteristic, in this instance side branch access.

In terms of mechanical properties, the longitudinal strength of a stent can be defined as its ability to resist a longitudinal distorting force, whereas radial strength is its ability to resist a compressing force. There are a number of design characteristics that...
influence the longitudinal and radial strength of a stent: strength of the stent hoops and the number and design of connectors between adjacent stent hoops.

The radial strength of the stent hoops is largely determined by three factors: the metal alloy (or polymer) chosen, the strut thickness and the stent design. First generation stents were mostly manufactured from 316L stainless steel. More recently, newer metal alloys, such as cobalt chrome and platinum chrome, have largely replaced stainless steel because they allow for reduced strut thickness, while maintaining radial strength and radio-opacity. Thinner struts provide a lower crimped profile and, at least in theory, better stent deliverability. There is also some evidence that, at least with bare metal stents, patients undergoing PCI with thinner strut stents have lower restenosis rates and better clinical outcomes than those treated with thicker strut designs. While the explanation for this finding is uncertain, thinner strut designs may cause less wall injury and less disturbance to blood flow. The reduction in strut thickness achieved over the last decade has been marked. Compared with the stainless steel BX Velocity/Cypher (Cordis Corporation) stent at 140µm, strut thickness has been reduced to 112µm with Nobori/Biomatrix (Biosensors International), to 91µm with the Resolute (Medtronic, Inc) stent, and to around 81µm with the Vision/Xience (Abbott Laboratories) and Omega/Promus Element (Boston Scientific) stents. Further reductions in strut thickness are currently being explored; for example, the next generation Synergy stent (Boston Scientific) has a strut thickness of 74µm.

The number and design of connectors between adjacent stent hoops is also an important predictor of longitudinal stent integrity and has a major influence on stent flexibility and deliverability. In recent years, there has been a reduction in the number of connectors in widely-used coronary stents. Compared with the BX Velocity/Cypher stent, which had 6, most current stents have either 2 or 3 connectors (fig. 3).

In addition to the number of connectors, other important factors include whether adjacent sinusoidal hoops are aligned in-phase (peak to trough) or out-of-phase (peak to peak), whether peaks or troughs are linked, whether the connectors are straight or curved, and how each connector is aligned relative to the long axis of the stent. The pattern of connectors over the length of the stent is also important; if in a row, the connectors may increase longitudinal integrity by effectively forming a “spine”.

**Bench-top testing of longitudinal compression and elongation**

Bench-top testing provides a standardized evaluation of various stent characteristics, and allows comparisons to be made between different
stent designs. For example, there are considerable differences between stents in terms of flexibility, both crimped on the delivery balloon and after expansion. Bench-top testing can also provide unique insights into more complex procedural techniques. For example, when evaluating strategies for treating bifurcation lesions, bench-top testing showed the importance of kissing balloon inflation to optimize strut apposition to the vessel wall.

We have previously assessed stent longitudinal integrity in a bench analysis of seven different stents: Cypher (Cordis Corporation), Driver and Integrity (Medtronic, Inc.); Omega and Liberté (Boston Scientific); Vision and MultiLink (Abbott Vascular) stents. The degree of compression in 10mL of exposed stent after the application of a force of 0.5 Newtons (N) is depicted in figure 4. There were clear differences between stents, with the Promus Element and Driver (Medtronic, Inc.) stents being the most likely to be compressed. Elongation was assessed by clamping the stent with 8 mm exposed, and applying traction with a hook through the stent struts at a force of 0.5 N (fig. 5). The results were similar to those of compression testing; the stents more easily compressed were also more easily elongated. Analysis of the distorted stents showed that their ends were frequently folded in on themselves causing the vessel lumen to become markedly compromised. The 6-connector, thick-strut Cypher stent was the least likely to be distorted, the 2-connector Promus Element and Driver stents the most likely, and the remaining 3-connector stents tested somewhere in between. Despite excellent resistance to longitudinal distortion, the Cypher stent is no longer widely used, in part because it is less flexible, deliverable and conformable than other stents.

Similar findings were described in another study comparing 14 examples from four families of stent designs. This work confirmed that the number of connectors predicted the degree of compression, but also suggested that whether or not connectors were peak-to-peak or peak-to-trough (which largely determines connector angle) was also of major importance.

