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Another View of Personalized Medicine: Optimizing Stent Selection on the Basis of Predicted Benefit in Percutaneous Coronary Intervention

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Abstract

Drug-eluting stents (DES) decrease the risk of restenosis compared to bare metal stents (BMS) for percutaneous coronary intervention (PCI). However, their use requires patients to take prolonged dual antiplatelet therapy which increases bleeding risk, and without which, patients have an increased risk of developing stent thrombosis. In light of these competing risks, understanding which patients derive the greatest benefit of DES compared to BMS is essential for guiding therapy. We review recent efforts to predict the magnitude of the restenosis benefit of DES compared to BMS for individual patients. Understanding and predicting the likelihood of benefit for individual patients is essential to rational decision-making with regard to the type of stent to use during PCI and will serve to increase the value of the healthcare clinicians deliver.

Introduction

Personalized, or precision, medicine is a concept that is often referred to in regard to genetics or molecular diagnostics and therapies. In a recent *New England Journal of Medicine* perspective, personalized medicine was defined as “coupling established clinical-pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies tailored to each patient’s specific requirements.” (Mirnezami et al. 2012) While the concept usually refers to the clinical use of molecular or genetic information merged with routine clinical metrics, it need not. Instead, the concept can be more broadly applied and can refer to delivering care in the most effective and efficient way possible for every individual in each unique clinical situation.

When caring for patients undergoing percutaneous coronary intervention (PCI), clinicians must make a series of choices that impact patient care. Making the right choice, at the right time, for the right patient, should be a goal of all of those in the cardiovascular community. This review will focus on the ability of clinicians to predict the potential benefits of drug-

eluting stents (DES) compared to bare metal stents (BMS) during PCI, as well as the downstream implications of this clinical decision.

The Clinical Problem

The goal of PCI is to establish arterial patency within the coronary tree at the site of a flow limiting stenosis. After PCI, there are several important possible complications, including restenosis and stent thrombosis, that factor into the decision to use DES compared to BMS (Figure 1).

The clinical presentation of these entities is usually markedly different. Restenosis, caused by arterial damage with subsequent remodeling and neointimal proliferation, most commonly presents in a gradual manner. (Kuntz and Baim 1993) Angina is the most frequent manifestation, and myocardial infarction is not the norm. (Bossi et al. 2000; Chen et al. 2006) In general, restenosis is considered relatively benign compared to stent thrombosis. (Dangas et al. 2010) With stent thrombosis there is acute loss of vessel patency. Thus, its clinical manifestations are often catastrophic and have high associated mortality, estimated between 20% to 40%, and high rates of myocardial infarction. (Holmes et al. 2010) In an attempt to prevent this rare but important complication, patients treated with DES are recommended to be treated with a prolonged course of dual antiplatelet therapy (DAPT), entailing treatment with aspirin in combination with a thienopyridine or ticagrelor. (Levine et al. 2011) In contrast, stable patients treated with BMS require a minimum of only 1 month of DAPT.

The Benefits of DES compared to BMS

For patients undergoing PCI, the use of DES significantly reduces the rate of restenosis of the target vessel compared with the use of BMS. (Tu et al. 2007; Marroquin et al. 2008; Kirtane et al. 2009; Greenhalgh et al. 2010) Decreased rates of restenosis, measured in clinical studies by measuring rates of target vessel (or target lesion) revascularization (TVR), have been noted in both clinical trials (Cheng et al. 2007; Greenhalgh et al. 2010) and in routine community use. (Tu et al. 2007; Kirtane et al. 2009)

A number of factors have been identified as predictors of restenosis and TVR after PCI. These include factors related to patient clinical characteristics (age, female sex, diabetes mellitus, multi-vessel coronary artery disease), factors related to the coronary lesion (the length and diameter of the lesion, previous in-stent restenosis, the presence of a lesion in a bypass graft, a chronic total occlusion, small vessels, calcified lesions, ostial lesions, left anterior descending artery lesions, and high shear stress), and procedural characteristics (treatment of multiple lesions at once, the type of DES used, and the final diameter stenosis). (Cutlip et al. 2002; Gibson et al. 2002; Thury et al. 2002; Zahn et al. 2005; Kastrati et al. 2006; Stone et al. 2010; Zahn et al. 2010) There are a number of limitations in using these characteristics in predicting TVR in routine clinical practice, however. Some were derived from restricted clinical trial patient populations, some can only be determined after the stent has already been deployed (and thus, cannot be used to guide stent selection prospectively), and some are not typically or easily assessed in routine clinical care. Many of these risk

factors were elucidated in the era when only BMS were available, but remain relevant to the DES era.(Cutlip et al. 2002; Curfman et al. 2007)

