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Should all Stents be Drug-Eluting Stents?

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ABSTRACT

Introduction: Drug-eluting stents (DES) are used for percutaneous coronary intervention to overcome problems with bare metal stents (BMS).
DES contain mitotic or anti-inflammatory drugs, which prevent re-stenosis and reduce the rate of revascularisation. However, they have been shown to cause late in-stent thrombosis.
Aim: Aim is to review the most recent evidence comparing DES with BMS in terms of efficacy and safety.
Method: Pubmed and Scopus were searched for relevant articles. Seven articles were found, reviewed and analysed.
Discussion: DES did not improve mortality compared with BMS but they reduced the rate of revascularization. Second generation DES showed more of a benefit than BMS. DES showed more benefit in women and in larger coronary arteries.
DES has shown an increased risk of late stent thrombosis compared with BMS and a possible increase in cardiac deaths. Second generation DES seem to be safer.
Conclusion: DES do not show a significant reduction in rates of MIs or cardiac deaths in comparison with BMS, but do show a reduction in revascularization rates.
While there are safety concerns with first generation DES, second generation DES seem to be safe. It does not seem that DES can replace BMS yet, but newer generations of DES have potential.

KEYWORDS: Coronary artery disease, Drug eluting stents, PCI

Introduction

Bare metal stents (BMS) have been used during percutaneous coronary intervention (PCI) to reduce the rates of acute vessel re-stenos is and reduce the need for revascularisation after performing balloon angioplasty, which occurred due to elastic recoil, vessel wall dissection, remodelling of vessel wall and proliferation of the intima layer of the vessel wall[1, 2]. One complication discovered from the use of the BMS was late in-stent re-stenosis. This occurred due to neointimal hyperplasia.

Neointimal hyperplasia occurs secondary to the trauma caused to the blood vessels during the process of stenting. The trauma triggers an inflammatory reaction, which cause platelet adhesion, activation and aggregation leading to the formation of microthrombi in the blood vessel. These microthrombi attract other inflammatory cells such as macrophages and lymphocytes which cause activation and proliferation of the smooth muscle cells. The proliferating smooth muscle cells migrate into the lumen of the blood vessel and form the neo-intimal layer. This neo-intimal layer continues to grow causing the in-stent re-stenosis complication of stenting[3].

To overcome this complication of BMS, the idea of drug-eluting stents (DES) was conceived. The DES attempts to disrupt the neo-intimal proliferation process by interrupting the pathway. This has been done by the use of stents containing a polymer, which can deliver drugs locally to the surrounding tissues[3]. The drugs looked at were either anti-inflammatory drugs or antimitotics. Anti-inflammatory drugs, such as Sirolimus, affect the neo-intimal proliferation process by reducing the amount of inflammation produced during the stenting process. The antimitotics, such as Paclitaxel, affect the neointimal proliferation pathway by decreasing local cell division, thereby reducing the local smooth muscle proliferation. The local delivery of these drugs limits the systemic side effects associated with these medications[2].

Despite reducing the rate of in-stent re-stenosis, DES have been shown to cause late or very late stent thrombosis, which results from delayed hypersensitivity reactions and

fibrin deposition leading to a delayed healing mechanism of the vessel wall, which increases thrombosis risk[4]. This complication can lead to occlusion of the vessels with a risk of myocardial infarction (MI)[1, 5].

DES was recommended for use in PCI for the treatment of ischemic heart disease by the national institute of clinical excellence (NICE) guidelines. Currently the recent review of their evidence by the NICE guidelines has recommended their use over BMS only if certain conditions are met. These conditions are: diameter of the vessels less than 3.00mm, size of the lesion to be stented less than 15mm and the cost of the DES compared with the bare-metal stent not exceeding £300[6].

This article will look at the potential benefits and risks associated with the use of DES, in comparison with BMS to see if they are worth using instead of BMS.

Aims

Review DES in terms of efficacy and safety in comparison with BMS.

Method

A literature search was conducted using Scopus and Pubmed search engines. The terms searched for were "Drug eluting stent", "bare metal stents" and "coronary artery disease". The search looked at original research, which has been conducted very recently, since 2013 due to the large number of studies covering this subject. A Large number of articles was excluded based on search criteria.

