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Should stent selection in diabetic patients be considered as a special case?

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Interventional cardiologists are very aware of the additional challenges of treating patients with diabetes. They recognise the likelihood of increased procedural complexity due to more diffuse vascular disease and the reduced certainty of long-term clinical outcomes due to accelerated rates of atheroma progression combined with increased rates of bare metal stent restenosis[1] and stent thrombosis[2]. However despite this solid knowledge base, diabetic patients entering the catheterisation laboratory are commonly treated with remarkably little additional consideration. Many operators decide revascularisation strategies based predominantly on anatomical characteristics and the choice of which type of stent to implant can appear to be arbitrary. In this edition of EuroIntervention, colleagues present comparative IVUS analysis following DES implantation in diabetics[3] and a cost-efficiency analysis of data from comparative randomised DES trials enrolling diabetic patients[4]. When we consider these new data, should we conclude that the outcomes associated with use of alternative DES in diabetic patients are sufficiently diverse to mandate a particular stent for this "special" group of patients?

It is easy to forget that DES technology entered our clinical practice less than ten years ago. Initial trial data from randomised trials of focal lesions in larger vessels demonstrated the additional benefits of drug elution compared with bare metal stents[5]. Intravascular ultrasound was an important part of these early DES trials. Measurement of neointimal volume allowed ready comparison of drug efficacy and insights into the moderated healing process. However, there was considerable debate concerning the clinical relevance of differing neointimal volume, the "optimal amount" of neointima and the desirability of stent strut coverage to minimise the risk of stent thrombosis. In their paper Jensen and colleagues show substantial differences in the median volume obstruction in diabetic patients after implantation of either the sirolimus-eluting Cypher stent or the first generation zotarolimus-eluting Endeavour stent (median volume obstruction 0% vs. 13%, respectively)[3]. They also make comparison with their previous similar investigations in diabetic patients undergoing implantation of either the Cypher or the paclitaxel eluting Taxus Express stent (median volume obstruction 0% vs. 7.5%, respectively)[6]. Interestingly these differences in biological efficacy between the Endeavour and Cypher stents in diabetic patients are consistent with clinical differences highlighted in SORT OUT III[7] and a large "all comers" clinical registry. In the Swedish Angiography and Angioplasty Registry, diabetic patients treated with the Endeavour had higher relative risks of restenosis than those treated with Cypher stents (adjusted relative risk 1.99 [CI. 1.4-2.7])[8]. No differences in the risk of restenosis between the Taxus and Cypher were evident in this registry or a recent summation of other registry data[9]. Therefore, we might conclude that differences (>10% volume obstruction) in the surrogate endpoint of neointimal volume can predict a clinically relevant difference in outcome. More recent data for the newer zotarolimus-eluting Resolute stent (with augmented drug release profile) suggest similar clinical outcomes in diabetic and non-diabetic subjects - IVUS data are awaited.

In 2008, NICE the Institute for Health and Clinical Excellence in the United Kingdom reviewed the cost effectiveness of DES and concluded that DES should be reserved for vessels <3 mm in diameter and or lesions >15 mm length[10]. These recommendations reflected the adequate results of BMS in focal disease, the additional cost of DES and the differences between angiographic restenosis in highly scrutinised clinical trials and clinically measurable differences in outcome in the real world practice (without the impact of follow-up

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angiography on repeat revascularisation). NICE did not consider that diabetes was a sufficiently powerful predictor of adverse outcome to mandate routine use of DES in diabetic patients regardless of lesion characteristics. These public health considerations illustrate some of the additional issues when attempting to compare DES outcomes. Demonstration of superiority is difficult when an existing technology is already performing well and large numbers of patients (ideally with complex disease) are consequently required to allow detection of differences in outcome.

Recently a number of large "head-to-head" comparative studies of different DES have been reported. Diabetic patients remain a minority within these studies and are certainly under represented compared to real world practice. However, outcomes of over 4,000 diabetic patients undergoing DES PCI in randomised clinical trials have been summarised by colleagues from Cordis and the Cornerstone Research Group[4]. Compared with the paclitaxel-eluting Taxus stent (usually on an Express platform), the Endeavour and Xcience stents they suggest a significant cost saving associated with the preferential use of the Cypher stent in this group of patients (TLR 3.2% Cypher, 7.1% Endeavour, 6.9%Taxus, 7.9% Xcience). Based on these outcomes and a standard stent price in the United States, the authors suggest a potential saving of at least $140 million annually associated with the preferential use of the Cypher stent in diabetic patients undergoing PCI. Notably, the comparison between Cypher and Xcience stents is an indirect one, and these data do not differentiate between outcomes with Taxus and Endeavour in contrast with the aforementioned IVUS and clinical data.

It would be naïve to think that selection of a particular stent during intervention is based entirely on the efficacy of the stent and drug ± polymer to inhibit neointima. Stents may be selected for their tracking ability, scaffolding, lack of recoil, side branch access, radio-opacity, etc. and the ultimate choice is based upon a summation of these properties. Successful treatment of a lesion is also a composite outcome based upon a number of factors other than the efficacy of neointimal suppression, including accurate stent placement, complete lesion coverage and optimal expansion. In the STLLR study, geographical miss (either "longitudinal" miss and/or incorrect sizing – "axial" miss) was associated with a doubled rate of TLR at one year and a tripled risk of myocardial infarction (2.4% vs. 0.8%, $p < 0.04$)[11]. It is sobering to learn that a combination of axial and geographic miss was evident in 16% of patients in this registry when we consider accurate placement of an appropriately sized stent as a basic requirement of any PCI procedure. These observed differences in clinical outcomes are as large as any of the theoretical differences between different DES. Moreover, since diabetic patients contributed less than one third of the study population, one can speculate that the magnitude of the effect of "suboptimal PCI technique" would have been even greater had the proportion of diabetics been higher.

