PCI of complex coronary lesions, new stent technologies, and clinical outcomes
Beijk, M.A.M.

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A retrospective analysis of consecutive patients undergoing non-urgent percutaneous coronary intervention comparing bare metal stents with drug-eluting stents using the National Institute for Clinical Excellence criteria

Marcel A.M. Beijk, MD; Karel T. Koch, MD, PhD; Jan G.P. Tijssen, PhD; José P.S. Henriques, MD, PhD; Jan Baan, MD, PhD; Marije M. Vis, MD; Martin G. Meesterman, RN; Jan J. Piek, MD, PhD; Robbert J. de Winter, MD, PhD.

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Abstract

Objective: In the National Institute for Clinical Excellence (NICE) guidelines, lesions with a reference vessel diameter of <3.0mm or lesions with a length of >15mm are considered carrying a high risk of restenosis. In contrast, lesions with a reference vessel diameter of ≥3.0 mm or a lesion length of ≤15 are considered at low risk of restenosis. We performed a retrospective analysis of consecutive patients undergoing non-urgent percutaneous coronary intervention (PCI) comparing bare metal stent (BMS) with DES using the NICE guidelines.

Methods and results: Between 2003 and 2007, a total of 3883 patients underwent a non-urgent PCI for a de novo coronary lesion, 2050 patients were considered at low risk and 1833 patients were considered at high risk of restenosis according to the NICE criteria. In the low risk group, the 1 year composite of cardiac death, myocardial infarction (MI), and target vessel revascularization (TVR) was 10.5% in the BMS group and 11.1% in the DES group (p=0.85). Target lesion revascularization (TLR) was 5.3% by PCI and 1.6% by coronary artery bypass grafting (CABG) in the BMS group and 4.0% and 3.0% in the DES group (p=0.59 and p=0.24). In the high risk group, the composite of cardiac death, MI, and TVR was 12.1% in the BMS group and 11.0% in the DES group (p=0.48). TLR was 6.7% by PCI and 1.3% by CABG in the BMS group and 3.9% and 2.8% in the DES group (p=0.01; p=0.02). Definite stent thrombosis (ST) was 0.8% in the BMS-treated patients and 1.7% in the DES-treated patients (p=0.09).

Conclusion: In patients with lesions carrying a low risk of restenosis, no differences were observed between BMS and DES in composite end points, TLR, or ST at 1-year follow-up. In patients with lesions carrying a high risk of restenosis, patients treated with BMS had a significantly higher rate of TLR by PCI but a significantly lower rate of TLR by CABG compared to patients treated with DES. A non-significant lower rate of definite ST was observed in the BMS group compared to the DES group.
Introduction

Pivotal randomized trials comparing bare metal stent (BMS) with drug-eluting stent (DES) have shown a significant reduction in in-stent restenosis [1-3], and the use of DES has rapidly been extended to all types of patients and lesions with varying degrees of complexity. Hence, several registries have evaluated a liberal, unrestricted use of DES showing favourable outcomes as compared with historical BMS results [4-6]. However, initial enthusiasm has been hampered after ‘real-world’ data elicited safety concerns with respect to late and very late stent thrombosis (ST) in unselected patients after DES placement [7, 8]. The rate of ST is reported to be continuously of 0.4% to 0.6% per year after DES placement up to 4 years, a phenomenon that was not apparent after BMS placement [7, 9]. These concerns have resulted in a prolongation of the duration of dual antiplatelet therapy after DES placement and in a re-evaluation of studies comparing DES with BMS. In a large meta-analysis of randomized clinical trials, no difference was observed in mortality or the incidence of non-fatal myocardial infarction (MI) between DES and BMS up to 4 years [10].

In early observational studies, BMS showed good clinical outcome with respect to restenosis for lesions in large vessels and in short lesions [11-15]. Moreover, in randomized trials, the clinical benefits of DES may have been overestimated due to protocol-driven angiography and subsequent repeat PCI in BMS treated patients as compared to daily routine practice. Furthermore, an unrestricted implementation of DES requires long-term dual antiplatelet therapy in all patients, and might be less cost-effective, except in high-risk patients [16].

At present, the European Society of Cardiology (ESC) guidelines for percutaneous coronary intervention (PCI) [17] refer to the National Institute for Clinical Excellence (NICE) Institute [18] guidance that indicates that DES are recommended for patients with symptomatic coronary artery disease, in whom the target coronary artery is < 3 mm in diameter or the lesion length is > 15 mm. We have evaluated the 1 year clinical outcomes of BMS versus DES in a large consecutive patient population undergoing non-urgent PCI using the NICE criteria.