The remaining articles were then scanned to find the remaining suitable articles. The criteria used while searching and scanning for the articles are listed below in table 1.

Results:

The Pubmed search produced 103 results, while scopus produced 215 results using the criteria below in table 1. After selective scanning, 7 articles were found. Reasons for exclusions were: duplicity between the 2 search engines and not meeting the search criteria outlined in table 1 below.

Table 1: search criteria

Keywords	Inclusion criteria	Exclusion criteria
Drug-eluting stents	Original research articles	Articles older than 2013
Bare metal stents	Articles with the keywords	Non-original research articles
Ischaemic heart disease	Research conducted on humans	Foreign language articles
	Articles in subject areas of medicine, pharmacology or biochemistry	Research conducted on non-humans
	Drugs comparing drug-eluting stents with bare metal stents	Case studies
		Studies carried out in a participants with a specific co-morbidity (e.g. diabetes)
		Studies with low subject numbers
		Studies not available to read
		Studies which do not compare Drug-eluting stents with bare metal stents directly

Table 2: Articles chosen for review

Article	Author	Title	Journal
1	K.W. Hansen , C. Kaiser , A.Hvelplund, R. Soerensen , J.K. Madsena, J.S. Jensen , S.H. Pedersen, F.R. Eberli , P. Erne, H. Alber, M. Pfisterer, S. Galatius	Improved two-year outcomes after drug-eluting versus bare-metal stent implantation in women and men with large coronary arteries: Importance of vessel size	International Journal of Cardiology, 2013. 169(1): p. 29-34.
2	Tomohisa Tada, MD, Robert A. Byrne, MB BCH, PHD, Iva Simunovic, MD, Lamin A. King, MS, **et al**	Risk of Stent Thrombosis Among Bare-Metal Stents, First-Generation Drug-Eluting Stents, and Second-Generation Drug-Eluting Stents	JACC: Cardiovascular Interventions, 2013. 6(12): p. 1267-1274
3	Lene Holmvang, MD, Henning Kelbæk, MD, Anne Kaltoft, MD, Leif Thuesen, MD **et al**	Long-Term Outcome After Drug-Eluting Versus Bare-Metal Stent Implantation in Patients With ST-Segment Elevation Myocardial Infarction	JACC. Cardiovascular Interventions, 2013. 6(6): p. 548-553

4	Paul C. Gordon, MD, David J. Cohen, MD, MSc, Neal S. Kleiman, MD, Jay A. Montgomery, MD, Christopher A. Semder, MD**, et al**	In-Hospital and One Year Outcomes with Drug-Eluting Versus Bare Metal Stents in Large Native Coronary Arteries: A Report From the Evaluation of Drug-Eluting Stents and Ischemic Events Registry	Catheterization and Cardiovascular Interventions, 2013. 82(4): p. E356-E364.
5	David E. Kandzari, MD,* Martin B. Leon, MD,† Ian Meredith, MBBS, BSC, PHD,‡ Jean Fajadet, MD,§ William Wijns, MD, PHD,_ Laura Mauri, MD, MSC	Final 5-Year Outcomes From the Endeavor Zotarolimus-Eluting Stent Clinical Trial Program Comparison of Safety and Efficacy With First-Generation Drug-Eluting and Bare-Metal Stents	JACC: Cardiovascular Interventions, 2013. 6(5): p. 504-512.
6	Ming-Jer Hsieh , Chun-Chi Chen , Shang-Hung Chang , Chao-Yung Wang , Cheng-Hung Lee , Fen-Chiung Lin , Chee-Jen Chang , I-Chang Hsieh	Long-term outcomes of drug-eluting stents versus bare-metal stents in large coronary arteries	International Journal of Cardiology, 2013. 168(4): p. 3785-3790.
7	Susumu Suzuki, MD; Hideki Ishii, MD, PhD; Kyoko Matsudaira, MD; Naoki Okumura, MD; Daiji Yoshikawa, MD; **et al**	Long-Term Outcome of Drug-Eluting vs. Bare-Metal Stents in Patients With Acute Myocardial Infarction	Circulation Journal: Official Journal Of The Japanese Circulation Society, 2013. 77(8): p. 2024-2031

Discussion:

Major Adverse Coronary Events (MACE):

This end point has been used in several of the studies chosen in the literature search. It includes Cardiacdeaths, MIs and the need for revascularisation procedures post-stenting. It has been used previously by the NICE guidelines for stenting to assess the clinical effectiveness of using stents[7]. With the direct link of this end point to the efficacy of the DES it forms a major part of the assessment of this type of stents in comparison with BMS.