Clinical longitudinal stent distortion
There have been several recent reports indicating that some of the newer generation stents may, in certain circumstances, be also prone to longitudinal compression and/or other distortion. However, this is not a new phenomenon: those who practised interventional cardiology late last century may recall similar complications occurring with many early stent designs, particularly those woven from a single wire. For example, shortening and elongation of the Wiktor stent (Medtronic, Inc) was described in 1994, with associated adverse clinical events including the need for coronary bypass graft surgery.
The first indication that there was a problem with recent-generation stents came from Pitney and colleagues from Sydney, Australia, who described 14 cases of major stent deformation in 1,000 consecutive procedures using the 2-connector Endeavor/Driver (Medtronic, Inc) stents. Distortion occurred in 1.8% of the 775 stents that were post-dilated. In those patients who experienced stent distortion, re-stenting was required in 9 patients and there were major adverse clinical sequelae in 5 patients (36%). They also noted that stent distortion could easily be mistaken for strut fracture. Distortion occurs at the index procedure and can be corrected if recognised, whereas strut fracture usually occurs later. However, both complications likely predispose the patient to stent thrombosis.

Hanratty and Walsh recently reported 3 cases of stent distortion occurring with ostial deployment of Promus Element, Biomatrix and Resolute Integrity stents, respectively. Soon after, 9 instances of stent distortion from approximately 9,400 stent deployments in 4,500 cases, giving a procedure occurrence rate of about 0.2%. It is clear, however, that stent distortion is a rare occurrence. Six of the 9 were with the Promus Element stent, and one each with Endeavor, Biomatrix and Taxus (Boston Scientific). There were multiple causes of stent distortion including the guide catheter, guide catheter extensions (Guideliner, Vascular Solutions; and Proxis, Velocimed) and post-dilation balloons. Two patients subsequently developed stent thrombosis, in both cases 2 months post-procedure, highlighting the importance of achieving satisfactory stent deployment.

The FDA Manufacturer and User Facility Device Experience (MAUDE) device-focused, adverse event database has recently been interrogated with regard to longitudinal stent deformation. Although there will be reporting biases in voluntary registries, the incidence of longitudinal...
stent deformation appears to have increased in the last two years, with most recently-reported cases occurring in stents using the Element platform. Similar findings have been observed in carotid artery stenting, where stent deformation is more likely to occur in stents with an open cell as opposed to a closed cell design. Guidewire induced stent damage has also been noted in iliac vessels after stenting.

Although it is difficult to precisely determine the incidence of stent distortion in the real world, available clinical data indicate the figure is likely to be low. However, awareness of the problem has only recently re-emerged, so conclusive data have yet to be prospectively collected. Furthermore, there is likely to be a spectrum with respect to the severity of the distortion, with more subtle deformation being easily missed during clinical and angiographic assessment. Although stent distortion almost certainly predisposes the patient to stent thrombosis, the magnitude of increased risk is difficult to assess from the case series reported to date.

Few centres or interventional cardiologists are likely to use all current generation stents in equal proportion. This, combined with the low overall incidence, makes it difficult to be certain about the relative likelihood of longitudinal distortion occurring with current-generation stents. To our knowledge, longitudinal distortion has not been reported in patients treated with a Cypher stent. While this may be due to its excellent resistance to longitudinal shortening and elongation noted in bench-top testing, it is also possible that a decline in use of the stent coincided with re-emergence of recognition of the problem. Furthermore, distortion in highly visible stents, such as Promus Element, is more likely to be detected angiographically than that in less visible stents. Despite these caveats, we believe that some stents are more likely to suffer distortion than others, and that the bench-top testing results usefully predict the likelihood of distortion occurring in clinical practice.

Prevention of longitudinal distortion

Most longitudinal distortion is a consequence of interventional equipment catching on the proximal end of a stent and there are a number of situations where the risk of longitudinal distortion is increased. For example, equipment can become stuck on stents with struts that are separated from the vessel wall. These so-called unapposed struts can occur in tapered vessels where initial sizing and deployment is matched to the distal reference diameter. Stents deployed around a tight bend may also be at increased risk because wire bias directs the nose of balloons or other devices against the edge of the stent, causing the devices to become stuck against struts. Balloons are the most commonly used device which re-cross the proximal stent struts; they should be advanced slowly and gently under fluoroscopic imaging. If the balloon does not cross easily, altering tension on the guide wire may change the angle of approach. Previously inflated balloons, particularly if non-compliant, tend to develop “wringing” and may be prone to catching on the proximal struts. If such a balloon is used and meets resistance, changing to a new, compliant balloon – perhaps with a smaller inflated diameter as these are less likely to catch on struts – is advisable. Care with procedural technique can therefore, in some cases, lessen the likelihood of longitudinal stent distortion.

