USE OF DRUG ELUTING STENTS AS A FUNCTION OF PREDICTED BENEFIT: CLINICAL AND ECONOMIC IMPLICATIONS OF CURRENT PRACTICE

BY

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**ABSTRACT**

**Background:** Benefits of drug-eluting stents (DES) in percutaneous coronary intervention (PCI) are greatest in those at the highest risk of target vessel revascularization (TVR). While DES reduce restenosis, they cost more than bare metal stents (BMS), and necessitate prolonged dual antiplatelet therapy (DAPT) that increases costs, bleeding risk, and risk of complications if DAPT is prematurely discontinued. Our objectives were to assess if DES are preferentially used in those with higher predicted TVR risk, and to estimate whether lower use of DES (50% less DES use among patients with low predicted TVR risk) would be more cost-effective as compared with the existing pattern of DES use.

**Methods:** We analyzed ~1.5 million PCI procedures in the NCDR CathPCI registry from Apr 2003 - Sept 2010. We estimated 1-year TVR risk assuming PCI with BMS using a previously validated prediction model. The main outcome measures were the rate of DES use and projected annual US societal costs at one year after PCI. We assessed the association between TVR risk with BMS DES use, and performed cost-effectiveness analysis of a lower use of DES (50% less DES use among patients with low predicted TVR risk) vs. existing DES use.

**Results:** There was marked variation in physicians’ use of DES (range = 2-100%). DES use was relatively high across all categories of predicted TVR risk (73.9% in patients with TVR risk <10%, 78.0% in TVR risk 10-20%, and 83.2% in TVR risk >20%), with a modest correlation between predicted TVR risk and DES use (RR 1.005/1% increase in predicted TVR risk [95% CI = 1.005, 1.006]). Reducing DES use by 50% among the lowest risk patients was projected to lower US healthcare costs by $205 million/year.
while increasing the overall TVR event rate by 0.5% (95% CI= 0.49%, 0.51%) in absolute terms.

**Conclusions:** DES use in the U.S. varies widely among physicians, with only modest correlation to patients’ risk of restenosis. Less DES use among patients with low risk of restenosis has the potential for significant cost savings for the US healthcare system, while minimally increasing restenosis events.
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INTRODUCTION

Percutaneous Coronary Intervention (PCI) is the most common cardiac procedure performed in the United States, being conducted >600,000 times per year.\textsuperscript{1} PCI was first introduced in 1979 as an alternative method of coronary revascularization to CABG surgery.\textsuperscript{2} Since then, PCI has gained in popularity and become widely accepted as a safe and effective treatment alternative for coronary artery disease (CAD). The introduction of coronary bare metal stents (BMS) marked a major turning point in the practice of interventional cardiology, which led to dramatic reductions in not only acute abrupt vessel closure, but also longer term in-stent restenosis (ISR). However, with the implantation of a bare metal stents the overall rate of in-stent restenosis (ISR) still remained high — approximately 20-30\% overall.\textsuperscript{3-6} Restenosis of the treated vessel seen after BMS implantation, typically results in renewed anginal symptoms and the need for repeat target vessel revascularization (TVR). Binary angiographic restenosis is defined as the re-narrowing of the vessel lumen to >50\% occlusion, usually within 3–6 months after PCI.\textsuperscript{3,4} Clinical restenosis is characterized by recurrent angina pectoris requiring TVR.\textsuperscript{3,4}

The advent of drug-eluting stents (DES) in the year 2003 was a second major advance that revolutionized the field of interventional cardiology by achieving dramatic decrease in the incidence of restenosis. Although drug eluting stents are much more expensive than BMS, they are highly effective in reducing restenosis, with an estimated 50-70\% relative risk reduction in target vessel revascularization (TVR) rates, as compared to BMS.\textsuperscript{7,8} These benefits led to their rapid adoption after 2003, with a precipitous drop in BMS stent use, such that by 2005, DES use in the US was nearly 90\%\textsuperscript{9-12}, and have persistently remained above 80\% despite their costs.\textsuperscript{9-11}
The widespread use of DES has raised questions about cost-effectiveness of this expensive technology.\textsuperscript{13-19} While trial-based economic analyses show DES are cost-effective from a societal perspective\textsuperscript{20,21}, analysis from a payer’s (Medicare) perspective has shown that widespread DES use ultimately increased Medicare expenditures by $544 million over 2-years.\textsuperscript{22} A more contemporary analysis of Medicare beneficiaries from 2002-2006 found that the annual costs attributable to DES were a staggering $1.57 billion.\textsuperscript{23} Additionally, DES require prolonged dual-antiplatelet therapy (DAPT)\textsuperscript{24-26} which not only add more costs, but also increases bleeding events.\textsuperscript{24,25,27}

Clinically, the benefit of DES is greatest among those at the highest risk for TVR.\textsuperscript{28-32} Work by Tu et al. suggested that patients’ TVR risk greatly impacted their benefit in terms of number needed to treat (NNT) to prevent TVR.\textsuperscript{29} Therefore, some have suggested that DES should be preferentially used for only the higher TVR risk lesions.\textsuperscript{28,29,32} Whether clinicians judiciously use DES with the clinical logic of maximizing their use in those with the greatest benefit is unknown.

To determine current patterns of DES utilization as a function of TVR risk and the potential clinical and economic implications of more tailored DES use, we analyzed data from the National Cardiovascular Disease Registry\textsuperscript{®} (NCDR). Specifically, we assessed 1) variation in use of DES among U.S. physicians participating in NCDR; 2) whether predicted TVR risk with BMS is associated with DES use, and 3) the estimated clinical and economic consequences of lower DES use among patients with low TVR risk.
METHODS

NCDR Population

The NCDR CathPCI Registry, co-sponsored by the American College of Cardiology (ACC) and the Society for Cardiovascular Angiography and Interventions (SCAI), is the largest U.S. clinical registry of patients undergoing diagnostic cardiac catheterization and PCI. Details of the CathPCI Registry have been previously described. In brief, trained data abstractors at each participating hospital collect detailed baseline clinical characteristics, in-hospital care processes, and outcomes retrospectively via chart review using a standardized set of data elements and definitions, which are available at http://www.ncdr.com/WebNCDR/elements.aspx. Systematic data entry, quality assurance, and auditing programs are employed to ensure that only data meeting predetermined criteria for completeness and accuracy are entered into the database.