Methods

Source population

The data analyzed in our study were obtained from patients who underwent PCI for a de novo coronary artery lesion at the Academic Medical Center – University of Amsterdam between April 2003 and March 2007. Our institution is a high volume tertiary referral hospital with on-site cardiac surgery. All interventions were performed according to standard PCI guidelines. All patients received aspirin, a loading dose of clopidogrel and unfractionated heparin 5000 IU at the start of the procedure. The use of glycoprotein IIb/IIIa inhibitors and/or anti-thrombotic medications was at the discretion of the operator. Patients were
treated with aspirin 100 mg indefinitely and clopidogrel 75 mg daily for at least 1 month after BMS implantation and at least 6 month after DES implantation.

The paclitaxel-eluting stent (PES) TAXUS™ EXPRESS or Liberté (Boston Scientific, MA, USA), the Endeavor® zotarolimus-eluting stent (ZES) (Medtronic Vascular Inc., CA, USA), and the XIENCE V® everolimus-eluting stent (EES) (Abbott Laboratories, Abbott Park, IL, USA) were the types of DES used during the duration of this study. The final choice of stent and interventional strategy was at the discretion of the operator. Repeat coronary angiography was performed routinely after left main lesion stenting and bifurcation lesion stenting between 6 and 9 months or. In all other patients a repeat coronary angiography was performed when clinically indicated for recurrence of anginal symptoms or documented myocardial ischemia. Patients that were referred from other hospitals and that required repeat revascularisation procedures were referred back to our institution.

Data source

Baseline clinical, angiographic and procedural information were retrieved from our electronic PCI database. One-year clinical follow-up was obtained by means of a paper survey filled out by the patient or by telephone contact. When no contact could be established, telephone contact with the patients’ relative, general practitioner, or referral cardiologist was used to complete follow-up. When a patient was lost to follow-up, the Statistics Netherlands-Health and Welfare registry (CBS) was consulted for information on patient’s vital status. When a major cardiac event was reported, review of hospital records, chart review, telephone contact with the referring cardiologists and/or the patient’s general practitioner were used to complete the information.

Patient population

We included all patients treated for a de novo coronary artery lesion between April 2003 and March 2007. Patients treated for unstable angina pectoris / acute coronary syndrome were also included. Patients undergoing a primary PCI for an acute ST-segment elevation myocardial infarction (STEMI) were excluded. Patients treated for a venous graft lesion or a (in-stent-) restenosis were also excluded. When patients had multiple procedures, we included the first procedure satisfying the inclusion criteria. A total of 3883 patients met the inclusion criteria (Figure 1). Patients were classified according to the type of stent received. Patients who only received BMS were assigned to the BMS group and patients who received at least one DES were assigned to the DES group.

NICE guidelines

The National Institute for Clinical Excellence (NICE) guidelines [18] on the use of coronary artery stents recommends the use of DES when a lesion has a reference diameter of <3.0mm or the lesion has a length of >15mm as these lesions are considered to carry a higher risk of restenosis. In contrast, a lesion with a reference diameter of ≥3.0 mm or a lesion length of ≤15 can be treated with a BMS as these lesions are considered at low risk of restenosis.
These criteria do not apply to patients treated for a STEMI or to patients in whom there is angiographic evidence of thrombus in the target artery. In this manuscript, the NICE guidelines were used to evaluate the 1 year clinical outcomes in patients with lesions carrying a low risk versus a high risk of restenosis, determined at the index procedure, treated with a BMS or DES.

**End points and end point definitions**

The primary end point was the composite of cardiac death, MI, and target vessel revascularisation (TVR). All deaths were considered cardiac death unless otherwise documented. MI was defined as any rise in the creatine kinase-MB (CK-MB) level or troponin T level above upper limit of normal. Peri-procedural MI was defined as a rise in the CK-MB level or troponin T level of more than 3 times upper limit of normal. TVR was defined as any repeat revascularization of a target vessel by repeat percutaneous intervention or coronary artery bypass grafting (CABG). Target lesion revascularisation (TLR) was defined as any
percutaneous or surgical revascularisation of the target lesion to treat restenosis within the stent or 5 mm distal or proximal margins adjacent to the stent. ST and end points definitions used are in accordance with the Academic Research Consortium (ARC) [19].

Statistical analysis
Continuous variables with normal distribution were presented as mean ± standard deviation (SD). Categorical variables were presented as counts (percentages). Cumulative event rates were presented in Kaplan-Meier curves.