Distortion appears most likely to occur in stents deployed in ostial or very proximal coronary lesions. Damage from the guide catheter, which is often pulled into the coronary artery as balloons are withdrawn, is a likely cause. This can be prevented by ensuring complete balloon deflation, applying forward pressure on the guidewire, and imaging the guide catheter tip when withdrawing the balloon from the coronary artery. If necessary, the guide can be disengaged from the coronary ostium before balloon withdrawal. The Guideliner has proven to be a very useful device to facilitate stent delivery through challenging anatomy, but should not be advanced through previously-deployed stents unless absolutely necessary, as it may catch on the proximal stent edge. Choosing a stent less prone to distortion might be prudent when treating very proximal disease. A guide catheter shape which provides good support without the need for deep engagement is also important.

Whilst distortion is more likely at the proximal end of a stent it can also occur at the distal stent edge. One situation where particular care is needed is withdrawing a Boston Scientific intravascular ultrasound (IVUS) catheter from the distal vessel beyond a stent. The catheter has a very short...
rapid exchange segment; if the wire separates from the catheter shaft proximal to this segment the V created between the two may catch on distal stent struts. If there is any resistance to IVUS catheter withdrawal through a stent, the IVUS catheter should be re-advanced, guidewire movement checked, and both the IVUS catheter and wire withdrawn together, at least until the IVUS catheter is back across the stent. As a general rule, if multiple lesions in the same vessel need treatment it is best to start distally and work back, rather than crossing and recrossing previously deployed stents.

Distortion in the mid-portion of the stent can also occur and usually happens during intervention for bifurcation lesions. When stenting across a bifurcation, there is often a size mismatch between the proximal and distal vessel, which can lead to initial underdeployment of the proximal portion of the stent. The proximal end of the stent should be post-dilated as soon as possible during the procedure to optimally appose stent struts to the vessel wall. Deep guide engagement and proximal stent damage may occur during the removal of a guidewire that has been deliberately trapped outside a stent to protect a side branch. If disengaging the guide catheter does not work, advancing a microcatheter over the wire to provide counter-traction might help prevent the guide being drawn down the vessel.

Recognition and management of longitudinal distortion
Longitudinal stent distortion should always be considered if there is any difficulty advancing balloons or additional stents during an interventional procedure. If a radio-opaque stent, such as Promus Element, has been distorted, there is a very characteristic but subtle “brightening” of the end of the stent evident on angiography, presumably due to the stent struts becoming more visible as they are bunched together. It may, however, be more difficult to recognize distortion in less radio-dense stents.

Once recognized, balloon re-dilation is the mainstay of treatment. It is often necessary to use very small balloons initially, and to increase balloon diameter from there on. If the smallest diameter balloons will not cross, advancing a Guideliner almost to the stent may help by changing the angle of approach and increasing the forward force able to be applied to the balloon. Deploying an additional stent, partially overlapping the distorted portion of the first stent, is often also necessary. Intravascular imaging with IVUS or optical coherence tomography may provide additional useful insights, albeit with a risk of causing further distortion.

Case example
The characteristic angiographic features of longitudinal stent distortion are shown in the following case from our unit. The management of this patient is also described.

A 61-year-old man presented with ischaemic chest pain of acute onset, intermittent ECG ST elevation in leads V2-V3, and an elevated high-sensitivity troponin level. Coronary angiography demonstrated diffuse atheroma with a critical distal right coronary lesion and a severe non-calcified proximal-mid left anterior descending artery (LAD) stenosis (fig. 6). Given uncertainty around the culprit lesion, the right coronary stenosis was first successfully treated with a 3.5 x 12 mm Promus Element stent. The LAD lesion was then pre-dilated and a 2.75 x 24 mm Promus Element stent was deployed at 18 atmospheres. A 3.0 x 15 mm non-compliant balloon was easily advanced into the stent for post-dilatation. However, when a further inflation was attempted the balloon would not re-advance into the stent. Repeat angiography revealed distal displacement and “brightening” of the proximal end of the stent, indicating that the proximal hoops had been distorted and bunched together. A new 1.5 mm diameter balloon was needed to regain access to the stent, followed by further inflations with larger diameter balloons. After deployment of a second 3.5 x 8 mm Promus Element stent, partially overlapping the proximal end of the first stent, the final angiographic appearances were satisfactory. The patient remains well 12 months later.