Data from 2,120,659 PCI admissions from 1,119 hospitals participating in the registry from April 1, 2003 to September 30, 2010 were initially included. To ensure a sample of patients who were “eligible” for both stent types, we then excluded patients receiving stents <2.25 mm and >4 mm in diameter for which DES were not available throughout the period of observation. We next developed a propensity-score model to predict DES (vs. BMS) use via logistic regression conditioned upon 46 demographic and clinical variables. After plotting the distribution of propensity-scores by stent type, we excluded patients falling into regions of non-overlapping propensity scores. These were patients in whom either DES or BMS were used almost exclusively and the choice of using an alternative stent was not likely feasible. The remaining PCI admissions were
included. For admissions where multiple PCIs were performed, we analyzed only the first PCI. The above inclusion and exclusion criteria are detailed in figure 1.

**Figure 1: Inclusion and exclusion criteria**

- 2120659 PCI Procedures
  - 159495 No Stents used
  - 1961164 PCI Procedures
    - 93565 Both DES & BMS used
    - 1867599 PCI Procedures
      - 76649 Minimum Stent Diameter < 2.5 mm
      - 1790950 PCI Procedures
        - 32294 Maximum Stent Diameter > 4 mm
        - 1758656 PCI Procedures
          - 2163 Missing data (no TVR probability)
          - 1756493 PCI Procedures
            - 249715 outside of optimal PS range (0.075 to 0.925)
  - 1506778 PCI Procedures
Predicting Risk of TVR

For each patient, we estimated the risk of TVR assuming treatment with BMS using a validated prediction model developed from the Massachusetts Data Analysis Committee (MassDAC) database (table 1). This model incorporates socio-demographic, clinical and angiographic variables to predict TVR and possesses superior discrimination as compared with the 3 commonly used variables of diabetes, vessel diameter and lesion length, which are all components of the MassDAC model (full model in table 1).

**Table 1: MassDAC TVR risk prediction logistic model**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>Wald Chi-Square</th>
<th>P value</th>
<th>Odds Ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-2.8867</td>
<td>0.1264</td>
<td>521.6982</td>
<td>&lt;.0001</td>
<td>0.526</td>
<td>0.473</td>
<td>0.586</td>
</tr>
<tr>
<td>Drug Eluting Stent</td>
<td>-0.6418</td>
<td>0.0546</td>
<td>138.2324</td>
<td>&lt;.0001</td>
<td>0.526</td>
<td>0.473</td>
<td>0.586</td>
</tr>
<tr>
<td>Age &lt;= 50</td>
<td>0.2913</td>
<td>0.0665</td>
<td>19.1988</td>
<td>&lt;.0001</td>
<td>1.338</td>
<td>1.175</td>
<td>1.524</td>
</tr>
<tr>
<td>Age &gt;= 80</td>
<td>-0.3942</td>
<td>0.0752</td>
<td>27.5041</td>
<td>&lt;.0001</td>
<td>0.674</td>
<td>0.582</td>
<td>0.781</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.1443</td>
<td>0.0509</td>
<td>8.0324</td>
<td>&lt;.0001</td>
<td>1.158</td>
<td>1.046</td>
<td>1.277</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>0.2683</td>
<td>0.0649</td>
<td>17.0624</td>
<td>&lt;.0001</td>
<td>1.308</td>
<td>1.151</td>
<td>1.485</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.1471</td>
<td>0.0604</td>
<td>5.9270</td>
<td>0.0149</td>
<td>1.158</td>
<td>1.029</td>
<td>1.304</td>
</tr>
<tr>
<td>Previous PCI &lt;= 1 Yr</td>
<td>0.9331</td>
<td>0.1402</td>
<td>44.3217</td>
<td>&lt;.0001</td>
<td>2.542</td>
<td>1.932</td>
<td>3.346</td>
</tr>
<tr>
<td>Previous PCI &gt; 1 Yr or Timing Unknown</td>
<td>0.2597</td>
<td>0.0571</td>
<td>20.6589</td>
<td>&lt;.0001</td>
<td>1.297</td>
<td>1.159</td>
<td>1.450</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>-0.1061</td>
<td>0.0782</td>
<td>1.8397</td>
<td>0.1750</td>
<td>0.899</td>
<td>0.771</td>
<td>1.048</td>
</tr>
<tr>
<td>NYHA Class III</td>
<td>-0.1073</td>
<td>0.0749</td>
<td>2.0560</td>
<td>0.1516</td>
<td>0.898</td>
<td>0.776</td>
<td>1.040</td>
</tr>
<tr>
<td>NYHA Class IV</td>
<td>-0.2120</td>
<td>0.0767</td>
<td>7.6327</td>
<td>0.0057</td>
<td>0.809</td>
<td>0.696</td>
<td>0.940</td>
</tr>
<tr>
<td>Atypical Chest Pain</td>
<td>0.0213</td>
<td>0.1500</td>
<td>0.0202</td>
<td>0.8868</td>
<td>1.022</td>
<td>0.761</td>
<td>1.371</td>
</tr>
<tr>
<td>Condition</td>
<td>Coefficient</td>
<td>Standard Error</td>
<td>Z Value</td>
<td>P Value</td>
<td>Hazard Ratio</td>
<td>95% CI Low</td>
<td>95% CI High</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>-------------</td>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
<td>--------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>0.3403</td>
<td>0.1025</td>
<td>11.0255</td>
<td>0.0009</td>
<td>1.405</td>
<td>1.150</td>
<td>1.718</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>0.2720</td>
<td>0.1002</td>
<td>7.3608</td>
<td>0.0067</td>
<td>1.313</td>
<td>1.078</td>
<td>1.598</td>
</tr>
<tr>
<td>Non-STEMI</td>
<td>0.0871</td>
<td>0.1074</td>
<td>0.6575</td>
<td>0.4174</td>
<td>1.091</td>
<td>0.884</td>
<td>1.347</td>
</tr>
<tr>
<td>STEMI</td>
<td>-0.0515</td>
<td>0.1384</td>
<td>0.1386</td>
<td>0.7096</td>
<td>0.950</td>
<td>0.724</td>
<td>1.246</td>
</tr>
<tr>
<td>Urgent Status</td>
<td>0.1623</td>
<td>0.0681</td>
<td>5.6883</td>
<td>0.00171</td>
<td>1.176</td>
<td>1.029</td>
<td>1.344</td>
</tr>
<tr>
<td>Emergent or Salvage</td>
<td>0.6207</td>
<td>0.1177</td>
<td>27.8230</td>
<td>&lt;.0001</td>
<td>1.860</td>
<td>1.477</td>
<td>2.343</td>
</tr>
<tr>
<td>&gt;= 2 Vessels w &gt;= 70% Stenosis</td>
<td>0.4765</td>
<td>0.0500</td>
<td>90.7346</td>
<td>&lt;.0001</td>
<td>1.611</td>
<td>1.460</td>
<td>1.776</td>
</tr>
<tr>
<td>Number of Lesions Treated</td>
<td>0.1877</td>
<td>0.0363</td>
<td>26.7748</td>
<td>&lt;.0001</td>
<td>1.206</td>
<td>1.124</td>
<td>1.295</td>
</tr>
<tr>
<td>Device Diameter &gt;= 3mm</td>
<td>-0.3908</td>
<td>0.0501</td>
<td>60.9505</td>
<td>&lt;.0001</td>
<td>0.677</td>
<td>0.613</td>
<td>0.746</td>
</tr>
<tr>
<td>Device Length &gt;= 30mm</td>
<td>0.2795</td>
<td>0.0555</td>
<td>25.3876</td>
<td>&lt;.0001</td>
<td>1.322</td>
<td>1.186</td>
<td>1.474</td>
</tr>
</tbody>
</table>

* This model had good discriminatory ability (C statistic = 0.655) and good calibration (Hosmer-Lemeshow P=0.90) without evidence of any over-fitting in a separate validation dataset.

