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Comparison of drug-eluting and bare-metal stents in patients with diabetes undergoing primary percutaneous coronary intervention: what is the evidence?

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Abstract

A best evidence topic was written according to a structured protocol. The question addressed was, should the practising interventional cardiologist use drug-eluting stents (DESs) or bare-metal stents (BMSs) when undertaking primary percutaneous coronary intervention (PCI) in diabetic patients. The relevant outcomes that were used to determine the answer to this question included: in-stent restenosis, target vessel revascularization (TVR), mortality, myocardial infarction and in-stent thrombosis. The OVID Medline database was used to carry out the reported search for abstracts of relevant journal articles. Altogether 102 papers were found, of which 7 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. From the evidence available, we conclude that in-stent restenosis is less likely to occur over a follow-up of at least 6 months if a DES is used instead of a BMS. Furthermore, TVR is less likely to be required in diabetic patients who receive a DES in comparison with a BMS. Nevertheless, no significant difference in mortality between stents was detected by the studies reviewed. This included no difference in the incidence of cardiac and non-cardiac causes of death. There was evidence showing that DESs are associated with a decrease in the risk of myocardial infarction and, in particular, a decrease in non-Q-wave myocardial infarction. However, there was also conflicting evidence demonstrating no significant difference in the incidence of myocardial infarction between diabetic patients who had received a BMS or a DES. Moreover, the available evidence showed no significant difference in the risk of in-stent thrombosis for all DESs with the exception of Sirolimus eluting stents in which the evidence was not consistent. In summary, the available evidence supports the use of DESs over BMSs in diabetic patients undergoing primary PCI.

Keywords: Diabetes • Bare-metal stent • Drug-eluting stent • Primary percutaneous coronary intervention • Restenosis • Stent thrombosis • Target lesion revascularization

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [diabetic patients undergoing primary percutaneous coronary intervention] are [drug-eluting stents superior to bare-metal stents] with regard to [restenosis, efficacy and complications]?

CLINICAL SCENARIO

A 55-year old male with known diabetes has been admitted to hospital with an acute ST-elevation myocardial infarction. He is a candidate for primary percutaneous coronary intervention. The on-call registrar suggests that, in light of this gentleman's diabetes, a drug-eluting stent (DES) may provide the most benefit, reducing the risk of in-stent restenosis and target vessel revascularization (TVR). You are called into theatre to assist the on-call consultant who is in the process of deploying a BMS. The consultant states that he uses bare-metal stents regardless of diabetic status; he claims that, in his experience, it improves his patient outcomes. Unclear on the best evidence surrounding the use of BMSs versus DESs in diabetic patients you resolve to check the literature yourself.

SEARCH STRATEGY

The Medline 1985 to February 2013 using the OVID interface was used. [Diabetes] OR [drug-eluting stents and bare-metal stents] OR [Restenosis rate] was searched to find all abstracts containing information on each individual part of the question. Subsequently, [Diabetes] AND [drug-eluting stents and bare-metal stents] AND