There have been attempts to identify simple selection criteria for the use of DES instead of BMS by determining which patients are at highest risk for TVR, and thus most likely to benefit from DES, after PCI. In a community sample of patient treated with DES or BMS in Ontario, Canada, Tu and colleagues suggested that DES were associated with reduced rates of TVR compared with BMS in patients with at least 2 of 3 simple risk factors for restenosis, but not among patients who did not have at least 2 of these factors.(Tu et al. 2007) The risk factors of interest were diabetes, vessel diameter ≥ 3 mm, and lesions length ≥ 20 mm. This finding has been supported in the clinical trial setting. In a subgroup analysis of the HORIZONS-AMI trial of patients presenting with ST-segment elevation myocardial infarction, investigators confirmed that insulin-treated diabetes mellitus, vessel diameter ≥ 3 mm in diameter, and lesion length ≥ 20 mm were independent predictors of target lesion revascularization.(Stone et al. 2010) They reported that in patients treated with either BMS or DES without any of these three risk factors, rates of TVR were low in both groups (3.3% versus 3.2%), but that in patients with at least two of these three risk factors, the rates of 12-month TVR were 19.8% in patients treated with BMS compared to 8.1% in those treated with DES ($p=0.003$).

Individualized Modeling

Recent work by our group better quantifies the expected benefit of DES compared to BMS with regard to restenosis and TVR.(Yeh et al. 2011) We developed and validated a model of TVR in a diverse, community-based sample of individuals undergoing PCI across Massachusetts over a period of 4 years, from October, 2004 to September, 2007. We used commonly collected clinical variables that are all routinely ascertained as part of the American College of Cardiology's National Cardiovascular Data Registry (NCDR) and that are available before PCI is attempted.

Of the 27,107 PCI admissions examined, 21,933 (80.9%) underwent PCI with DES and 5,174 (19.1%) underwent PCI with BMS. By one year after the initial PCI, 7.6% of patients had TVR (6.7% of DES patients and 11.0% of BMS patients). We generated models predicting TVR using simple demographic and clinical information only. We then added angiographic variables to these simple models, which significantly improved model discrimination ($p<0.001$). As is demonstrated in Figure 2, models were able to accurately predict the rates of TVR and segregate patients into different risk groups. Both discrimination and calibration were demonstrated by examining an independent sample of the data.

Within the non-angiographic model, DES was associated with a significant decrease in one-year TVR compared to BMS (odd ratio 0.57; 95% confidence interval, 0.52–0.64). Our final models, including those without angiographic variables, were considerably more complicated than the three-variable model previously described (Table 1). However, in comparison to the simplified model that included only diabetes, stent diameter and stent length, the full models had significantly better discrimination ($p<0.001$). To facilitate

clinical use of this model, we created an open-access online tool to help clinicians predict the risk of TVR in their patients prior to PCI (available at http://www.massdac.org/riskcalc_revasc).

Most interesting for clinical practice, the distribution of predicted rates of TVR varied broadly across the range of individuals with different patterns of clinical and angiographic risk factors, varying from 2.7% to 57.4% at 1 year. These values correspond to absolute TVR reductions associated with DES use ranging from 1.2% (95% confidence interval 0.9% to 1.6%) to 15.9% (95% confidence interval from 13.0% to 18.4%). Thus, the number needed to treat (NNT) with DES, compared with BMS, to prevent 1 TVR outcome varies from 6 patients in those at high risk of TVR to 80 patients in those at low risk of TVR, depending on the individual being treated (See Figure 3). This tremendous clinical variability demonstrates the need for rational decisions regarding DES use depending on the individual likelihood of preventing TVR.

The Clinical Costs of DES compared to BMS

The wide range of benefit associated with DES make the consideration of their potential clinical and economic costs paramount. The primary issue is that DES inhibit re-endothelialization such that patients are at greater risk for stent thrombosis if not treated with sufficient antithrombotic therapy. Due to the rare nature of this outcome and the possible differences in the stent thrombosis rates between different DES platforms, quantifying this exact risk is difficult.(Holmes et al. 2010) However, because stent thrombosis is associated with high rates of death or myocardial infarction, preventive strategies have assumed central importance. The most important strategy now employed is prolonged DAPT.

