Research Highlights

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Safety and efficacy of drug-eluting stents: a meta-analysis of 76 randomized trials

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Evaluation of: Bangalore S, Kumar S, Fusaro M *et al.* Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 125(23), 2873–2891 (2012).

Since the introduction of drug-eluting stents (DES) in the 2000s, there have been dramatic reductions in both the rate of restenosis and the need for repeat revascularization compared with bare-metal stents (BMS). This improvement is largely thanks to the addition of cytotoxic medications fixed directly to these stents. There are now numerous different DES each with its unique characteristics; however, the short- and long-term efficacy (target-vessel revascularization [TVR], target-lesion revascularization [TLR]) and safety (death, myocardial infarction and stent thrombosis) of these DES are less well defined [1]. This was the objective of a recent meta-analysis by Bangalore *et al.*, the largest of its kind to offer important insights into their relative safety and efficacy [2]. The meta-analysis was comprised of 76 randomized clinical trials, totaling 57,138 patients and 117,762 patient-years of follow-up, mean follow-up duration of 2.1 years. Of the 76 trials, 61 used clopidogrel for at least 6 months in the DES arm. Six different types of stents, including BMS, sirolimus-eluting stent, paclitaxel-eluting stent, everolimus-eluting stent (EES), zotarolimus-eluting stent (ZES), and ZES-Resolute (Medtronic, CA, USA), were compared. The short-term efficacy of the stent (less than 1 year) demonstrated that compared with BMS, all of the DES reduced TVR from 39 to 61% depending on the type of DES. The degree of reduction of TVR varies with different DES. Interestingly, as one of the first-generation stents, sirolimus-eluting stent was shown to have the highest TVR reduction of 74% compared with BMS. This is followed by EES at 72% and the newer ZES-Resolute at 69%. The paclitaxel-eluting stent and the older ZES both reduced TVR by 53 and 52%, respectively. Clearly, the degree of reduction by DES on TVR rate did vary significantly between different DES and similar results were demonstrated when examining TLR. When comparing DES with BMS, the most important finding was that there was no increased risk of death with any of the DES when compared with BMS; short-term mortality rate was <0.3%. In fact, all of the DES except the paclitaxel-eluting stents were also found to reduce the rate of myocardial infarction. The median stent thrombosis rate for any stent was <0.2%. Comparing EES with BMS, EES reduced the risk of stent thrombosis by 56%, with BMS at 0.18% and EES at <0.10%.

The long-term results (greater than 1 year) revealed similar conclusions as the short-term analysis. Again, DES had lower incidences of myocardial infarction was observed when compared with BMS. EES continued to demonstrate the greatest reduction. Stent thrombosis was not observed to be increased compared with BMS. Overall, the safest DES appeared to be EES with a significant reduction in stent thrombosis risk of 49%.

This study is important as it addressed the safety and efficacy concerns of DES and demonstrated that even with BMS there is a small risk for late stent thrombosis [3]. As the largest meta-analysis comparing the different types of DES with BMS, the presented data demonstrate that DES

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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are highly efficacious at reducing the risk of TVR/TLR and myocardial infarction without an increase in any safety outcomes, including stent thrombosis, compared with BMS. Amongst the different DES, EES have shown to be the safest and may suggest its place as the future benchmark for comparison.

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Switch therapy in patients with drug-eluting stent restenosis

Evaluation of: Alfonso F, Perez-Vizcayno M, Dutary J *et al.* Implantation of a drug-eluting stent with a different drug (switch strategy) in patients with drug-eluting stent restenosis. *JACC Cardiovasc. Interv.* 5(7), 728–737 (2012).