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Patti *et al.* (2008), Am J Cardiol, Italy [2] Meta-analysis (level 1)	Meta-analysis of 9 randomized, clinical trials (RCT) evaluating outcome after DES vs BMS implantation in diabetic patients with a follow-up of ≥6 months (1141 patients)	Death (cardiac and non-cardiac causes)	DES vs BMS: 2.4 vs 2.3%, ($P = 0.91$)	This meta-analysis demonstrates that, in diabetic patients, DESs are superior to BMSs with regards to in-stent restenosis, TVR and myocardial infarction, and that there is no significant difference in stent thrombosis and mortality
		Myocardial infarction (Q-wave and non-Q-wave)	DES vs BMS: 3.5 vs 7.2% (52% risk decrease, $P = 0.02$)	
		In-stent restenosis	DES vs BMS: 8 vs 41% (OR = 0.13, 95% CI 0.09–0.20, $P < 0.00001$)	
		TVR	DES vs BMS: 8 vs 27% (OR = 0.23, 95% CI 0.16–0.33, $P < 0.00001$)	
		Stent thrombosis	DES vs BMS: 1.1 vs 1.2%, ($P = 0.98$)	
Stettler *et al.* (2008), BMJ, Switzerland, Italy, Germany, UK, Netherlands, USA, Denmark, Spain, Belgium, Latvia [7] Meta-analysis (level 1)	Meta-analysis of 35 RCTs comparing DESs (Sirolimus or Paclitaxel) with BMSs in diabetic patients with signs or symptoms of myocardial ischaemia and a follow-up of ≥6 months Restricting the analysis to trials with a duration of dual antiplatelet therapy of ≥6 months (3852 patients)	Overall mortality	Sirolimus ES vs BMS: HR = 0.88, 95% CI 0.55–1.30 Paclitaxel ES vs BMS: HR = 0.91, 95% CI 0.60–1.38	This meta-analysis indicates that both types of DESs are superior to BMS with respect to TVR in diabetic patients undergoing PCI. Furthermore, this study shows that DESs are not associated with an increased risk of myocardial infarction or mortality when compared with BMSs
		Myocardial infarction	Sirolimus ES vs BMS: HR = 0.68, 95% CI 0.43–1.12 Paclitaxel ES vs BMS: HR = 0.85, 95% CI 0.54–1.43	
		TVR	Sirolimus ES vs BMS: HR = 0.29, 95% CI 0.19–0.45 Paclitaxel ES vs BMS: HR = 0.38, 95% CI 0.26–0.56	
		Stent thrombosis (as per protocol in individual trials)	Sirolimus ES vs BMS: HR = 0.20, 95% CI 0.05–0.68 Paclitaxel ES vs BMS: HR = 0.73, 95% CI 0.19–2.80	
Kimura *et al.* (2008), Am J Cardiol, USA, UK, Germany [4] Meta-analysis (level 1)	Meta-analysis of 3 RCTs used serial intravascular ultrasound to compare Paclitaxel ES and BMS with respect to in-stent neointima formation (Diabetes was present in 273 of 956 patients)	In-stent late loss (mm)	BMS vs Paclitaxel ES: 1.05 vs 0.48 ($P < 0.0001$)	This meta-analysis shows that the use of Paclitaxel-eluting stents in diabetic patients is associated with reduced in-stent and in-segment stenosis when compared with BMSs
		In-stent diameter stenosis (%)	BMS vs Paclitaxel ES: 43.6 vs 22.5 ($P < 0.0001$)	
		In-segment late loss (mm)	BMS vs Paclitaxel ES: 0.69 vs 0.29 ($P < 0.0001$)	
		In-segment diameter stenosis (%)	BMS vs Paclitaxel ES: 46.9 vs 32.3 ($P < 0.0001$)	
Kumbhani *et al.* (2008), Am Heart J, USA [5] Meta-analysis (level 1)	Meta-analysis of 16 RCTs comparing either the Paclitaxel- or Sirolimus-eluting stent with the BMS or with each other in diabetic patients during a follow-up of at least 6 months (2951 patients)	TVR	DES vs BMS: RR = 0.35, 95% CI 0.27–0.46 ($P < 0.0001$)	This study demonstrates that diabetic patients who receive DESs have a significantly lower incidence of TVR, in-segment restenosis and myocardial infarction at 6–12 months, compared with BMSs and that there is no difference in mortality and stent thrombosis
		Major adverse cardiovascular events	DES vs BMS: RR = 0.42, 95% CI 0.31–0.56 ($P < 0001$)	
		In-segment restenosis	DES vs BMS: RR = 0.31, 95% CI 0.25–0.40 ($P < 0.0001$)	

