Drug-eluting stents: NICE guidelines and the reality

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Abstract

The National Institute for Clinical Excellence (NICE) stent appraisal (2003) defined criteria for the use of drug-eluting stents (DES) on the basis of lesion length, vessel diameter and the absence of recent myocardial infarction or intra-luminal thrombus. The appraisal suggested that as many as one third of all stents may need to be DES.

In order to determine the requirement for DES and adherence to these guidelines, we assessed 1,673 consecutive patients undergoing coronary intervention over a 17-month period. A total of 2,513 stents were implanted, of which 50.1% were DES. In all, 77.4% of patients fulfilled NICE criteria for at least one DES. A further 7.3% of patients were excluded because of either a recent (< 24 hours) myocardial infarct or visible intra-luminal thrombus. A total of 33.4% of patients who did fulfil NICE criteria for DES deployment inappropriately received a bare-metal stent (BMS) whilst 5.7% patients inappropriately received a DES. These results would suggest that NICE have grossly underestimated the need for DES in 'real world' practice. Despite our centre using a high volume of DES, significant numbers of patients were inappropriately treated with BMS, with a smaller number inappropriately treated with DES, according to NICE criteria.

Key words: drug-eluting stents, NICE guidelines, compliance.

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Introduction

The main limitation of percutaneous coronary intervention (PCI) is the risk of target vessel restenosis and thus the need for further intervention. The use of bare-metal stents (BMS) significantly reduces restenosis rates compared with balloon angioplasty alone but rates of re-intervention still remain unacceptably high, especially in patients with complex disease.[1,2] Drug-eluting stents (DES) significantly reduce the risk of restenosis even further.[3-6] The comparative reduction is greatest when treating complex lesions, where the risks of restenosis are highest.[7,8] Both types of DES commercially available, the sirolimus-eluting stent (Cypher®) and the paclitaxel-eluting stent (Taxus®), have equally impressive results compared with BMS. The major limitation of the DES is the current cost, on average € 1,000 more per stent than a standard BMS.

The National Institute for Clinical Excellence (NICE) published its Technology Appraisal on the use of coronary artery stents in October 2003[9] in order to try to clarify which patients should receive a DES. They recommended that the decision to use either a BMS or a DES should be based solely on the anatomy of the target vessel being stented. To this end, DES were recommended for symptomatic patients in whom either the target artery was smaller than 3.0 mm in calibre (internal diameter) or the length of the lesion was greater than 15 mm. Patients were excluded if they had a history of an acute myocardial infarct (MI) within the preceding 24 hours, or angiographic evidence of thrombus within the target artery. In these patients NICE recommended the insertion of a BMS. Finally, NICE estimated that the need for DES could potentially be as high as a third of all stents in clinical practice.

The aim of this study was to identify the proportion of patients undergoing PCI in a tertiary referral centre who according to NICE criteria, should receive a DES; and, as a result, to determine whether NICE had underestimated the potential requirement for DES in 'real-world' cardiology. In addition, we wanted to calculate our own compliance with the current guidelines.

Methods

The study was a retrospective analysis of the records of 1,673 consecutive patients who underwent PCI at our centre over a 17-month period between April 2002 (when DES first became commercially available in the UK) and September 2003.

From these records, patients with either a recent MI (less than 24 hours) or angiographic evidence of thrombus within the target artery were only deemed compliant with NICE guidelines if they received a BMS.

Patients were identified as fulfilling NICE angiographic criteria for a DES (target vessel < 3.0 mm or lesion length > 15 mm) if they received either a stent $\leq$ 3.0 mm or $\geq$18 mm in length.

The rationale behind selecting these dimensions is as follows. First, optimal stent deployment is achieved using a ratio of 1.1:1

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Table 1. Numbers of patients with lesions fulfilling NICE criteria for DES

Criteria	< 3.0 mm diameter + 15 mm length	< 3.0 mm diameter	> 15 mm length
Total number of patients (n)	582	582	131
Received DES (n)	442	238	57
Received BMS (n)	140	344	74
NICE compliant (n)	76	41	44

Key: DES = drug-eluting stent; BMS = bare-metal stent; NICE = National Institute for Clinical Excellence

Table 2. Numbers of patients with lesions fulfilling NICE criteria for BMS

Criteria	> 3.0 mm diameter + < 15 mm length	Acute MI or thrombus
Total number of patients (n)	256	122
Received DES (n)	52	44
Received BMS (n)	204	78
NICE compliant (n)	80	64

Key: DES = drug-eluting stent; BMS = bare-metal stent; MI = myocardial infarction; NICE = National Institute for Clinical Excellence

(diameter of expanded stent to diameter of target vessel lumen): for example, a 3.0 mm stent would be implanted in a target vessel with a reference diameter of less than 3.0 mm, the NICE reference diameter for implantation of a DES. Secondly, stent length should be slightly longer than lesion length in order to ensure complete coverage of the lesion, thus reducing the chance of an 'edge effect' leaving the edges of the lesion exposed and predisposing to restenosis. A lesion measuring greater than 15 mm (the length of lesion used by NICE for a DES) therefore requires a stent with a corresponding length of at least 18 mm because a 16 mm stent would not cover this lesion adequately.