In terms of cardiac deaths, the trial by Kandzari et al 2013 [8] showed a reduction in MIs between the second generation DES studied and BMS in the follow up throughout the study period but did not otherwise show a statistically significant difference in cardiac deaths. In terms of revascularisation, the second generation DES showed a significant reduction in these events.It appears that while the study showed a significant reduction in MACE, this seems to be driven mainly by the reduction in the revascularisation procedures as opposed to reductions in cardiac deaths. The long term outcome of the study did show a similar pattern but the results were not statistically significant. The study by Hansen et al (2013) [9] showed a similar pattern. There was a lower risk of MACE overall for the group between the group on DES stents and the group on BMS stents. This was due to a lower risk of non-fatal MIs in men on DES compared to men on BMS, and lower rate of revascularisation across both genders in the study.

The study by Gordon et al (2013) [10], has found no significant difference in MACE between the DES group and the BMS group. However, it did find that the use of DES has reduced the need for revascularisation when compared with BMS. These findings were similar to the findings in the studies by Hsieh et al (2013)[11] and Suzuki et al (2013)[12], where in the latter study, the author also found that the benefit from the DES, disappeared after 1 year post treatment.

The study by Holmvang et al (2013) also showed a significantly lower rate of revascularisation for the patients treated with a DES compared to the patients treated with a BMS like the studies above, with again a reduction in benefit after 1 year of treatment. However, the study also showed a significant increase in the number of cardiac deaths associated with DES in comparison with BMS. The author concluded that this difference is likely to be due to stent thrombosis mainly.

The studies used in this literature review have shown that the use of DES, rather than BMS reduce the rates of revascularisation post PCI. This drove the reduction in the rates of MACE in these studies. These studies have also demonstrated that this effect is possibly only significant in the early stages of treatment with benefits wearing off after the first year [12, 13]. However, the effects of DES on MIs and cardiac deaths are less clear, with only 2 of the studies researching MACE showing a reduction in non-fatal MIs but not cardiac deaths and one study in fact showing an increase in cardiac deaths. One can conclude that the studies have therefore not shown DES to have a benefit in terms of mortality. These findings match the findings of previous reviews, such as the review done by the Cochrane collaboration [14]. The review by the Cochrane collaboration found that DES can reduce the rates of revascularisation but show no benefit in terms of mortality or reduction of MIs.

There were several factors, which seemed to affect the outcomes, which should be considered. First of these is the use of second generation DES, where a benefit was shown by Kandzari et al (2013) [8] in comparison with first generation DES. This finding could be useful to show that if

DES are to produce maximum benefits, then second generation DES should be used. It also highlights that there is potential for better outcome with DES with newer development.

The second factor is the artery calibre. Some of the articles in this literature review have shown a decreased benefit for DES in larger blood vessels, where the rates of MACE become similar as the artery calibre increases [10, 11]. This has been suggested to be due to the greater benefit of DES in preventing vessel re-stenosis in smaller vessels; since it has been shown that smaller vessels have a higher risk of re-stenosis post PCI [15]. Possible mechanisms of this is the ability of large arteries to adapt to neointimal hyperplasia and re-stenosis, with a less chance of a haemo-dynamically significant compromise[9, 10]. Hsieh et al (2013)[11] has found an artery calibre of 3.75mm to be a cut off point for achieving benefit with DES. As mentioned in the introduction, NICE has already looked at this factor, and added artery calibre as a condition for the use of the DES[6]. The findings from this article certainly support this recommendation.