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
		Non-Q-wave myocardial infarction	DES vs BMS: RR = 0.57, 95% CI 0.32–0.99 (P = 0.046)	
		Q-wave myocardial infarction	DES vs BMS: RR = 0.72, 95% CI 0.25–2.07 (P = 0.54)	
		Stent thrombosis	DES vs BMS: RR = 0.41, 95% CI 0.13–1.27 (P = 0.12)	
		Death	DES vs BMS: RR = 0.64, 95% CI 0.32–1.28 (P = 0.20)	
Kirtane *et al.* (2008), J Am Coll Cardiol. USA, UK, Italy Germany [6] Pooled analysis (level 1)	Pooled analysis of 5 RCTs of Paclitaxel ESs vs BMSs in single, non-complex lesions over a 4-year follow-up (827 of 3513 patients were diabetic)	Death	Paclitaxel ES vs BMS: 8.4% vs 10.3% (P = 0.61)	This study showed that there was no significant difference between DESs and BMSs in terms of mortality, in-stent restenosis and stent thrombosis. On the other hand, the study demonstrates DESs require significantly less target lesion revascularization
		Myocardial infarction	Paclitaxel ES vs BMS: 6.9 vs 8.9% (P = 0.17)	
		Stent thrombosis	Paclitaxel ES vs BMS: 1.4 vs 1.2% (P = 0.92)	
		TVR	Paclitaxel ES vs BMS: 12.4 vs 24.7% (P < 0.0001)	
Boyden *et al.* (2007), Am J Cardiol, USA [3] Meta-analysis (level 1)	Meta-analysis of 8 RCTs comparing either Paclitaxel or Sirolimus ESs vs BMSs in diabetic patients and providing data on ≥1 of the following outcomes: late lumen loss, in-stent restenosis or target lesion revascularization (1520 patients)	Mean late lumen losses	BMS vs DES: 0.93 mm (95% CI 0.51–1.34) vs 0.18 mm (95% CI 0.08–0.45)	This study shows that, in diabetic patients, DESs are superior to BMSs with respect to late lumen loss, in-stent restenosis and target lesion revascularization
		In-stent restenosis	BMS vs DES: 42% (239/569) vs 5.9% (30/510). 86% decrease in risk of developing restenosis (RR = 0.14, 95% CI 0.10–0.22, [P < 0.001])	
		TVR	BMS vs DES: 22.9% (177/773) vs 7.5% (53/703). 66% decrease in the need for TVR (RR = 0.34, 95% CI 0.26–0.45, [P < 0.001])	
Bangalore *et al.* (2012), BMJ, USA, Germany [8] Meta-analysis (level 1)	Meta-analysis of 42 RCTs comparing different DESs (Sirolimus, Paclitaxel, Everolimus and Zotarolimus) vs BMSs (in *de novo* coronary lesions). In 34 of the 42 trials, clopidogrel was used for at least 6 months in the drug-eluting stents arm (10 714 patients)	TVR	BMS vs Sirolimus ES: RR = 0.34 (95% CI 0.25–0.44) BMS vs Paclitaxel ES: RR = 0.46 (95% CI 0.34–0.63) BMS vs Everolimus ES: RR = 0.28 (95% CI 0.15–0.45) BMS vs Zotarolimus ES: RR = 0.77 (95% CI 0.47–1.31)	This study shows that in diabetic patients who have undergone PCI; Sirolimus, Paclitaxel and Everolimus ESs are superior to BMSs with regards to target lesion revascularization. Zotarolimus was not shown to be superior. Death, myocardial infarction and stent thrombosis were all non-significant
		Death	BMS vs Sirolimus ES: RR = 1.00 (95% CI 0.73–1.39) BMS vs Paclitaxel ES: RR = 0.96 (95% CI 0.70–1.38) BMS vs Everolimus ES: R = 0.83 (95% CI 0.42–1.46) BMS vs Zotarolimus ES: RR = 1.14 (95% CI 0.58–2.27)	