DES have been extensively used since their development because of their ability to slowly release antiproliferative drugs that prevent in-stent restenosis (ISR). However, DES are not resistant to ISR. The initial randomized trials comparing DES with BMS compared patients with *de novo* native coronary lesions and ISR was observed at follow-up in <6% patients [1]. Subsequent trials conducted in more complex patients and lesions demonstrated higher ISR rates. Several treatment options are available for DES ISR, including balloon angioplasty, vascular brachytherapy (VBT), BMS and repeat DES implantation, but the intervention of choice remains to be a challenge. The SISR trial compared the long-term outcome of patients treated for BMS ISR with SES or VBT. At 3-year follow-up, patients treated with SES had improved survival free of TLR compared with patients treated with VBT. VBT was initially found to be effective but at follow-up the initial benefit of reduced restenosis gradually lost significance after the first year [2]. The exact mechanism for DES ISR remains unclear, but the concept of drug resistance has led to the investigation of the use of a different DES for patients with DES ISR. The ISAR-DESIRE 2 study was a recent randomized study that compared 450 patients with SES ISR to those treated with either repeat SES or a paclitaxel-eluting stent. They found that minimal lumen diameter, late lumen loss and binary restenosis were similar in both arms [3]. Limitations to that study were that two-thirds of enrolled patients presented ISR of the polymer-free SES, a stent not available widely, and previous studies have shown that SES is more effective than paclitaxel-eluting stent in inhibiting tissue proliferation [1]. In a new study published in the *Journal of American College of Cardiology: Cardiovascular Interventions*, Alfonso *et al.* conducted a large prospective, multicenter study to investigate the use of a different DES in patients presenting with DES ISR [4]. The study included 363 patients with DES ISR from 12 different sites. The different DES strategy (switch strategy) was used in 274 patients (75%) and 89 patients (25%) received alternative therapeutic strategies (no switch). The type of alternative therapeutic strategies were determined by the local investigator including same DES, BMS or balloon angioplasty. Baseline characteristics were similar amongst the two groups, but lesion length was longer in the switch group. At follow-up, (median: 278 days) minimal lumen diameter was larger and recurrent restenosis rate lower (22 vs 40%; p = 0.008) in the different DES group. At the last clinical follow-up (median: 771 days), the main clinical end point, which was a composite of death, myocardial infarction and TLR, occurred less frequently (23 vs 35%; p = 0.039) in the switch strategy group. The results of this study suggest that patients treated with the switch strategy have better clinical and angiographic long-term results compared with those treated with alternative therapy. Limitations to this particular study are that a wide variety of DES with ISR were used and treated with many different strategies including first- and second-generation DES in the switch strategy group. This provided multiple small-treatment subgroups and made it difficult to analyze the effectiveness of a particular DES. Another limitation is that the study was nonrandomized and the particular reason for a patient to not receive the switch strategy for treatment of DES ISR could not be fully elucidated. The intervention of choice for treatment of DES ISR remains to be a challenge and the role of drug resistance in each particular patient seems to have a major role in DES ISR.

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A global risk approach to identify patients with left main or three-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention

Evaluation of: Serruys PW, Farooq V, Vranckx P *et al.* A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc. Interv.* 5(6), 606–617 (2012).

The Global Risk classification is a scoring system devised to assess the outcomes of patients with coronary artery disease undergoing revascularization. It incorporates both the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, an objective anatomical classification of the coronary artery tree, and the European System for Cardiac Operative Risk Evaluation (EuroSCORE), an objective clinical risk score used in cardiac surgery [1]. The SYNTAX score was calculated by adding up the score of the individual lesions (≥50% stenosis in a vessel ≥1.5 mm) based the location of the lesion and the at-risk distal myocardium and morphologic features [2,3]. The Global Risk classification is calculated by dividing the EuroSCORE into three tertiles (low 0–2, intermediate 3–5 and high ≥6) and the SYNTAX score into three tertiles (low ≤22, intermediate 22–32 and high ≥33). Then both scoring systems were combined into three Global Risk groups: low – SYNTAX score <33 and EuroSCORE <6; intermediate – SYNTAX score ≥33 and EuroSCORE <6 or EuroSCORE ≥6 and SYNTAX score <33; and high – SYNTAX ≥33 and EuroSCORE ≥6 [4]. In this *post hoc* analysis of the original SYNTAX trial at 3 years, Serruys *et al.* examined whether the Global Risk could identify a group of low-risk patients for whom either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) approach could be safely and successfully performed [5].