Results

Baseline and lesion characteristics
The study population consisted of 3883 patients, 2050 patients (52.8%) were considered at low risk and 1833 patients (47.2%) were considered at high risk of restenosis. Baseline clinical characteristics are shown in table 1 for all patients, patients with lesions considered carrying a low risk per stent type, and with lesions carrying a high risk. Of all DES-treated patients, 159 patients (19%) also received one or more BMS. Lesion characteristics are shown in table 2. In DES-treated patients, stent length was longer and the diameter was smaller than the BMS-treated patients.

Cardiac death, myocardial infarction and target vessel revascularization
Clinical events at 1-year follow-up are listed in table 3. In the overall group, the rate of the composite end point of cardiac death, MI, and TVR was 11.0%. TLR by PCI was 5.4% and TVR (by either PCI or CABG) was 8.6% in the overall group. When utilizing the NICE guidelines, in patients with lesions considered carrying a low risk of restenosis the composite of cardiac death, MI, and TVR was 10.5% in the BMS group versus 11.1% in the DES group (p=0.85). No significant differences were observed between BMS or DES in clinical end points except for TVR/non-TLR which was significantly higher in the DES treated patients.

In patients with lesions considered carrying a high risk of restenosis, the composite of cardiac death, MI and TVR was 12.1% in the BMS group versus 11.0% in the DES group (p=0.48). No differences were observed between BMS and DES in cardiac death and MI. BMS-treated patients had a significantly higher TLR rate by PCI compared to DES-treated patient, 6.7% versus 3.9% (p=0.01). In contrast, in the BMS group fewer CABG were performed compared to the DES group, 1.3% versus 2.8% (p=0.02). A non-significant lower rate of definite ST was observed in the BMS group compared to the DES group, 0.8% versus 1.7% (p=0.09).

Kaplan-Meier survival curves for the composite of cardiac death, MI and TVR; and cumulative TVR for patients with lesions carrying a low risk of restenosis and for patient with lesions carrying a high risk of restenosis are presented in figures 2 till 5.
Discussion

In this single-center study, the 1 year clinical outcome was evaluated in a large cohort of consecutive patients undergoing non-urgent PCI comparing BMS-treated patients to DES-treated patients using the NICE criteria. The primary finding of our study was that in patients with lesions carrying a low risk of restenosis, no differences were observed between BMS and DES in composite end points, TLR, or ST. In patients with lesions carrying a high risk of restenosis, patients treated with BMS had a significantly higher rate of TLR by PCI.
but a significantly lower rate of TLR by CABG as compared to patients treated with DES. A non-significant lower rate of definite ST was observed in the BMS group compared to the DES group.

On a daily basis, the interventional cardiologist is confronted with clinical decision making on which patient / lesion to select to treat with DES or BMS taking into account the long-term safety and efficacy. The recently published Ontario registry [20] provides evidence which patients can be treated safely with BMS without a substantial increase in the TVR rate. This registry evaluated a well-balanced large patient cohort, matched on the basis of propensity score, who received either BMS or DES. DES were effective in reducing the need for TVR in patients at the highest risk for restenosis (i.e. those who had two or three risk factors - presence of diabetes, small vessels, and long lesions), without significantly increasing the rate of death or MI. In contrast, non-significant small reductions were found in the rates of TVR among patients at low or intermediate risk for restenosis (i.e. those without diabetes and with large vessels or short lesions) between BMS and DES. Our study adds evidence to the findings from the Ontario registry. We show that using a BMS in lesions carrying a low risk of restenosis does not lead to a substantial increase in TLR. In lesions carrying a high risk of restenosis, DES is more beneficial than BMS in preventing restenosis.