Conclusions
Efforts to improve stent deliverability by reducing strut thickness and removing connectors between adjacent hoops has led to stents with less longitudinal integrity than those of the past. Longitudinal stent distortion, an old problem, has subsequently re-emerged as an infrequent but worrying complication of contemporary PCI. Stent manufacturers need to consider longitudinal integrity as an important stent characteristic.
that should be maintained when refining other desirable features. Some current stent designs appear to excessively favour stent deliverability and flexibility over longitudinal integrity.

Interventional cardiologists should be aware that longitudinal distortion can happen, and should incorporate simple strategies into their routine practice to lessen the likelihood of it occurring. Stents with better longitudinal integrity should be considered for higher-risk lesions, such as those near coronary ostia. Clinicians should also be aware of the clinical and angiographic signs that indicate there is a problem, and understand the strategies needed to resolve it.

**REFERENCES:**

The ISCHEMIA Trial will assess whether an early invasive strategy with catheterization and optimal revascularization is superior to continued intensive optimal medical therapy and lifestyle changes, with catheterization reserved for those who fail medical therapy, in patients with moderate or severe ischemia.

Confluence spoke to the Study Chair, Professor Judith Hochman, Co-director, Clinical and Translational Science Institute, New York University School of Medicine, New York City, about how this trial might impact clinical practice.

Should interventionists be afraid of ISCHEMIA?

The ISCHEMIA Trial will assess whether an early invasive strategy with catheterization and optimal revascularization is superior to continued intensive optimal medical therapy and lifestyle changes, with catheterization reserved for those who fail medical therapy, in patients with moderate or severe ischemia.

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INTERVIEW

J Hochman

Clinically, what does ischemia mean for patients?

From a patient perspective, it doesn't mean a lot if they don't have symptoms. However, we know a lot of ischemia is associated with an increased risk of death or myocardial infarction (MI). In terms of what it means for a patient, once again, it means something if it's associated with angina, but we know that not all the ischemia is associated with symptoms.

How is ischemia currently managed? What kind of drugs are used? Are all patients treated with just basic medical therapy, or are other interventions used?

There are a range of medications that are used to treat stable coronary artery disease (CAD). Firstly, there are risk factor modifiers, the secondary preventive medications that are meant to change the natural history of plaque, plaque rupture, atherothrombotic disease and to protect against arrhythmias precipitated by unstable plaque. This includes statins and other lipid-lowering agents to lower LDL cholesterol, agents that control blood pressure, and medicines that help to control HbA1c. Lifestyle factors are also important including the management of obesity and sedentary lifestyle, etc. Secondly, there are the drugs that reduce the risk of sudden death and also reduce exercise-induced ischemia, beta-blockers, for example. This also includes ACE inhibitors, which are especially efficacious in patients with left ventricular dysfunction, diabetes and hypertension. Finally, there are others medications that help manage ischemia and angina, including calcium channel blockers, nitrates and ranolazine.

In addition to medical therapy, we have data on the use of strategies such as catheter-based revascularization. Right now, in clinical practice, despite the fact that when you talk to people at academic centres and they think that all these patients with ischemia are getting cath, this is not the case: it is about 50/50, even in patients with at least moderate ischemia. Rory Hachamovitch has investigated referral data in 5,833 patients with moderate or severe ischemia on myocardial perfusion imaging from nine different US studies. Within 90 days of testing, the rate of referral for catheterization was only 35–65%. We can see there really is quite a variety in treatment, and equipoise about whether they need upfront, early invasive management after a positive stress test.

What will the ISCHEMIA trial investigate and why is it important?