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
		Myocardial infarction	BMS vs Sirolimus ES: RR = 0.71 (95% CI 0.49–1.05)	
			BMS vs Paclitaxel ES: RR = 0.82 (95% CI 0.21–1.09)	
			BMS vs Everolimus ES: RR = 0.52 (95% CI 0.21–1.09)	
			BMS vs Zotarolimus ES: RR = 2.16 (95% CI 0.91–8.45)	
		Any stent thrombosis	BMS vs Sirolimus ES: RR = 0.64 (95% CI 0.36–1.14)	
			BMS vs Paclitaxel ES: RR = 0.78 (95% CI 0.45–1.54)	
			BMS vs Everolimus ES: RR = 0.56 (95% CI 0.20–1.46)	
			BMS vs Zotarolimus ES: RR = 2.75 (95% CI 0.60–14.85)	

DES: drug-eluting stent; BMS: bare-metal stent; TVR: target vessel revascularization; PCI: percutaneous coronary intervention.

[Restenosis rate] was searched to find all abstracts containing information on the three sections combined together as one question.

SEARCH OUTCOME

One hundred and two papers were found using the reported search. From these, seven papers were identified that provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

Patti *et al*. [2] demonstrated that in 1141diabetic patients who had undergone PCI, in-stent restenosis was less likely to occur over a follow-up period of at least 6 months in patients who received DESs compared with BMSs (8 vs 41%, respectively [odds ratio (OR) = 0.13, 95% confidence interval (CI) 0.09–0.20, $P < 0.00001$]). Furthermore, Boyden *et al*. [3] showed that in comparison with BMSs, DESs were associated with an 86% decrease in the risk of in-stent restenosis. (42 vs 5.9% [relative risk (RR) = 0.14, 95% CI 0.10–0.22, $P < 0.001$]). Additionally, it was shown by Kimura *et al*. [4], via the use of serial intravascular ultrasound, that specifically Paclitaxel ESs are associated with less in-stent late loss (mm), (0.48 vs 1.05 [$P < 0.0001$]) and decreased in-stent diameter stenosis (%), (22.5 vs 43.6 [$P < 0.0001$]).

Patti *et al*. [2] found that TVR was less likely to be performed in diabetic patients who had received DESs in contrast to BMSs (8 vs 27%, respectively [OR = 0.23, 95% CI 0.16–0.33, $P < 0.00001$]). Likewise, Boyden *et al*. [3] demonstrated, in 1520 diabetic patients, that the use of a DES was associated with a 66% decrease in TVR (22.9 vs 7.5%, [RR = 0.34, 95% CI 0.26–0.45, $P < 0.001$]). Similarly, Kumbhani *et al*. [5] found that diabetic patients who received either a Paclitaxel or Sirolimus ES were less likely to require TVR in a follow-up of at least 6 months (RR = 0.35 [95% CI 0.27–0.46, $P < 0.0001$]). With regard to patients who received specifically Paclitaxel ESs, Kirtane *et al*. [6] showed that, over a 4-year follow-up period, TVR was carried out less frequently than in patients who had received BMSs (12.4 vs 24.7% [$P < 0.0001$]). Moreover, Stettler *et al*. [7] found that in follow-up of at least 6 months, Paclitaxel ESs were associated with a decreased rate of TVR (hazard ratio (HR) = 0.38 [95% CI 0.26–0.56]). Additionally, Stettler *et al*. [7] demonstrated that Serolimus ESs are also less likely than BMSs to require TVR (HR = 0.29 [95% CI 0.19–0.45]).

As a direct corollary, Bangalore *et al*. [8] carried out a large-scale meta-analysis that included 10 714 diabetic patients, which compared BMSs with different types of DESs. As this is the most recent study, it is likely that these results are the most reliable. Bangalore *et al*. [8] showed that three types of ESs were superior to BMSs with TVR (Sirolimus RR = 0.34 [95% CI 0.25–0.44], Paclitaxel RR = 0.46 [95% CI 0.34–0.63] and Everolimus RR = 0.28 [95% CI 0.15–0.45]. Conversely, Bangalore *et al*. [8] found that there was no significant difference with Zotarolimus ESs and BMSs (RR = 0.77 [95% CI 0.47–1.31]).