The distribution of TVR risk with BMS in the NCDR CathPCI patient population varied widely from 2-80% is shown in figure 2.

**Figure 2: Distribution of the predicted TVR risk.**
Statistical Analysis

Baseline clinical and demographic patient characteristics by groups of low, moderate and high TVR risk were compared using the chi-square test for categorical variables and Student’s t test for continuous variables. TVR risk was categorized into three clinically relevant groups of low (<10%), moderate (10% to <20%) and high (≥20%). We then compared the rates of DES use in low, medium and high TVR risk groups, and estimated the unadjusted association of TVR risk with DES use by means of modified Poisson regression. Because this association might have changed after concerns regarding stent thrombosis led to declines in DES use after 2006, we included an interaction term between time (before and after October 2006) and TVR risk on the outcome of DES use.

To identify the variation in DES use among physicians that was not attributable to differences in patients’ TVR risk, we developed a multilevel Poisson regression model by including ‘physician’ as a random effect in the model of DES use, with predicted TVR risk as a covariate, and estimated the Median Rate Ratio (MRR) for receipt of DES for patients with similar predicted TVR risk treated by 2 random hospitals. Since physician level information was only available in version 4.0 of the NCDR CathPCI data, this analysis was restricted to PCIs performed between July 1st, 2009 to September 30th, 2010 (n = 415,115).

Finally, we estimated the economic and clinical impact of a hypothetical reduction in the rate of DES use among the low TVR risk patients who received DES within the US PCI population (~600,000 PCIs per year). For this analysis, we assumed that the distribution of TVR risk as well as the use of DES among groups of TVR risk
within the NCDR population was representative of that seen in the US PCI population. We used previously described assumptions to estimate clinical outcomes and costs from the perspective of the US healthcare system, as detailed in the Appendix. The model considered the cost of stents, the cost of repeat revascularization procedures for the treatment of restenosis (and their associated hospitalizations), and the cost of dual antiplatelet therapy after either DES or BMS. For patients whose PCI was performed electively, we assumed the duration of DAPT would be 1 month after BMS and 12 months after DES. However, for PCI in the setting of an acute coronary syndrome, we assumed that DAPT would be used for 1 year regardless of stent type. We modeled the uncertainty observed in real-world clinical practice around these assumptions used in estimating costs and TVR events by performing sampling-based probabilistic sensitivity analysis in which we executed the cost-effectiveness model repeatedly (1000 samples) for combinations of values sampled randomly from the probability density functions of the input factors known to vary in real clinical practice.

In addition to probabilistic sensitivity analysis, we performed additional deterministic sensitivity analyses assuming alternate proportions of DES use with a ‘lower use’ strategy only among patients at low TVR risk (i.e. from existing rates of DES use [74% - see results] to 0% DES use in 1% increments). Finally, we assumed that clopidogrel was available in generic form at a cost of $1/day. All analyses were conducted in SAS version 9.2 software (SAS Institute, Cary, NC) and TreeAge Pro 2011 software (TreeAge Inc., Williamstown, MA).
RESULTS

A total of 1,506,758 PCI admissions met the inclusion criteria for the analysis. (Appendix Figure 1). Of these, 648,292 (43.0%) patients were predicted to be in the low TVR risk group, 659,838 (43.8%) in the moderate TVR risk group, and 198,628 (13.2%) in the high TVR risk group. As expected, patients with a high predicted TVR risk were more likely to be of older age, male, with diabetes, chronic kidney disease, and prior PCI. (Table 2) They were also more likely to present with stable angina rather than an unstable coronary syndrome. Lastly, they were more likely to have severe 3-vessel CAD, with smaller diameter and longer lesions.

Table 2: Baseline demographic and clinical patient characteristics by low, moderate and high probability of TVR groups.