Current guidelines suggest at least 12 months of DAPT after DES placement. (Levine et al. 2011) The optimal duration for DAPT, however, is not known despite several prior observational and randomized studies(Spertus et al. 2006; Schulz et al. 2009; Park et al. 2010; Valgimigli et al. 2012) and a large, multicenter randomized trial that is underway. (Mauri et al. 2010) Prolonged DAPT is associated with increased major bleeding,(Latib et al. 2008) as well as an increase in nuisance bleeding which may negatively impact patient quality of life.(Roy et al. 2008) In addition, the out-of-pocket costs to patients for prolonged DAPT may lead to premature discontinuation, which is associated with a two-fold increase in death or myocardial infarction.(Ho et al. 2008) Studies have suggested that as many as 20.4% of patients prematurely discontinue DAPT within 6 months after DES placement.(Ho et al. 2007)

Financial Costs of DES compared to BMS

Besides clinical issues, the financial cost is also an issue when deciding to deploy BMS or DES. DES are significantly more expensive than BMS (as is the prolonged dual antiplatelet therapy), so the cost-effectiveness of their use is dependent on the expected absolute reduction in restenosis for a given patient.(Ryan and Cohen 2006) While there is much debate about whether financial costs should be, in and of themselves, incorporated into clinical decision-making, the excess costs of DES and associated DAPT therapy may directly lead to adverse clinical events. Estimates in Medicare beneficiaries, for instance, are

that the use of DES results in an additional \$1.57 billion dollars annually in Medicare spending among beneficiaries aged 66 to 85 years. (Groeneveld et al. 2011)

The Clinical Decision for a Particular Patient

In aggregate, a clinician should decide to use DES, as opposed to BMS, when the overall likelihood of benefit from DES for a particular patient outweighs the associated risks and costs. This decision can only be made on an individual patient basis, weighing the specific clinical circumstances of the patient as well as his/her particular preferences. The relevant factors in the decision should be the potential decrease in restenosis and the decreased likelihood for the need for TVR compared with the need for prolonged dual antiplatelet therapy and its associated risks and costs. As in all of clinical medicine, this calculus is not the same for any two patients.

Future Directions

Future work in this area should focus on generating robust, community-based models predicting bleeding with DAPT and then combining these models with those predicting stent efficacy as described in this review. Finally, all of these predictive models should be tested prospectively in clinical use for their ability to improve patient safety and improve cost-effectiveness in routine use. Without prospective testing, we cannot know if the use of predictive models to guide therapy is resulting in the anticipated consequences. Models that guide clinical practice should also be periodically scrutinized and updated to reflect current practice patterns and modern technology.

Summary, Conclusion, and Future Directions

We have reviewed recent research demonstrating individual variability in the efficacy of DES compared to BMS. Importantly, the variable response for an individual can be predicted before PCI. Once the likelihood of efficacy for DES and BMS have been explicitly articulated for a given patient, clinicians should integrate issues of cost and the risks associated with prolonged DAPT when making their final decision about the type of stent to use for an individual.

The research highlighted in this review also suggests potential benefits in efficiency for the medical system overall. DES should be used when use will positively impact patient care in a cost-effective manner. The models described above have demonstrated that in some patients there is likely little benefit in using DES (where the NNT to prevent TVR is high). Using DES in these situations likely increases overall medical costs and exposes patients to more risk by exposing them to prolonged DAPT without a benefit in preventing restenosis. In other patients, however, where the NNT to prevent TVR is low, DES likely enhances patient safety and may actually enhance overall cost savings (given less repeat procedures due to restenosis in the future).

In the future, similar modeling approaches should be applied to other areas of new medical technology and medical decision making. The efficient use of new medications, new

procedures, or new strategies can only be achieved when “personalized medicine” and rational decision making is expanded beyond the traditional realm.

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Figure 1. Potential complications of coronary stenting. Restenosis with a bare-metal stent and stent thrombosis with a drug-eluting stent.(Curfman et al. 2007) (With permission from Curfman GD, et al., *The New England Journal of Medicine*, 2007;356:1059.)

Figure 2. Observed versus predicted occurrence of 1-year target vessel revascularization (TVR) in the validation cohort for both the non-angiographic (A) and full (B) models for approximately 10 equally sized groups of patients ordered by predicted TVR risk. (With permission from Yeh RW, et al. *Circulation*, 2011, 124:1557).

Figure 3.

Relationship between predicted 1-year TVR with bare metal stents (BMS) and number needed to treat (NNT) with drug-eluting stents to prevent a single occurrence of TVR. The dashed line shows the threshold of predicted 1-year TVR risk below which the NNT is >25. CI indicates confidence interval. ((With permission from Yeh RW, et al. *Circulation*, 2011, 124:1557).

Table 1

Variables included in TVR prediction model (both clinical only and full model with angiographic variables).

Variables included in final prediction models	
Clinical model (without angiographic predictors)	Full model (including angiographic predictors)
Use of DES	Use of DES
Age (years)	Age (years)
Diabetes mellitus	Diabetes mellitus
Peripheral vascular disease	Peripheral vascular disease
Hypertention	Hypertension
Prior PCI	Prior PCI
Prior coronary artery bypass graft	Admission symptoms
Admission symptoms	Canadian Cardiovascular Society/New York Heart Association class
Canadian Cardiovascular Society/New York Heart Association class	2 vessels with 70% stenosis
PCI indication	Number of lesions treated
	Stent diameter 3.0 mm
	Stent length 30 mm