Kumbhani *et al*. [5] demonstrated, in a meta-analysis that included 2951 diabetic patients, that there was no significant difference between DESs and BMSs with regard to the risk of death (RR = 0.64 [95% CI 0.32–1.28, $P = 0.20$]). Furthermore, Patti *et al*. [2], Kirtane *et al*. [6], Stettler *et al*. [7] and Bangalore *et al*. [8] all showed no significant difference in mortality between DESs and BMSs in diabetic patients.

Patti *et al*. [2] demonstrated that the incidence of myocardial infarction was significantly decreased in the DES group in comparison with the BMS group (3.5 vs 7.2%, respectively [$P = 0.02$]).

Therefore, DESs were associated with a 52% decrease in the risk of myocardial infarction. Conversely, Stettler *et al.* [7] found no significant difference between Serolimus ESs vs BMSs, (HR = 0.68 [95% CI 0.43–1.12]) and also Paclitaxel ESs vs BMSs (HR = 0.85 [95% CI 0.54–1.43]). In agreement with this, Kirtane *et al.* [6] and Bangalore *et al.* [8] found no significant difference between DESs and BMSs with regard to myocardial infarction. However, Kumbhani *et al.* [5] showed that there was a significant difference with respect to non-Q-wave myocardial infarction (RR = 0.57 [95% CI 0.32–0.99, $P = 0.046$]) but not Q-wave myocardial infarction (RR = 0.72 [95% CI 0.25–2.07, $P = 0.54$]).

Both Patti *et al.* [2] and Kumbhani *et al.* [5] demonstrated non-significant difference between DESs and BMSs with regard to stent thrombosis ($P = 0.98$ and 0.12, respectively). Furthermore, in specifically Paclitaxel ESs, Kirtane *et al.* [6] found no significant difference in stent thrombosis (1.4 vs 1.2% [$P = 0.92$]). Likewise, Stettler *et al.* [7] showed a non-significant difference between Paclitaxel ESs and BMSs (HR = 0.73 [95% CI 0.19–2.80]). However, it was shown by Stettler *et al.* [7] that there is a significant difference in stent thrombosis when comparing Sirolimus ESs against BMSs; Sirolimus ESs were associated with a decrease in stent thrombosis (HR = 0.20 [95% CI 0.05–0.68]). Conversely, Bangalore *et al.* [8] found that Sirolimus ESs were not superior to BMSs (RR = 0.64 [95% CI 0.36–1.14]). The two confidence intervals do cross over and so it is possible that the true value lies between 0.36 and 0.68; however, the RR and HR may not be comparable. Both are large sample sizes, 3852 vs 10 714.

A total of 73 references were used in the meta-analyses/pooled analyses that had been identified for this BET. Furthermore, 26 (35.6%) were referenced in more than one study. Therefore, there is a degree of duplication in results. Kimura *et al.* [4] and Kirtane *et al.* [6] had 0 exclusive references, whereas the meta-analyses published by Stettler *et al.* [7] and Bangalore *et al.* [8] had 17 and 21 unique references, respectively. Nevertheless, this does not decrease the validity of the conclusions drawn in this BET.

CLINICAL CONCLUSION

The evidence demonstrates that in-stent restenosis and TVR are less likely to occur in diabetic patients who receive a DES compared with a BMS. Furthermore, the evidence shows that there is no significant difference in mortality between DESs and BMSs. On the other hand, there is conflicting evidence with regard to myocardial infarction and stent thrombosis; nevertheless, the evidence favours a non-significant difference in both outcomes. In summary, DESs are superior to BMSs with regard to clinical outcomes and should be used routinely in diabetic patients undergoing primary PCI.

Conflict of interest: none declared.

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