<table>
<thead>
<tr>
<th>Demographics and Admission</th>
<th>Total (n = 1,506,758)</th>
<th>Low (n = 648,292)</th>
<th>Moderate (n = 659,838)</th>
<th>High (n = 198,628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Age *</td>
<td>64.96 ± 12.22</td>
<td>66.02 ± 12.39</td>
<td>64.44 ± 12.04</td>
<td>63.17 ± 11.92</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male Gender</td>
<td>998,753 (66.28%)</td>
<td>41,489,00 (64.00%)</td>
<td>44,801,6 (67.90%)</td>
<td>135,847,68 (68.39%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Caucasian</td>
<td>1,263,730 (84.01%)</td>
<td>548,800 (84.80%)</td>
<td>551,233 (83.67%)</td>
<td>163,697 (82.53%)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>99,692 (6.63%)</td>
<td>40,045 (6.19%)</td>
<td>44,736 (6.79%)</td>
<td>14,911 (7.52%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>48,181 (3.20%)</td>
<td>19,095 (2.95%)</td>
<td>21,802 (3.31%)</td>
<td>7,284 (3.67%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>19,178 (1.27%)</td>
<td>7,662 (1.18%)</td>
<td>8,770 (1.33%)</td>
<td>2,746 (1.38%)</td>
<td></td>
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<tr>
<td>Native American</td>
<td>4,929 (0.33%)</td>
<td>1,845 (0.29%)</td>
<td>2,258 (0.34%)</td>
<td>826 (0.42%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>68,576 (4.56%)</td>
<td>29,702 (4.59%)</td>
<td>29,984 (4.55%)</td>
<td>8,890 (4.48%)</td>
<td></td>
</tr>
<tr>
<td>Insurance Payer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Government</td>
<td>830,629 (55.16%)</td>
<td>347,832 (53.68%)</td>
<td>366,041 (55.51%)</td>
<td>116,756 (58.82%)</td>
<td></td>
</tr>
<tr>
<td>Commercial</td>
<td>417,538 (27.73%)</td>
<td>190,276 (29.36%)</td>
<td>179,987 (27.29%)</td>
<td>47,275 (23.81%)</td>
<td></td>
</tr>
<tr>
<td>HMO</td>
<td>163,192 (10.84%)</td>
<td>75,164 (11.60%)</td>
<td>70,024 (10.62%)</td>
<td>18,004 (9.07%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>92,991 (6.17%)</td>
<td>34,054 (5.26%)</td>
<td>42,692 (6.47%)</td>
<td>16,245 (8.18%)</td>
<td></td>
</tr>
<tr>
<td>Non U.S. Insurance</td>
<td>1,594 (0.11%)</td>
<td>655 (0.10%)</td>
<td>708 (0.11%)</td>
<td>231 (0.12%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History and Risk Factors</th>
<th>Total (n = 1,506,758)</th>
<th>Low (n = 648,292)</th>
<th>Moderate (n = 659,838)</th>
<th>High (n = 198,628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior MI (&gt;7 Days)</td>
<td>380,599 (25.26%)</td>
<td>106,300 (16.40%)</td>
<td>191,620 (29.04%)</td>
<td>82,679 (41.63%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior History of CHF</td>
<td>164,873 (10.94%)</td>
<td>56,043 (8.64%)</td>
<td>76,133 (11.54%)</td>
<td>32,697 (16.46%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes *</td>
<td>486,189 (32.27%)</td>
<td>150,000 (23.14%)</td>
<td>240,944 (36.52%)</td>
<td>95,245 (47.95%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Total (n = 1,506,758)</td>
<td>Low (n = 648,292)</td>
<td>Moderate (n = 659,838)</td>
<td>High (n = 198,628)</td>
<td>P-Value</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------------------</td>
<td>------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Prior History of Renal Failure</td>
<td>90209 (5.99%)</td>
<td>28627 (4.42%)</td>
<td>42265 (6.41%)</td>
<td>19317 (9.73%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>179672 (11.93%)</td>
<td>62085 (9.58%)</td>
<td>83836 (12.71%)</td>
<td>33751 (16.99%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Peripheral Vascular Disease *</td>
<td>182894 (12.14%)</td>
<td>38342 (5.91%)</td>
<td>92915 (14.08%)</td>
<td>51637 (26.00%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chronic Lung Disease</td>
<td>260056 (17.26%)</td>
<td>103407 (15.95%)</td>
<td>115104 (17.44%)</td>
<td>41545 (20.92%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hypertension *</td>
<td>1163297 (77.21%)</td>
<td>455151 (70.21%)</td>
<td>532579 (80.71%)</td>
<td>175567 (88.39%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>History of Tobacco Use</td>
<td>574947 (38.16%)</td>
<td>267742 (41.31%)</td>
<td>242575 (36.77%)</td>
<td>64630 (32.54%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Never</td>
<td>504736 (33.50%)</td>
<td>211654 (32.65%)</td>
<td>223083 (33.81%)</td>
<td>69999 (35.25%)</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>426827 (28.33%)</td>
<td>168781 (26.04%)</td>
<td>194080 (29.42%)</td>
<td>63966 (32.21%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1110810 (73.73%)</td>
<td>448319 (69.16%)</td>
<td>500765 (75.90%)</td>
<td>161726 (81.43%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Family History of CA D age &lt;55</td>
<td>355744 (23.61%)</td>
<td>147800 (22.80%)</td>
<td>158478 (24.02%)</td>
<td>49466 (24.91%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior PCI *</td>
<td>467484 (31.03%)</td>
<td>102630 (15.83%)</td>
<td>239491 (36.30%)</td>
<td>125363 (63.12%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prior CABG *</td>
<td>253157 (16.80%)</td>
<td>58416 (9.01%)</td>
<td>140964 (21.37%)</td>
<td>53777 (27.08%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Last Creatinine</td>
<td>1.19 ± 0.92</td>
<td>1.14 ± 0.79</td>
<td>1.21 ± 0.94</td>
<td>1.31 ± 1.18</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GFR (MDRD) ml/min</td>
<td>73.06 ± 30.20</td>
<td>73.82 ± 29.42</td>
<td>72.82 ± 30.57</td>
<td>71.38 ± 31.36</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Cardiac Status

<table>
<thead>
<tr>
<th>CHF During Current Admission</th>
<th>Total (n = 1,506,758)</th>
<th>Low (n = 648,292)</th>
<th>Moderate (n = 659,838)</th>
<th>High (n = 198,628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA *</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1</td>
<td>459673 (30.51%)</td>
<td>194923 (30.07%)</td>
<td>202028 (30.62%)</td>
<td>62722 (31.59%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Class 2</td>
<td>330706 (21.95%)</td>
<td>151896 (23.43%)</td>
<td>139249 (21.11%)</td>
<td>39561 (19.92%)</td>
<td></td>
</tr>
<tr>
<td>Class 3</td>
<td>395951 (26.28%)</td>
<td>163646 (25.25%)</td>
<td>176539 (26.76%)</td>
<td>55766 (28.09%)</td>
<td></td>
</tr>
<tr>
<td>Class 4</td>
<td>320122 (21.25%)</td>
<td>137722 (21.25%)</td>
<td>141890 (21.51%)</td>
<td>40510 (20.40%)</td>
<td></td>
</tr>
</tbody>
</table>

Cardiogenic Shock

<table>
<thead>
<tr>
<th>Admission Presentation</th>
<th>Total (n = 1,506,758)</th>
<th>Low (n = 648,292)</th>
<th>Moderate (n = 659,838)</th>
<th>High (n = 198,628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Symptoms</td>
<td>200248 (13.29%)</td>
<td>103667 (15.99%)</td>
<td>78241 (11.86%)</td>
<td>18340 (9.23%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Atypical Chest Pain</td>
<td>106552 (7.07%)</td>
<td>65126 (10.05%)</td>
<td>35455 (5.37%)</td>
<td>5971 (3.01%)</td>
<td></td>
</tr>
<tr>
<td>Stable Angina</td>
<td>213836 (14.19%)</td>
<td>82579 (12.74%)</td>
<td>98574 (14.94%)</td>
<td>32683 (16.46%)</td>
<td></td>
</tr>
<tr>
<td>ACS:Unstable Ang</td>
<td>460478 (30.56%)</td>
<td>179086 (27.63%)</td>
<td>208976 (31.67%)</td>
<td>72416 (36.46%)</td>
<td></td>
</tr>
<tr>
<td>ACS:Non-STEMI</td>
<td>269461 (17.89%)</td>
<td>116844 (18.03%)</td>
<td>116609 (17.67%)</td>
<td>36008 (18.13%)</td>
<td></td>
</tr>
<tr>
<td>ACS:STEMI</td>
<td>256050 (16.99%)</td>
<td>100928 (15.57%)</td>
<td>121937 (18.48%)</td>
<td>33185 (16.71%)</td>
<td></td>
</tr>
</tbody>
</table>