The third factor is the gender of the patient. The author of the study by Hansen et al (2013) [9] concluded that in women DES have more benefit compared to BMS. The author suggested that the reason for this pattern observed could be due to the difference in plaque characteristics in women compared with men. This observation could be important in deciding the role of DES in clinical practice, where DES could prove to have more of a role in women.

Incidence of Stent Thrombosis:

Stent thrombosis, which is one of the complications mentioned for DES, has been looked at by several of the articles found during the literature search conducted. The incidence of stent thrombosis should be a suitable reflection of the safety of DES in comparison with BMS.

Tada et al 2013 [16] looked at the risk of stent thrombosis by comparing first and second generation DES with BMS. The research found that the first generation stents did in fact increase the risk of late stent thrombosis compared with BMS. However, the article concluded that second generation DES have a better safety profile in this regard with a similar risk of stent thrombosis as BMS. The study by Kandzari et al (2013), also found similar findings.

Other studies found no differences in the rates of stent thrombosis between DES and BMS. This lack of a difference was reported by Gordon et al (2013) [10], Suzuki et al (2013) [12] and by Holmvang et al (2013) [13]. While the study by Holmvang et al (2013)[13] found that the rates of very late stent thromboses was low and there was no difference between the groups, the study reported that the incidents of sudden cardiac death associated with stent thromboses occurred more often in the group with DES.

The study by Hsieh et al (2013)[11] in addition to reporting equal risk of stent thrombosis with DES as with BMS, has also reported that the stent thrombosis that occurs with DES tends to occur later, while with BMS, the thrombosis tends to be more acute. This study has also speculated that the difference in dual anti-platelet therapy could be a reason for a factor in reducing the risk of stent thrombosis. This is significant as this is certainly a modifiable risk factor.

Considering that late stent thrombosis was a risk of DES, the studies seem to show that this risk is more apparent with first generation DES, and happens late in the treatment. Stent thrombosis lead to very serious consequences in the Holmvang et al (2013) [13] study, resulting in sudden cardiac deaths. In the long term, second generation DES have shown better safety profile compared to the first generation stents, with at least a safety profile similar to the bare metal stents.

Therefore, it can be concluded that while first generation stents have a safety risk, the second generation stents are safer, and with their use safety concerns could be dismissed if they offer a benefit. These findings are slightly different from the findings by the Cochrane collaboration review (2010)[14], which showed that there was no difference between DES and BMS in the rates of stent thrombosis. This could be due to the fact that the papers in this review which reported a difference ([8, 16]), were comparing the first generation DES with the second generation DES and the second generation DES did not actually show a difference in the rates of stent thrombosis.

Limitations of the Study:

There were various limitations in the study selection which could negatively affect any conclusion drawn from the study. The study only focused on 7 articles which were released since 2013, with a strict inclusion and exclusion criteria. This was done to ensure that only the very latest evidence is looked at in this review, therefore it was deemed preferable to pick a small selection of very recent articles and focus on reviewing them in detail.

For the 2 outcomes chosen in this review, there was only 6 articles looking at each. This was due to the fact that Hansen et al (2013)[9] did not look at the rates of stent thrombosis due to low occurrence of this outcome in that study and due to the Tada et al study (2013)[16] only looking at rates of stent thrombosis rather than efficacy of DES.

The Kandzari et al study (2013) [8] looked mainly at the effect of one type of second generation stent in comparison with both a BMS and first generation DES. This limited the usefulness of this study in the context of this review, since the aims of that study differed from the aims of this review. The study by Tada et al (2013) [16] also had a similar issue although it did compare first generation DES with BMS. Similarly the study by Hansen et al (2013)[9] focused heavily on the comparison between men and women, while the study by Hsieh et al (2013)[11] focused on artery size. The effects of this difference in aims could lead to a skewed conclusion regarding the safety and efficacy of DES in

comparison with BMS, since the effects were obtained indirectly from these studies. However, using these studies had an additional benefit of looking at the effects of differing generations, genders and artery sizes in the assessment of the efficacy and safety of DES, which helped to obtain further useful information about the role of DES in clinical practice.

Conclusion

DES seems to have equal efficacy to BMS in preventing MIs and cardiac deaths. They have shown however, a benefit in reducing the rates of revascularisations necessary.