Quantitative coronary arteriography (QCA) was carried out on a sample size of 100 consecutive lesions, measuring both lesion length and internal vessel luminal diameter just proximal to the lesion. These measurements were then compared to the diameter and the length of the stents implanted using the Bland and Altman method.

The results of the QCA confirmed the accuracy of these assumptions: mean luminal diameter was found to be 0.14 mm less than stent diameter (Spearman's coefficient of rank correlation r=0.89, 95% confidence intervals (CI) 0.84 to 0.92) and mean lesion length was found to be 1.3 mm less than stent length (Spearman's coefficient of rank correlation r=0.89, 95% CI 0.84 to 0.92).

Results

Patient demographics

The study group consisted of 1,673 patients with a mean age of 63.3 (range 22.9–89.6) years; 1,238 patients were male (74%) and 210 were medically treated diabetics (12.6%). A glycoprotein IIb/IIIa inhibitor (abciximab) was given as adjunctive therapy in 1,018 patients (60.9%). A total of 157 patients (9.4%) had either sustained a recent (< 24 hours) MI or had visible intraluminal thrombus. Fifty-two patients (3.1%) had intervention to saphenous vein grafts. A total of 2,513 stents were implanted (average 1.5 stents per patient) into 2,462 lesions involving 2,044 vessels. In all, 50.1% of the stents used were DES, and they were implanted into 830 patients (49.6% of patients).

Applying NICE guidelines

Overall, 77.4% (1,295/1,673) of patients undergoing PCI were eligible for at least one DES, with only 22.6% fulfilling NICE criteria for a BMS alone.

An additional 122 patients (7.3%) fulfilled NICE criteria for DES with regard to target vessel anatomy but were excluded because of either a recent MI or the presence of thrombus. Thus, a total of 84.6% (1,417/1,673) of our case-mix angiographically fulfilled NICE criteria for a DES by virtue of being a small vessel (74.9%), a long lesion (48.1%) or both (38.3%).

Compliance with NICE guidelines

Overall, NICE compliance was 60.9% (1,019/1,673 patients). A total of 737 patients (44.1%) appropriately received a DES, giving a compliance rate of 57% with NICE guidelines (table 1). A total of 558 patients (33.4%) were incorrectly given a BMS despite fulfilling NICE criteria for DES. Some 282 patients (16.9%) appropriately received a BMS, a compliance rate of 75% with NICE guidelines (table 2), whereas a total of 96 patients (5.7%) received a DES inappropriately.

Where the lesion satisfied the guidelines in being both small (< 3.0 mm) and long (> 15 mm) and therefore at the highest risk of restenosis, the compliance rate was 76% (442/582). This figure fell if the lesion only fulfilled one of the NICE criteria: it was 41% (238/582) and 44% (57/131) for small vessels and long lesions, respectively.

Where the anatomy of the target artery did not fulfil NICE criteria for a DES, a BMS was appropriately inserted in 80% (204/256) of patients.

When the anatomy did fulfil NICE criteria but the patient had either a recent MI or angiographic evidence of thrombus, compliance fell to 64% (78/122).

Discussion

Compliance with NICE

In comparison with other centres in the UK, we had a high DES implant rate at the time the data were collected: 1,259/2,513 of the total number of stents used were drug-eluting (50.1%). This ensured that the overall compliance with NICE guidelines was reasonably high, at 61% of (1,019/1,673) patients. Our current rate of DES implantation is approximately 90%. This steep increase in the use of DES is the reason why NICE compliance improved over the 17-month-period – it was 33% over the first

nine months compared with 80% over the subsequent eight months. Yet this improvement was at the expense of compliance with BMS insertion, which fell from 96% to 64% over the same period.

Not all patients who fulfil NICE criteria for a DES can actually receive one. Lesions longer than 15 mm that exist in either large arteries or saphenous vein grafts where the reference vessel diameter is $\geq$ 4.0 mm are not able to receive a DES because there are no DES of this diameter (maximum lumen diameter 3.75 mm) commercially available. This applied to 34 patients (2.0%) in this study, in whom there was no choice but to insert a BMS despite fulfilling NICE criteria for a DES (lesion length), and therefore these patients were listed as having inappropriately received a BMS. In reality, the risks of restenosis in this patient subgroup are unlikely to justify the use of a DES. This factor means that BMS were inappropriately inserted in 31.4% of our patients.