Angiographic and PCI Procedure Characteristics
### Total TVR risk group (n = 1,506,758)

<table>
<thead>
<tr>
<th>PCI Status *</th>
<th>Low (n = 648,292)</th>
<th>Moderate (n = 659,838)</th>
<th>High (n = 198,628)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elective</td>
<td>670147 (44.48%)</td>
<td>332654 (51.32%)</td>
<td>269566 (40.86%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urgent</td>
<td>559774 (37.16%)</td>
<td>237197 (36.59%)</td>
<td>247221 (37.47%)</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>271934 (18.05%)</td>
<td>77088 (11.89%)</td>
<td>140500 (21.29%)</td>
<td></td>
</tr>
<tr>
<td>Salvage</td>
<td>4704 (0.31%)</td>
<td>1245 (0.19%)</td>
<td>2495 (0.38%)</td>
<td></td>
</tr>
</tbody>
</table>

| DES used     | 1158534 (76.89%) | 478779 (73.85%)        | 514600 (77.99%)   | < 0.001 |

| Minimum lesion diameter (mm) * | 3.01 ± 0.42 | 3.13 ± 0.40 | 2.96 ± 0.41 | 2.80 ± 0.37 | < 0.001 |

| Total lesion length (mm) *    | 27.75 ± 17.68 | 21.77 ± 12.00 | 30.23 ± 18.44 | 39.05 ± 22.51 | < 0.001 |

| Number of diseased vessels *  | 65501 (4.35%) | 39628 (6.11%) | 22412 (3.40%) | 3461 (1.74%)  | < 0.001 |
| 0                            | 783617 (52.01%) | 507330 (78.26%) | 245278 (37.17%) | 31009 (15.61%) |
| 1                            | 406325 (26.97%) | 62276 (9.61%) | 244194 (37.01%) | 99855 (50.27%) |
| 2                            | 251315 (16.68%) | 39058 (6.02%) | 147954 (22.42%) | 64303 (32.37%) |

*Indicates variables included in the MassDAC TVR risk prediction mode

### Physician Variation in DES Use

We found extensive variation in physician patterns of DES use (Figure 3). Among the 2715 physicians performing 415,115 PCI procedures (at least >75 procedures/year), DES use ranged from 2%-100%. The variation across physicians, as described by the MRR was 1.8, suggesting that if 2 patients, predicted to be at similar TVR risk, presented to 2 random interventionalists participating in NCDR, there was, on average, a 1.8-fold greater probability of receiving a DES with one physician as compared with another.

**Figure 3: Physician level variation in the use of DES.**
Individual Physicians (Performing >75 PCI per Year)
Ranked in Ascending Order of DES use

X-axis shows the individual physicians (n=2715) in NCDR version 4 data performing >75 PCI annually. These physicians have been ranked in ascending order of rate of DES use, such that those using the least DES are to the left and those using the highest DES are to the right. Physician use of DES ranged from 2 to 100%. The median rate ratio for this physician level variation was 1.8, implying an almost 2 fold variation in the use of DES directly attributable to physician preference, even after adjusting for patient factors related to DES use.

**Relations between predicted TVR risk and DES use**

The median predicted TVR risk was 11% (IQR 8% to 16%, Figure 2). DES use was 73.9% among those at a low risk for TVR, 78.0% among those at moderate risk for TVR and 83.2% among those at the highest TVR risk (Table 1 and Figure 4). When analyzed as a continuous variable, there was a 0.53% (95% CI = 0.50%, 0.56%) relative increase in the rate of DES use for each 1% increase in the predicted risk of TVR with BMS. In addition, despite an overall decline in DES use over time (30% decline in DES use after October 2006), the relationship between TVR risk and DES use was modest in both time periods (RR 1.0020 [95% CI 1.0016 to 1.0025] before October 2006 vs. RR
1.0086 [95% CI 1.0082 to 1.0089] after October 2006, interaction P-value < 0.01)
(Figure 4).

**Figure 4: Rates of DES use over time**

The first set of bar graphs shows the rates of DES use in the overall population. The next two sets of bar graphs show rates of DES use before October 2006 (this date marks the date of the ‘stent thrombosis scare’ which led to a 30% decline in DES use in 2007).

**Potential Cost Implications of Lower DES Use Among Low Risk Patients**

A 50% reduction in the use of DES only among those with the low risk of TVR was estimated to result in potential net savings of $204,654,000 per year in the US (Figure 3), or $34,109 per 100 PCIs performed, as compared with current practice. These estimated net savings accounted for an estimated increase in costs of repeat procedures due to TVR (absolute increase in TVR rate = 0.50%, 95% CI 0.49%-0.51%), which were estimated to cost $64,728,000, and an estimated decrease in costs resulting from a decrease in clopidogrel use only among the elective PCI patients) (Figure 5).
Cost-effectiveness analysis showed an incremental cost-effectiveness ratio of $68,230/TVR avoided when comparing ‘Existing DES use’ against the alternative of ‘Judicious DES use’ (Figure 5). In the 1000 NCDR samples generated by sampling-based probabilistic sensitivity analysis, the incremental cost-effectiveness ratio for ‘Existing use’ vs. ‘Judicious use’ strategy exceeded the $10,000/TVR avoided willingness-to-pay threshold in 98.3% of the 1000 trial replicates (Figure 6).
Figure 6: Incremental cost-effectiveness (A) and cost-effectiveness acceptability curve (B) of ‘Existing use strategy’ vs. ‘Judicious use strategy’ (base case) in the 1000 NCDR samples generated by sampling-based probabilistic sensitivity analysis.

Panel A:

Incremental Cost-Effectiveness, Judicious DES use in low-risk pts vs. Existing pattern of DES use

Panel B:

‘Existing use strategy’ vs. ‘Judicious use strategy’ (Base case) in the 1000 NCDR samples generated by sampling-based probabilistic sensitivity analysis.

Panel A:
X-axis shows incremental effectiveness (TVR events) of ‘Existing use strategy’ - ‘Judicious use strategy’. Points to the left of ‘0’ indicate decreased efficacy (more TVR events with ‘Judicious use strategy’ vs. ‘Existing use strategy’). Y-axis shows incremental costs ‘Judicious use strategy’ - ‘Existing use strategy’. Points below ‘0’
indicate costs saved from a ‘Judicious use strategy’. The ellipse represents the 95% confidence ellipse, and contains 95% of the simulations.