In summary, there are many cogent reasons to pay particular attention to diabetic patients. Careful study of IVUS derived surrogate endpoints in complex patient subsets –including diabetics– provides valuable insights worthy of future examination. In our clinical practices, we should begin before diabetic patients arrive in the catheterisation lab with a careful review of their cardiac and diabetic medication and an individualised review of the potential risk / benefit of the procedure. Scrupulous PCI technique is essential including an active decision regarding the merits of individual commercially available DES. Those with a proven safety profile and evidence of attenuated neointimal proliferation (particularly in diabetic patients) are most likely to have superior long-term results. Post-procedural follow-up should include particular attention to the blood pressure, lipid status and diabetic control. Ultimately, if we wish to improve the care of our diabetic patients undergoing PCI where optimal outcomes are arguably the hardest to achieve, we must employ our most efficacious treatments judiciously and with fastidious technique.

Conflict of interest statement

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References

1. Jensen LO, Maeng M, Thayssen P, Kaltoft A, Tilsted HH, Lassen JF, Hansen KN, Bottcher M, Rasmussen K, Madsen M, Johnsen SP, Sørensen HT, Thuesen L. Long-term outcomes after percutaneous coronary intervention in patients with and without diabetes mellitus in Western Denmark. *Am J Cardiol.* 2010;105:1513-9.

2. Urban P, Abizaid A, Banning AP, Bartorelli AL, Dvavik V, Ellis SG, Gao R, Holmes D, Jeong J, Legrand V, Neumann F, Nyakern M, Spaulding C, Stoll HP, Worthley S. Stent thrombosis, major bleeding and antiplatelet therapy in the e-SELECT registry. *J Am Coll Cardiol.* 2011;57:1445-54.

3. Jensen LO, Maeng M, Thayssen P, Villadsen A, Krusell L, Botker HE, Pedersen KE, Aaroe J, Christiansen EH, Vesterlund T, Hansen KN, Ravkilde J, Tilsted HH, Lassen JF, Thuesen L. Late lumen loss and intima hyperplasia after sirolimus-eluting and zotarolimus-eluting stent implantation in diabetic patients: the diabetes and drug-eluting stent (DiabeDES III) angiography and intravascular ultrasound trial. *EuroIntervention* 2011;7:323-31.

4. Saadi R, Cohen S, Banko D, Thompson M, Duong M, Ferko N. Cost analysis of four major drug-eluting stents in diabetic populations. *EuroIntervention*. 2011;7:332-39.

5. Colombo A, Drzewiecki J, Banning AP, Hauptmann K, Grube E, Dudek D, Fort S, Schiele S, Silber S, Zmudka Z, Guagliumi G, Russell ME. A Randomized Study to Assess the Benefit of Paclitaxel-Eluting Stents for Coronary Revascularization using Two Different Release Kinetics in De Novo Coronary Lesions (TAXUS 2). *Circulation*. 2003;108:788-94.

6. Jensen LO, Maeng M, Thayssen P, Christiansen EH, Hansen KN, Galloe A, Kalbaek H, Lassen JF, Thuesen L Neointimal hyperplasia after sirolimus-eluting and paclitaxel eluting stent implantation in diabetic patients: the randomised Diabetes and drug eluting stent (diabeDES) Intravascular Ultrasound trial. *Eur Heart J* 2008;29:2733-2741.

7. Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, Abildgaard U, Christiansen EH, Engstrom T, Krusell LR, Ravkilde J, Hansen PR, Hansen KN, Abildstrom SZ, Aaroe J, Jensen JS, Kristensen SD, Botker HE, Madsen M, Johnsen SP, Jensen LO, Sorensen HT, Thuesen L, Lassen JF. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet* 2010;375:1090-1099.

8. Frobert O, Lagerqvist B, Carlsson J, Lindback J, Stenestrand U, James SK. Differences in restenosis rate with different drug-eluting stents in patients with and without diabetes mellitus: a report from the SCAAR (Swedish Angiography and Angioplasty Registry). *J Am Coll Cardiol* 2009;53:1660-1667.

9. Banning AP, Hood KL, Finn AV. Patterson C, Abizaid A, Eppiher MJ, Dawkins K, Baim DS. Differential drug eluting stent effects in patients with diabetes-bench to bedside evidence for neointimal suppresion and restenosis reduction. *Interventional Cardiology* 2010;5:27-34.

10. http://egap.evidence.nhs.uk/TA152/contents

11. Costa MA, Angiolillo DJ, Tannenbaum M, Driesman M, ChuA, Patterson J, Kuehl W, Battaglia J, Dabbons S, Shamoon F, Flieshman B, Niederman A, Bass TA. Impact of Stent Deployment Procedural Factors on Long-Term Effectiveness and Safety of Sirolimus-Eluting Stents (Final Results of the Multicenter Prospective STLLR Trial). *Am J Cardiol* 2008;101: 1704 -1711.