### Table 2 Lesion characteristics of the overall population and subgroups

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 3883)</td>
<td>(N = 1951)</td>
<td>(N = 1112)</td>
</tr>
<tr>
<td></td>
<td>L = 5270</td>
<td>L = 2319</td>
<td>L = 1643</td>
</tr>
<tr>
<td></td>
<td>(N = 99)</td>
<td>L = 119</td>
<td>L = 1189</td>
</tr>
<tr>
<td>Treated vessel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>1636 31</td>
<td>647 28</td>
<td>39 33</td>
</tr>
<tr>
<td>Left main coronary artery</td>
<td>123 2.3</td>
<td>84 3.6</td>
<td>4 3.4</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>2135 41</td>
<td>954 41</td>
<td>46 39</td>
</tr>
<tr>
<td>Left circumflex artery</td>
<td>1376 26</td>
<td>634 27</td>
<td>30 25</td>
</tr>
<tr>
<td>Type of lesion*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>379 7.2</td>
<td>257 11.1</td>
<td>9 7.6</td>
</tr>
<tr>
<td>B1</td>
<td>1479 28</td>
<td>838 36</td>
<td>39 33</td>
</tr>
<tr>
<td>B2</td>
<td>2190 42</td>
<td>941 41</td>
<td>40 34</td>
</tr>
<tr>
<td>C</td>
<td>1222 23</td>
<td>283 12</td>
<td>31 26</td>
</tr>
<tr>
<td>Chronic total occlusion</td>
<td>736 14</td>
<td>160 7</td>
<td>29 24</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>666 13</td>
<td>290 13</td>
<td>10 8</td>
</tr>
<tr>
<td>Calcified lesion</td>
<td>1882 36</td>
<td>687 30</td>
<td>49 41</td>
</tr>
<tr>
<td>Stent diameter, (mm)</td>
<td>3.2 ±0.4</td>
<td>3.3±0.3</td>
<td>3.2±0.3</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>19.6±8.8</td>
<td>15.1±4.4</td>
<td>20.9±9.2</td>
</tr>
</tbody>
</table>

Values are L (%) or mean±SD. L number of lesions *According to ACC-AHA classification.

BMS bare metal stent, DES drug-eluting stent.
Whether the benefit of DES in reducing TVR is outweighed by the risk of late ST was evaluated by Garg et al. [21] using an analytic Markov model. DES was compared with BMS strategies in a contemporary United States PCI population using procedure-related morbidity and mortality data from several published reports. They identified the net benefit of DES versus BMS in terms of quality-adjusted life expectancy and concluded that an increase of more than 0.14%/year incremental risk of ST in DES might be sufficient to outweigh the benefit of preventing restenosis and favour BMS use for the overall PCI popu-
Our results support the data from Garg et al. that it might be appropriate to use a rational approach for the use of DES and to perform an estimation of the risk of restenosis in patients treated electively. The current NICE guidelines, as referred to by the ESC guidelines for PCI, provide a limited but reasonable recommendation which patients could be treated with BMS. Although not stated in the NICE criteria, other high risk lesions, i.e., chronic total occlusion, all lesions in a diabetic patient, should preferably be treated with DES as several studies have shown DES being superior compared to BMS [22, 23].

Figure 4 Kaplan-Meier TVR for patients with a high-risk according to the NICE guidelines

Figure 5 Kaplan-Meier cumulative incidence of cardiac death, MI, TVR for patients with a high-risk according to the NICE guidelines
ST is a serious clinical event that in approximately 70% of patients leads to a MI and short-term mortality has ranged from 15% to 45% [24-26]. In particular, the incidence of late ST with DES is source of concerns with respect to the long-term safety [7, 8, 24, 26-30]. The Rotterdam-Bern cohort study [7, 31] evaluated the occurrence of angiographic documented ST in a large population using 100% DES strategy. At 1 year the cumulative incidence of ST was 1.7% with late ST occurring at a constant rate of 0.4% to 0.6% per year between 1 and 4 years. In our study, definite ST occurred in 0.7% in the overall population. In patients with lesions carrying a low risk of restenosis ST rates were very low at 1 year in both the BMS group and the DES group. In patients with lesions carrying a high risk a non-significant difference was observed in the rate of ST, 0.8% in the BMS group and 1.7% in...
the DES. The risk of ST can be reduced with the use of dual anti-platelet therapy, however, the optimal duration of dual antiplatelet therapy after DES placement is yet unknown. In addition, there is an associated small risk of bleeding when using dual antiplatelet therapy [21, 30, 32]. Use of the NICE guidelines on the use of coronary artery stents may avoid the risk of very late stent thrombosis and the need for long-term dual antiplatelet therapy that is associated with DES in a substantial number of the patients treated with coronary stents.

A potential limitation of this study was the single-center design in a tertiary referral center. Moreover, the DES group was mainly treated with a first generation PES, second generation DES might further improve outcomes in lesions with a high risk of restenosis. Furthermore, we did not record the duration of dual anti-platelet therapy prescribed by the referring cardiologists after DES placement although it was recommended for at least 6 months. Finally, this registry only provides 1-year follow-up and long-term follow-up needs to be collected to determine the risk of late ST.

Conclusion

This study demonstrates that in patients with lesions carrying a low risk of restenosis, no differences were observed between BMS and DES in the 1 year clinical outcomes. In patients with lesions carrying a high risk of restenosis, patients treated with BMS had a significantly higher rate of TLR by PCI but a significantly lower rate of TLR by CABG as compared to patients treated with DES. A non-significant lower rate of definite ST was observed in the BMS group compared to the DES group.
References