**Panel B:**
X-axis shows the willingness-to-pay threshold. The solid vertical line represents the $10,000/TVR avoided threshold. Values above this threshold are generally considered unfavorable. Y-axis shows the proportion of simulations that are cost-effective. The solid blue curve is the cumulative probability density function of the 1000 trial replicates. 98.3% of the 1000 trial replicates showed an incremental cost-effectiveness ratio for ‘Existing use’ vs. ‘Judicious use’ strategy that exceeded $10,000/TVR avoided.

The projected impact of alternative rates of DES use among patients at low risk of TVR with BMS is shown in Figure 7. As the rate of DES use among low risk patients decreases, the potential cost savings are projected to increase substantially with minimal change in clinical outcomes. For example, use of only BMS among patients at low risk of TVR would be projected to reduce current healthcare expenditures by $409,317,379/year with only a 0.99% absolute increase in the risk of TVR at a population level. Finally, with the assumption that the cost for dual antiplatelet therapy would decrease to $1/day (with the expected approval of generic clopidogrel in 2012), the estimated net cost savings with a 50% reduction in DES use in the low TVR risk group was projected at $127,950,000/year.

**Figure 7: Sensitivity of projected cost-savings to assumed reductions in DES use in low TVR risk patients.**
X-axis shows the proportion by which DES use is reduced in the low TVR risk group patients who received a DES in NCDR. The first bar represents 100% BMS use in this low predicted TVR risk group, while the last bar represents ‘Existing use’ or 74% DES use in the low TVR risk group. Y-axis on the left shows the US annual costs saved ($)/year in patients undergoing PCI and is represented by the light gray bars. Y-axis on the right shows the absolute increase in TVR event rate (%) and is represented by the black line.
DISCUSSION

The present study demonstrates that in current US practice, DES use remains prevalent, even among patients at low risk to develop restenosis. There was also significant variation in the rate of DES use by individual physicians. A reduction in DES use among patients at low risk for restenosis was projected to be associated with substantial costs savings with only a small increase in TVR events.

The use of advanced medical technology such as DES remains an important driver of increasing healthcare costs in the US and worldwide. Groeneveld et al\textsuperscript{14} analyzed Medicare data on 2 million beneficiaries from 2002 to 2006 and found that the additional costs attributable to DES use were $1.57 billion annually. Given the costs to patients and society of DES technology, and the potential risks of the requirement for long term DAPT after DES (increased bleeding with therapy, increased stent thrombosis with premature discontinuation), there appears to be an important opportunity to tailor DES use to those with the greatest potential to benefit and reduce its use in those with favorable outcomes after BMS alone. From an economic perspective, this study projected that adopting a strategy that reduced the current use of DES in those with the lowest predicted risk of TVR by 50% could be associated with cost savings of ~$200 million every year in the United States alone, even after accounting for a small increase (< 0.5%) in the need for subsequent PCI for restenosis – a relatively benign and stable condition. Collectively, these findings suggest that current DES utilization patterns offer an important opportunity to tailor therapy to patient risk and reduce costs to the healthcare system.

Several previous studies have compared the clinical benefits of DES vs. BMS
among patients across different levels of restenosis risk. Tu and colleagues analyzed data from Ontario’s Cardiac Care Network and found that the benefits of DES were substantially greater in those patients with diabetes, small target vessels \(<3 \text{ mm in diameter}\), and long lesions \(\geq 20 \text{ mm}\). The number needed to treat (NNT) to prevent one TVR event with the use of DES ranged from 10 to 27 in those individuals with 2 or more of these risk factor for TVR, while in those with fewer risk factors the effectiveness of DES did not differ significantly from that of BMS and the NNT ranged from 53 to 167. More recently, a post-hoc analysis from the HORIZONS-AMI trial of acute MI patients demonstrated that in patients at highest risk for restenosis, use of DES resulted in a marked reduction in TLR at 12 months, but that no differences in TLR at 12 months were present between DES and BMS in patients at low risk for restenosis. The current study extends these previous findings by using national clinical practice data to examine how DES are being utilized in relation to patient risk for restenosis, and to estimate how changes in practice could affect healthcare costs on a population level.

The findings of this study also extend recent insights from the EVENT investigators who found that the \(~25\%\) reduction in DES use after the 2006 was accompanied by a small increase in clinical restenosis, but no differences in the rates of death or myocardial infarction. However, this decrease in DES use after 2006 led to substantial reductions in the cost of cardiovascular care of \(~$400\) per PCI patient. In this study, while reduced DES use after 2006 was associated with risk factors for restenosis, these associations were modest, implying that reductions in DES weren’t necessarily in low TVR risk patients. Our findings now build upon this concept and suggest that further reductions in DES use only among patients at low risk of TVR may translate into
additional cost savings with an even smaller impact on overall clinical TVR outcomes than that observed in the EVENT study.

We found that the projected cost-savings associated with lower use of DES were extremely sensitive to the magnitude of reduction in DES use among low TVR risk patients, while estimated increases in TVR events were largely insensitive to these reductions. Changes in clinical practice patterns leading to even a small reduction in DES use in low risk patients may result in substantial cost savings. This begs the question of how to change clinical practice regarding the choice of DES versus BMS. The MassDAC TVR risk prediction model could potentially offer an evidence-based solution to this problem. The MassDAC model is freely available as an online tool (http://massdac.org/riskcalc/revasc) and could be used to prospectively inform clinicians and patients of patients’ TVR risk prior to stent implantation.44 Use of the model could not only promote evidence-based care but also shared decision-making with patients’ so that patients’ preferences for small reductions in TVR could be integrated with their desires to adhere to DAPT and its potential costs and bleeding risks.

We purposefully selected to model a strategy of reducing DES by 50% in the low risk group, in order to give clinicians and patients the ability to exercise their judgment and preferences on a case-by-case basis, while setting a target goal that could potentially lead to substantial cost savings. The intention was to illustrate the potential for costs savings without a significant increase in patient morbidity that could be achieved with a more selective and evidence-based approach to the stent selection than is currently observed, and without advocating a sweeping policy change that would limit both physician and patient autonomy.
This study should be interpreted in the context of several potential limitations. First, the discrimination of the model used to estimate predicted TVR risk was modest (c-statistic = 0.66). However, this model had better discrimination than the more commonly applied risk factors of diabetes, vessel diameter and lesion length (0.66 vs. 0.60, p<0.0001)  

In addition, model calibration, a metric for assessing a model’s ability to identify a low TVR risk group of patients, was excellent (Hosmer-Lemeshow P=0.90). Thus, the projections of the increase in TVR events with the lower DES use strategy among low risk patients and associated TVR costs are likely to be accurate. Next, we did not account for either the potential costs of major or nuisance bleeding or the potential ischemic benefits of prolonged DAPT, as these represent areas of uncertainty in the literature that are currently under investigation. Third, we did not have any assessment of patients’ preferences for DES. It is possible that many patients at low risk would prefer to accept the costs and risks of prolonged DAPT in exchange for a reduced risk of repeat procedures. Such patients could still be among the 50% of low risk patients who receive DES in our proposed strategy. Fourth, while our model of clinical and economic outcomes of PCI procedures was based on the best available clinical and economic data, the resulting projections cannot be directly verified using empirical data at present.