The landmark COURAGE and BARI 2D trials demonstrated that an initial management strategy of revascularization and optimal medical therapy (OMT) did not reduce the risk of death or MI in stable CAD patients compared with initial OMT alone. However, the COURAGE trial was not without its drawbacks. There was possible selection bias (all patients underwent coronary angiography so the role of selection bias based on perceived risk/benefit is difficult to assess). It is also unknown how much baseline ischemia was present in many patients.

The ISCHEMIA trial will investigate stable patients with moderate or severe ischemia on nuclear (e.g., ≥10% left ventricle ischemia), echo, or cardiac MRI stress testing. The trial will assess whether an invasive strategy with cardiac catheterization
and optimal revascularization plus OMT reduces cardiovascular death or MI compared with a conservative strategy comprising OMT with catheterization reserved for patients with refractory angina despite maximal medical therapy, or those with acute coronary syndrome, acute ischemic heart failure or resuscitated cardiac arrest. It is a superiority trial, so the hypothesis is a positive one: that the routine, early invasive strategy with catheterization and what we call optimal revascularization) will be superior to continued intensive OMT and lifestyle changes.

The ISCHEMIA trial is going to be very important for interventional cardiologists, because since COURAGE was published, the use of PCI in stable ischemic heart disease (SIHD) has been decreasing because of the lack of evidence for a reduction in death or MI when added to medical therapy. A key aim of the ISCHEMIA trial is to try to redress some of the limitations of those landmark trials. The trial is also important because it will have implications for guidelines, performance metrics and reimbursement. In the current economic climate, there is a huge focus, both nationally and internationally, on cost. Following the two negative trials, COURAGE and BARI 2D, payors are likely to say ‘well, why are we paying for this?’. The trial is really designed to be well-powered and well-positioned to demonstrate that there is superiority for an invasive strategy if in fact the hypothesis is correct. Patient quality of life will also be assessed throughout the study. The withdrawal of medications due to side effects and the numbers of patients who require catheterization for angina will also be recorded.

How will ISCHEMIA address the limitations of these previous studies?

The first attribute is that we intend to recruit 8,000 patients, which is over three times as many as COURAGE and BARI 2D, meaning the study is very well powered. Another critical issue is that randomization will take place following a stress test but before cardiac catheterization. Patients (without renal failure) who qualify on the basis of ischemia will undergo blinded coronary CT angiography (CCTA) to exclude left main disease and to confirm the presence of obstructive coronary artery disease prior to randomization. This is a concern from many previous trials, not only COURAGE and BARI 2D (RITA-2 was another stable CAD study that randomized after catheterization).

Once you see the angiogram, it has been argued that those who would have seen the most potential benefit from revascularization may have already been excluded. There may be a lot less bias in terms of who you include if you randomize before catheterization. The next potential limitation of the prior trials is that they did not require a specific threshold of ischemia to get into the study. They required an anatomic definition of coronary disease but not necessarily ischemia. The ISCHEMIA trial will actually require at least moderate ischemia in all patients that are enrolled, and therefore it should be adequately powered for the sub-set patients that got into COURAGE and BARI 2D that had moderate or more ischemia.

The other key variable is that the protocol for the ISCHEMIA trial focuses on complete revascularization of all the ischemic segments, that wasn’t specifically emphasized in COURAGE and BARI 2D. The PCI is going to be guided by the functional testing, stress imaging, or fractional flow reserve and SYNTAX score. We believe it to be important that this is not just anatomical revascularization, it is revascularization based on functional testing. Also, our definition of MI is going to be very conservative in terms of the peri-procedural MI. We will have a high threshold, meaning specificity in terms of clinically important infarcts.

Also, the techniques and devices have continued to evolve over time, and we are going to use the most up-to-date practice and materials. All stents will be drug-eluting stents unless it is indicated to use a bare metal stent. They will be the most recent stent types that have shown at least equivalence or superiority to older generation stents.