The original SYNTAX trial using predictive models at 3 years. The original SYNTAX trial was a randomized, prospective, multicenter trial that used an 'All-Comers' approach. Patients were randomized to either PCI or CABG. There was also a nested group that was deemed unsuitable for randomization by the heart team; these patients were assigned to a specific approach, either PCI or CABG. The patients were classified into two groups: a left main disease group (LM; alone or with one-, two-, or three-vessel disease [3VD]) and a 3VD group [6].

The results show that the Global Risk was able to differentiate clinical outcomes in the 'All-Comers' group with either LM or 3VD between a Global Risk low group and a higher-risk group (Global Risk intermediate and high) for all-cause mortality and major adverse cardiac and cerebrovascular events (MACE). For patients in the LM group there was a clear ability of the Global Risk to identify low-risk patients in whom either PCI or CABG could be performed. In the 3VD group the EuroSCORE was better at identifying patients more appropriately suited to CABG compared with PCI than the SYNTAX score; the Global Risk offered little further risk stratification. In the CABG group, the Global Risk was able to differentiate between low-risk groups and intermediate/high-risk groups only for all-cause mortality and MACE in both the randomized and All-Comers groups. Also in the CABG group the Global Risk offered little or no improvement compared with the EuroSCORE alone.

Comparison of CABG and PCI in regards to the Global Risk low group with LM showed, in the randomized cohort, that CABG had a higher 3-year mortality compared with PCI (CABG: 7.5%, PCI: 1.2%, 95% CI: 0.03–0.70; p = 0.0054). No significant difference was found between MACE, myocardial infarction, stroke or all-cause revascularization. In the Global Risk low group, All-Comers in the LM cohort had no statistical difference in mortality or MACE. A significant difference in stroke was seen with CABG compared PCI (CABG: 4.0%, PCI: 0.6%, 95% CI: 0.02–01.05; p = 0.025). A significant difference was also seen in myocardial infarction with PCI compared CABG (CABG: 0.9%, PCI: 3.9%, 95% CI: 89–20.70; p = 0.047). No significant difference was seen in all-cause revascularization.

Comparison of CABG and PCI in the randomized 3VD resulted in no significant difference in mortality, MACE or stroke. PCI had a significantly increased risk of all-cause revascularization compared with CABG (CABG: 10.5%, PCI: 18.5%, 95% CI: 1.19–12.96; p = 0.0055). In the All-Comers there was no significant difference in mortality. A significantly higher incidence of MACE was seen with PCI compared with CABG (CABG: 17.9%, PCI: 24.4%, 95% CI: 1.03–1.96; p = 0.031) and a significantly higher incidence of all-cause revascularization with PCI compared with CABG (CABG: 9.1%, PCI 18.5%, 95% CI: 1.44–43.35; p = 0.0002). No significant difference was seen in strokes rate.

In the reclassified groups, patients in the Global Risk low group with LM, PCI resulted in a lower mortality at 3 years

compared with CABG. In the Global Risk high group CABG was more favorable compared with PCI, as a result of decreased MACE. Patients with 3VD in the Global Risk low group had more favorable outcomes with CABG compared with PCI. In a subgroup analysis of 3VD patients in the Global Risk low group with a low SYNTAX score PCI was comparable to CABG.

This study shows the Global Risk classification is able to identify a low-risk group of patients for whom PCI and CABG have comparable outcomes. It also shows that clinical factors are more predictive of clinical outcomes (all-cause death and MACE) compared with SYNTAX score alone in patients undergoing PCI. In regards to LM, the Global Risk is better able to identify a group of low-risk patients for whom PCI is comparable to CABG compared with either the SYNTAX score or EuroSCORE alone. In regards to patients with 3VD, the Global Risk is able to identify a group of patients of whom CABG is superior to PCI compared with the SYNTAX score alone.

The strengths of this study are that it can be broadly applied to many patients. Also, the EuroSCORE is a simple calculation that can be easily added to the SYNTAX score at the bedside to create a simple algorithm that allows for enhanced risk stratification of paitents with LM and 3VD. The study limitations are that this is a retrospective, *post hoc* analysis. It also had limited statistical power for CABG compared with PCI in patients with stroke and myocardial infarction and in reclassified patients. Validation of these results is still needed. The Global Risk classification provides as simple algorithm that is able to identify a low-risk group for which PCI and CABG have comparable outcomes.

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