Conclusions

Although the benefits of DES are greatest among patients at the highest risk for restenosis, DES use is common even among those predicted to be at the lowest risk for TVR. Given marked variation in physicians’ DES use, a strategy of lower DES use among patients at low risk of TVR could present an important opportunity to reduce healthcare expenditures while preserving the vast majority of their clinical benefit.
References


(30) Stone GW, Parise H, Witzenbichler B et al. Selection criteria for drug-eluting versus bare-metal stents and the impact of routine angiographic follow-up:


(33) The NCDR® CathPCI Registry®. 2011. Ref Type: Generic


Centers for Medicare & Medicaid Services. 2011. Ref Type: Generic

APPENDIX A – Supplementary Materials
Assumptions for Costing Methods

The cost of a TVR event was $19,000 per episode in 2004\textsuperscript{20,21,46}. When inflated to US $2009 the cost of TVR was estimated to be $21,578. DES costs $1200 more than BMS (need reference the IMS survey), the cost of clopidogrel therapy was estimated using the average wholesale price (AWP) of clopidogrel in 2009 ($4.62 per day)\textsuperscript{47}. The duration of clopidogrel therapy was assumed to be 12 months for DES patients and 1 month for BMS patients undergoing elective PCI.\textsuperscript{48} Since clopidogrel is recommended for a year in patients with an acute coronary syndrome (ACS) undergoing PCI, the cost of clopidogrel was assumed to be equal in the ACS patients, irrespective of DES or BMS used.\textsuperscript{41,42} We also assumed an average of 1.5 stents used per PCI procedure (from NCDR), TVR rates as predicted by the MassDAC model (low risk group 7.32%; moderate risk group 13.98%; high risk group 26.09%), the cost of index PCI procedure in 2009 US$ - $ 10,435.\textsuperscript{49} This was estimated from Medicare reimbursements to hospitals for 294,737 PCI procedures in year 2009 as a weighted average of 4 DRGs for PCI [DRG 246 (PCI with DES With MCC, cost $16,702, 14.6% procedures), DRG 248 (PCI with BMS With MCC, cost $15,546, 6.7% procedures), DRG 247 (PCI with DES without MCC, cost $9,113, 59.9% procedures) and DRG 249 (PCI with BMS without MCC, cost $7,924, 18.7% procedures)]\textsuperscript{49} Thus, costs included direct costs to Payers (cost of procedures), and also societal costs (cost of clopidogrel), but not indirect costs – and hence referred to as a modified US societal perspective. Efficacy of DES vs. BMS for the outcome of TVR was assumed to be a relative risk of 0.57 as predicted by the MassDAC\textsuperscript{34} as well as prior studies of DES vs. BMS in real-world data\textsuperscript{50}. All cost savings were estimated for a single PCI procedure in the overall NCDR population in the
‘Judicious DES use’ strategy as compared to the ‘Existing DES use’ strategy. Since 600,000 PCI procedures are performed annually in the US currently\(^1\), these cost savings were multiplied by a factor of 600,000 to estimate the yearly cost savings in the US.

**Assumptions for Probabilistic Sensitivity Analysis Methods**

To model the uncertainty observed in real-world clinical practice around some of the assumptions used in estimating costs and TVR events, we performed a sampling-based probabilistic sensitivity analysis in which we executed the above cost-effectiveness model repeatedly (for 1000 NCDR samples) for combinations of values sampled randomly from the probability density functions of the following input factors known to vary in real clinical practice and would affect the cost-effectiveness of DES in this setting - TVR risk in NCDR (normal distribution, low risk group \(\mu = 7.32\%\) and \(\sigma = 1.61\%\); moderate risk group \(\mu = 13.98\%\) and \(\sigma = 2.75\%\); high risk group \(\mu = 26.09\%\) and \(\sigma = 5.90\%)\), number of DES used per case in NCDR (normal distribution, \(\mu = 1.5\) stents and \(\sigma = 0.82\) stents, distribution trimmed to not allow ‘negative’ number of stents), the cost of index PCI procedure in 2009 US$ - $10,435 (lognormal distribution), the cost of TVR inflated to US $ 2009 - $ 21,578 (lognormal distribution), monthly cost of clopidogrel at $4.62/day (or $138.6/month) in 2009 (lognormal distribution), the additional cost of a DES in 2009 over a BMS $1200/stent (lognormal distribution) and the duration of clopidogrel therapy with DES use (normal distribution, \(\mu = 12\) months and \(\sigma = 0.5\) months, truncated at 12 months). The duration of clopidogrel therapy with BMS use in an elective PCI case was assumed to be 1 month, while it was assumed to be again 12 months (normal distribution, \(\mu = 12\) months and \(\sigma = 0.5\) months, truncated at 12 months).
when BMS was used in the setting of an acute coronary syndrome (unstable angina, non-STEMI and STEMI PCI procedures).\textsuperscript{41,42}
APPENDIX B - SAS Program Code

/*311P*/
libname v3 'S:\acc-ncdr\cathpci\data\v3\analysis\crosswalk';
options fmtsearch=(v3) nofmterr;
libname tvr 'S:\acc-ncdr\Analysis\2011\311P\Data';
%let output=S:\acc-ncdr\Analysis\2011\311P\Output;

proc means data=tvr.final;
  where phat_group=1;
  var phat_bms;
run;

proc means data=tvr.final;
  where phat_group=2;
  var phat_bms;
run;

proc means data=tvr.final;
  where phat_group=3;
  var phat_bms;
run;