The last thing is that there is a group of leading interventional cardiologists and surgeons (representing the ‘Heart Team’ concept) who are leading this study. As there is going to be bypass surgery in this trial as opposed to COURAGE, all of these specialties have had substantial input into all aspects of this trial. The Leadership Committee includes interventional cardiologists, Gregg Stone, David Williams, Bob Harrington, and a cardiac surgeon, Bruce Ferguson. Bill Boden is Chair of the OMT Committee and I am acting as Study Chair, working with David Maron as PI and Study Co-Chair. It is a very well-balanced Leadership Team and we have been working hard.
Do you think there are any limitations to this present study design?
A major limitation of this study will be if people don’t support the trial and patients don’t get enrolled; we need to enrol people that represent a broad cross-section of patients with SHID and at least moderate ischemia, so long as they don’t have symptoms that are refractory to medical management. We know that PCI and CABG improve angina. If a patient needs revascularization to improve their angina they are not going to be targeted for this trial as they will only end up crossing over from the conservative group to the invasive group, which is something we want to avoid. It is really in the best interest of the whole cardiology community to enrol a broad cross-section of patients, so we have the true answers and we are able to test the hypothesis of superiority. The study will therefore exclude: 1) patients with an unacceptable level of angina despite maximal medical therapy (i.e., requiring revascularization) and 2) patients who are very dissatisfied with medical management of angina at present.

As study Chair, what does your role involve?
Overseeing all the moving parts! As I mentioned, it is our intention to include 8,000 patients in this study and recruitment will start in approximately 500 centres in over 30 countries this summer. We also have a clinical coordinating centre that I run at New York University (NYU), in our Cardiovascular Clinical Research Centre; we have a statistical and data coordinating centre at Duke (DCRI); an Ischemia Imaging Coordinating Centre at Emory, that Leslee Shaw will oversee; and a stress nuclear core lab, a stress MRI core lab, and stress echo core lab. We have a coronary angiography core lab, we have a CCTA core lab, and of course we have all of our country-leaders and academic research organizations – and most importantly – our sites. I am coordinating all of these facilities together with David Maron.

How do you think the results of this study are going to change clinical practice and benefit patients?
If the trial shows superiority of an early invasive strategy, more patients should be getting it and we would have another proven strategy for these patients. If it is a positive trial, the increased use of an invasive strategy would be the goal.

Obviously, if the trial does not show superiority, it shows that you can wait and make judgements about catheterization based on how patients respond to therapy; this would of course lead to a reduction in unnecessary procedures and a significant cost saving. As cost is as huge a concern in the US as elsewhere, the study will make a notable contribution in this area. There will also be a lot of education for the sites regarding the quantitative analysis of ischemia, which will be directed by members of our leadership group. I think there are going to be a lot of positive things that will come out of this study, beyond just answering of the primary question.

Do you think interventionists are going to have something to fear from the outcomes of the study? Do you think the results could prove controversial?
I suggest they look at the design of the trial, see that it’s very well-powered and positioned to test the hypothesis, and they should not be afraid of the trial. It is possible that COURAGE and BARI 2D were limited in their ability to show a benefit for revascularization because interventionists refused to offer trial participation to their higher risk patients. ISCHEMIA has been designed to show a benefit from revascularization in SIHD if one exists, but if interventionists do not offer trial participation to their higher risk patients, they could unwittingly undermine the ability of the trial to prove the hypothesis.

Every clinical trial has some controversy! We have worked very, very hard on designing this study – a process which has taken three years. Also, a lot of people have had input into the planning stages and we hope that people will acknowledge their depth of expertise and knowledge. Therefore, I feel the results here will stir up a lot less controversy than many other trials.

Are you assessing differences between patient groups?
We will certainly look at sub-groups, including the usual sub-groups: by age, by sex, by diabetes, by ischemia location, for example. We are most particularly interested in patients with anterior ischemia and patients with more extensive coronary disease. We have noted that most patients, aside from those with chronic kidney disease, will have a blinded CT coronary angiogram, so as we will have baseline information...
about the coronary anatomy, we have a sub-group based on those data as well.

What are you looking for in prospective study sites?

It should be stated that we have very strict criteria to determine which sites can participate because we want to make sure that the quality of the intervention and the quality of the surgery is very high. We believe that the outcome, obviously, will be very sensitive to how well the procedures are performed. This is something else that should be reassuring to the interventional community: that we are only selecting for sites that have high quality interventionists and excellent surgical outcomes. We are, therefore, looking for those kinds of sites to participate in the study.

How can people contact the Leadership Team if they would like further information or are interested in participating?

They can visit the study website, http://ischemiatrial.org/ or they can email the study at ISCHEMIA@nyumc.org.