NICE guidelines

The risk of restenosis following PCI relates directly to the size of the vessel and the lesion length treated: the smaller the vessel and the longer the lesion, then the higher the risk. The use of a DES rather than a conventional BMS based on target vessel anatomy alone has been shown to reduce significantly the incidence of in-stent restenosis and therefore the need for repeat target vessel revascularisation.[7,8]

NICE has recognised this benefit and used it as the basis for its recommendations suggesting that where the vessel is either of small calibre (< 3 mm) or where the lesion is long (> 15 mm), a DES should be used. Using these figures NICE estimated that a third of all cases would fulfil the criteria for a DES. This appears to have been a serious underestimation of 'real world' clinical practice since more than three quarters (77.4%) of our study population were eligible for at least one DES.

It may be that our case-mix is somewhat biased towards the more complex cases as only 15.4% of our population fulfilled the angiographic NICE criteria for a BMS alone, nevertheless, these figures are similar to 'real world' data held in both the RESEARCH and WISDOM registries.[10,11] These registries keep records of sirolimus-eluting and paclitaxel-eluting stents, respectively, and confirm the prevalence of multivessel disease within the clinical spectrum.

NICE recommends the use of a BMS in the setting of an acute MI (< 24 hours) or angiographic evidence of thrombus because of a theoretical increase in the risk of acute stent thrombosis, although this risk was not confirmed in the RESEARCH registry.[10] In fact, recent evidence suggests that not only is the use of DES safe in primary angioplasty but also that it significantly reduces the need for repeat intervention.[12] In our study, 122 patients (7.3%) fulfilled NICE criteria for a DES on anatomical grounds but had either a recent MI, angiographic evidence of thrombus, or both. Of these 122 patients, 44 (2.6% of total) inappropriately received a DES, yet none had acute stent thrombosis within the first 90 days post-procedure.

Not all risk of restenosis can be attributable to target vessel dimensions alone. For example, bifurcation lesions are regarded as complex and they have higher rates of restenosis. The SIRIUS bifurcation study looked at this issue and their results at six-month follow-up compared favourably to historical controls.[13,14] As yet, there have been no direct randomised trials comparing DES and BMS in bifurcation lesions.

Diabetes *per se* has also been shown to be a predictor for restenosis independent of vessel size and lesion length. The use of a DES rather than a BMS not only significantly reduces the need for repeat target vessel revascularisation but also reduces major adverse cardiac event rates.[15]

With the numbers of PCI and stent insertions rapidly increasing in the UK, patients are presenting more often with in-stent restenosis (ISR). In the majority of these patients the primary treatment strategy has been simple balloon angioplasty alone, although use of DES has now been shown to be safe[16,17] and also to reduce target vessel revascularisation.[18] This last indication is currently not included in the NICE recommendations for the use of DES.

NICE is due to review its appraisal for coronary artery stents in March 2006. The justification for recommending the use of a DES in the setting of a small vessel or a long lesion is supported by robust evidence from randomised trials. There are already sufficient published data to support the use of a DES in other patients deemed at 'high risk' for restenosis, including those with bifurcation lesions, diabetics and those with in-stent restenosis. Early evidence would also appear to support their use in the setting of primary angioplasty if indicated by target vessel anatomy. Although cost considerations will continue to limit the use of DES, initial assessments of cost-effectiveness appear favourable, with the reduction in need for repeat revascularisation helping to offset the higher initial cost of the device.[19,20]

Study limitations

This was a retrospective audit and therefore the data collected are likely to be less accurate than in a prospective study. An element of error may have been introduced by using assumptions with respect to target lesion characteristics: a 3.0 mm stent was taken to be used in a vessel with an internal lumen of < 3.0 mm, and a stent with the length of $\geq$ 18 mm was taken to be required to cover a lesion length of > 15 mm. These assumptions are logical and reflect everyday hospital practice. They also appeared to be valid in a subset of 100 consecutive patients assessed by quantitative coronary arteriography.

Conclusions

This study suggests that NICE appears to have significantly underestimated the requirement for the use of DES in the 'real world' of clinical practice, with three-quarters of our population (not the one third estimated by NICE) eligible for at least one DES using the NICE criteria. Despite our aggressive policy toward the use of DES, a third of our patients received a BMS inappropriately in spite of fulfilling NICE criteria for a DES, whilst only 6% of our patients received a DES when they should have been given a BMS.

Key messages

- NICE recommended use of a drug-eluting stent (DES) in symptomatic patients with a target artery smaller than 3.0 mm in calibre or a lesion longer than 15 mm
- NICE estimated that as many as one third of stents should be drug-eluting, using these criteria
- This study suggests that NICE grossly underestimates the need for DES in 'real-world' practice
- More than three quarters of this study population were eligible for at least one DES
- Use of a DES may be supported in patients deemed at high risk for restenosis and in primary angioplasty

Formal audit on an individual patient basis is required if DES are to be used appropriately.

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Conflict of interest

KD is a Consultant to Boston Scientific Corporation. TW – no conflict of interest declared.

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Keith Dawkins is Principal Investigator of the TAXUS VI study.

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