In terms of safety, there is a less clear picture available but it is apparent that the first generation DES are at least not safer than BMS, while the second generation DES should have an equal safety profile as BMS.

There is a role for DES to play in order to reduce the revascularization rates in comparison with BMS. This has to be weighed carefully with the risk and cost, which is what NICE has been doing already [6]. With the advent of second generation stents, biodegradable stents and other newer DES [17], the benefit-risk profile of DES could improve which would allow more widespread use. Hence it is necessary to review newer DES again in the future.

Other aspects which could affect the performance of DES, such as gender and artery size should also be studied further and considered to provide a suitable role for DES in clinical practice. For the moment DES do not seem to be effective or safe enough to fully replace BMS.

References

1. Toklu, B. and S. Bangalore, Choosing the Right Coronary Stent in the Modern Era. Current Cardiology Reports, 2014. 16(4): p. 1-10.
2. Hill, R.A., et al., Drug-eluting stents: a systematic review and economic evaluation. Health Technology Assessment, 2007. 11(46): p. iii.
3. Htay, T. and M.W. Liu, Drug-eluting stent: a review and update. Vascular health and risk management, 2005. 1(4): p. 263-276.
4. Palmerini, T., et al., Stent thrombosis with drug-eluting stents: Is the paradigm shifting? Journal of the American College of Cardiology, 2013. 62(21): p. 1915-1921.
5. Simard, T., et al., The evolution of coronary stents: a brief review. The Canadian Journal Of Cardiology, 2014. 30(1): p. 35-45.
6. NICE, TA152 Coronary artery disease - drug-eluting stents: guidance. National Institute of Clinical Excellence Technology appraisal guidance, 2008 (152).
7. NICE, Guidance on the use of coronary artery stents. National Institute of Clinical Excellence Technology Appraisal Guidance 2003. 71.
8. Kandzari, D.E., et al., Final 5-year outcomes from the endeavor zotarolimus-eluting stent clinical trial program: Comparison of safety and efficacy with first-generation drug-eluting and bare-metal stents. JACC: Cardiovascular Interventions, 2013. 6(5): p. 504-512.
9. Hansen, K.W., et al., Improved two-year outcomes after drug-eluting versus bare-metal stent implantation in women and men with large coronary arteries: Importance of vessel size. International Journal of Cardiology, 2013. 169(1): p. 29-34.
10. Gordon, P.C., et al., In-hospital and one year outcomes with drug-eluting versus bare metal stents in large native coronary arteries: A report from the evaluation of drug-eluting stents and ischemic events registry. Catheterization and Cardiovascular Interventions, 2013. 82(4): p. E356-E364.
11. Hsieh, M.J., et al., Long-term outcomes of drug-eluting stents versus bare-metal stents in large coronary arteries. International Journal of Cardiology, 2013. 168(4): p. 3785-3790.
12. Suzuki, S., et al., Long-term outcome of drug-eluting vs. bare-metal stents in patients with acute myocardial infarction. Subgroup analysis of the nagoya acute myocardial infarction study (NAMIS). Circulation Journal: Official Journal Of The Japanese Circulation Society, 2013. 77(8): p. 2024-2031.
13. Holmvang, L., et al., Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 5 years follow-up from the randomized DEDICATION trial (Drug Elution and Distal Protection in Acute Myocardial Infarction). JACC. Cardiovascular Interventions, 2013. 6(6): p. 548-553.
14. Greenhalgh, J., et al., Drug-eluting stents versus bare metal stents for angina or acute coronary syndromes. Cochrane Database Of Systematic Reviews, 2010(5).
15. Elezi, S., et al., Vessel size and long-term outcome after coronary stent placement. Circulation, 1998. 98(18): p. 1875-1880.
16. Tada, T., et al., Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: Results from a registry of 18,334 patients. JACC: Cardiovascular Interventions, 2013. 6(12): p. 1267-1274.
17. Bangalore, S., et al., Bare metal stents, durable polymer drug eluting stents, and biodegradable polymer drug eluting stents for coronary artery disease: Mixed treatment comparison meta-analysis. BMJ (Online), 2013. 347.