/*get total stent leng and min dia*/
proc sql;
create table desbms as select UIdPatStay, Nattempt, DevDiam, DevLen, ICDevType
  from v3.icdev
  where ICDevType in
  ;
quit;

proc sql;
create table desbms2 as select unique(uidpatstay),nattempt,min(devdiam) as min_diam,max(devdiam) as max_diam,
  sum(devlen) as total_length, sum(ICDevType=11) as num_des,
  sum(icdevtype=3) as num_bms
  from desbms
  group by uidpatstay
  ;
quit;

proc sql;
create table desbms3 as select *
  from v3.analysis as a left join desbms2 as b on a.uidpatstay=b.uidpatstay
  ;
quit;
data tvr.data;
set desbms3;
/*number dz vessels*/
/*indicator for sig vessel dz*/
if lmpr>=50 then do;
   if rcapr>=70 then num_dis_ves=3;
   else num_dis_ves=2;
end;
else if lmpr<70 then do;
   num_dis_ves=(pladpr>=70 or mdladpr>=70) + (rcapr>=70) + (circpr>=70 or
   rampr>=70);
end;
num_dis_ves_svg=num_dis_ves+(PLADgPr>=70 or MDLADgPr>=70 or CIRCgPr>=70
or RCAgPr>=70 or RAMgPr>=70);
if prpci=1 then do;
   priorpcitime=datepart(procdt)-datepart(prpcidt);
end;
/*full model probabilities*/
g=-2.8867+ (.2913*(age<=50)) + (-.3942*(age>=80)) + (.1443*diabetes) + (.2683*pvd)
+ (.1471*hypertn) + (.9331*(prpci=1 and 0<=priorpcitime<=365)) + (.2597*(prpci=1 and
(priorpcitie<0 or priorpcitime>365))
+ (-.1061*(ClassNYH=2)) + (-.1073*(ClassNYH=3)) + (-.2120*(ClassNYH=4)) +
(.0213*(admsxpre=2))
+ (.3403*(admsxpre=3)) + (.2720*(admsxpre=4)) + (.0871*(admsxpre=5)) + (-
.0515*(admsxpre=6))
+ (.1623*(PCIStat=2)) + (.6207*(PCIStat>=3)) + (.4765*(num_dis_ves>=2)) +
(.1877*Ndilated) +
+ (-.3908*(min_diam>=3)) + (.2795*(total_length>=30));
phat_bms=exp(g)/(1+exp(g));
g_des=-2.8867 + (-.6418) + (.2913*(age<=50)) + (-.3942*(age>=80)) + (.1443*diabetes)
+ (.2683*pvd)
+ (.1471*hypertn) + (.9331*(prpci=1 and 0<=priorpcitime<=365)) + (.2597*(prpci=1 and
(priorpcitie<0 or priorpcitime>365))
+ (-.1061*(ClassNYH=2)) + (-.1073*(ClassNYH=3)) + (-.2120*(ClassNYH=4)) +
(.0213*(admsxpre=2))
+ (.3403*(admsxpre=3)) + (.2720*(admsxpre=4)) + (.0871*(admsxpre=5)) + (-
.0515*(admsxpre=6))
+ (.1623*(PCIStat=2)) + (.6207*(PCIStat>=3)) + (.4765*(num_dis_ves>=2)) +
(.1877*Ndilated) +
+ (-.3908*(min_diam>=3)) + (.2795*(total_length>=30));
phat_des=exp(g_des)/(1+exp(g_des));
nnt=1/(phat_bms-phat_des);

DES_used=(num_des>0);
/*exclusions*/
if num_des=. then ex=1;
else if num_des>0 and num_bms>0 then ex=2;
else if min_diam<2.5 then ex=3;
else if max_diam>4 then ex=4;
else if phat_bms=. then ex=5;
else ex=0;
run;

proc freq data=tvr.data;
tables ex;
run;
/*propensity model*/
proc logistic data=tvr.data descending;
where ex=0;
class race gender payor tobacco classnyh admsxpre mlesscai pcistat;
model des_used=age gender payor prchf prvalve diabetes renfail cvd pv deldiabetes
hypertn tobacco hyprchol fhcad prpci prcab chf classnyh carshock admsxpre
mlesscai mprestepr mpretimi mlesrisk min_diam total_length pcistat num_dis_ves;
output out=pred p=ps_des xbeta=logit;
run;

data graph;
set pred(keep=logit ps_des des_used);
run;

data graph;
set graph;
if des_used=0 then group=2*uniform(0);
if des_used=1 then group=((2*uniform(0))+5);
run;
symbol1 height=.1 interpol=none value=dot color=black;
axis1 value=('' 'BMS' '' '' '' '' 'DES' '') minor=none major=none;
axis2 label=(a=90 'Logit DES') order=-5 to 6 by 1;
title;

proc gplot data=graph;
plot logit*group/vaxis=axis2 haxis=axis1 vref=2.5 -2.5;
run;
quit;

proc sort data=graph;by des_used;run;
proc capability data=graph;
  comphistogram logit/class=(des_used)
                  endpoints= -4 -3.5 -3 -2.5;
run;
quit;

proc means max data=graph;
  var logit;
run;

%optimala(data=GRAPH,p=ps_des,group=des_used);
/*optimal range (.075,.925)*/
data optimal;
set pred;
if 0<ps_des<.075 or ps_des>.925 then ex=6;
run;

proc freq data=optimal; tables ex; run;
data tvr.final;
set optimal;
where ex=0;
run;

data tvr.final;
set tvr.final;
g_noangio=-2.6444+ (.2380*(age<=50)) + (-.3062*(age>=80)) + (.1848*diabetes) +
  (.2878*pvd)
  + (.1759*hypertn) + (.7720*(prpci=1 and 0<=priorpcitime<=365)) + (.2265*(prpci=1 and
  (priorpcitime<0 or priorpcitime>365)))
  + (.3694*prcab) + (.0941*(ClassNYH=2)) + (.0845*(ClassNYH=3)) + (-
  .1853*(ClassNYH=4)) + (-.0643*(admsxpre=2))
  + (.2849*(admsxpre=3)) + (.2173*(admsxpre=4)) + (.0828*(admsxpre=5)) + (-
  .1028*(admsxpre=6))
  + (.1497*(PCIStat=2)) + (.6204*(PCIStat>=3));
phat_bms_noangio=exp(g_noangio)/(1+exp(g_noangio));

/*phat groups spertus wants*/
if phat_bms<.1 then phat_group=1;
else if .1<=phat_bms<.2 then phat_group=2;
else if phat_bms=.2 then phat_group=3;
run;

/*****random phys effect********/
proc glimmix data=model;
where pcioperatorkey^=-1 and num_proc>=100;
class PCIOperatorKey;
model des_used=phat100/dist=bin link=logit solution;
nloptions tech=nrridg maxiter=1000;
random intercept /subject=pcioperatorkey type=un solution g;
ods output solutionr=random;
covtest 'Ho: No random effects' ZeroG;
run;

/**********phat*time interaction test**********/
proc glimmix data=time2 ;
class time;
model des_used=phat100|time/dist=poi link=log;
*oddsratio phat100/at(time='1');
*oddsratio phat100/at(time='2');
estimate 'p overall' phat100 1/exp cl;
estimate 'p early' phat100 1 phat100*time 1 0/exp cl;
estimate 'p late' phat100 1 phat100*time 0 1/exp cl;
lsmeans time/pdiff;
run;