DISCLOSURES: The opinions and factual claims herein are solely those of the authors and do not necessarily reflect those of the publisher, editor-in-chief, editorial board and supporting company.

JH is a member of Steering Committees for clinical trials sponsored by Eli Lilly and Co. and GlaxoSmithKline.

REFERENCES:
Two-year updates from the RESOLUTE clinical programme

There are wide-ranging challenges associated with the management of patients with coronary artery disease (CAD) and diabetes. Such patients tend to exhibit unfavourable coronary anatomy and experience higher adverse event rates owing to – amongst other complications – endothelial dysfunction, impaired platelet function and increased smooth muscle cell proliferation.\(^1,2\) Indeed, diabetes has continued to be associated with an increased risk of restenosis and poor clinical outcomes, even with the use of drug-eluting stents.\(^3,4\) In addition, patients with diabetes who are undergoing stent implantation have increased on-treatment platelet reactivity, which may contribute to a higher rate of post-procedural bleeding events. Efforts to use platelet function testing to identify patients at increased risk of stent thrombosis show a modest predictive value\(^5\), suggesting that alternative avenues should be pursued to improve treatment for patients with diabetes.

Progress has been made recently in this field, with data presented at the 61st Annual Scientific Sessions of the American College of Cardiology (ACC) from the global RESOLUTE clinical programme\(^6–8\) and the approval by the U.S. Food and Drug Administration of the novel Resolute Integrity zotarolimus-eluting stent (ZES; Medtronic, Inc.) for the treatment of CAD in patients with diabetes. This stent is constructed from a single, continuous strand of sinusoid cobalt alloy wire, helically wrapped and then fused into a distinctive pattern. The structure provides excellent flexibility combined with radial strength, giving easier access to, and smoother tracking within, distal and tortuous vessels\(^9\); this is likely to be pertinent in the treatment of patients with diabetes, owing to their challenging coronary anatomy.

Within the global RESOLUTE programme – which consists of a large randomized controlled trial and multiple confirmatory single-arm studies – 5,130 patients received a Resolute ZES. Because of similarities between the stent platforms employed in the Resolute and the Resolute Integrity ZES, clinical results generated with the Resolute ZES are also applicable to the Resolute Integrity ZES.

A two-year pooled analysis of safety outcomes assessed cumulative incidences in patients who had received a Resolute ZES (N=5,130) up to 720 days post-implantation. Data showed a relatively low cumulative incidence of target lesion failure, cardiac death and target vessel myocardial infarction, target lesion revascularization and definite/probable stent thrombosis (table 1).\(^6\) The proportion of patients using dual antiplatelet therapy across all study regions was 89.4% at 12 months and 45.6% at 24 months.\(^6\) Ongoing follow-up will evaluate the generalizability of the safety data beyond two years and in specific higher-risk patients. A two-year update was also provided on 1,535 patients with diabetes in the RESOLUTE programme.\(^8\) These patients had higher comorbidities at baseline compared with those without diabetes, and 43% were classed as ‘complex diabetics’. Even in this challenging patient population, data were encouraging. Similarly to patients without diabetes, relatively low two-year cumulative incidences of cardiac events were observed (table 1).\(^8\) Interestingly, similar data were reported for the for the high-risk subgroup of patients with insulin-dependent diabetes and with those who were not insulin-dependent (fig. 1).\(^8\) These data pave the way for improved treatment for patients with diabetes and CAD.

### Table 1

<table>
<thead>
<tr>
<th>Cumulative incidence at two years (%)</th>
<th>Target lesion failure</th>
<th>Cardiac death and target vessel myocardial infarction</th>
<th>Target lesion revascularization</th>
<th>Definite/probable stent thrombosis</th>
<th>Cardiac death</th>
<th>Target vessel myocardial infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall pooled analysis (N=5,130)</td>
<td>9.3%</td>
<td>5.4%</td>
<td>4.7%</td>
<td>0.9%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Analysis of diabetic patients (n=1,535)</td>
<td>11.1%</td>
<td>Not reported</td>
<td>5.8%</td>
<td>1.2%</td>
<td>3.4%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>
**RESOLUTE Pooled Diabetic Analysis (All Diabetic Patients, 24 Months)**

- **Non-Diabetics (N=3,595)**
- **Non-IDDM (N=1,060)**
- **IDDM (N=455)**

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