Stents

Stent Thrombosis With Second-Generation Drug-Eluting Stents Compared With Bare-Metal Stents

Network Meta-Analysis of Primary Percutaneous Coronary Intervention Trials in ST-Segment–Elevation Myocardial Infarction

Femi Philip, MD; Shikhar Agarwal, MD; Matthew C. Bunte, MD; Sachin S. Goel, MD; E. Murat Tuzcu, MD; Stephen Ellis, MD; Samir R. Kapadia, MD

Background—The relative safety of drug-eluting stents (DESs) and bare-metal stents (BMSs) with respect to stent thrombosis (ST) continues to be debated. There are limited data comparing safety and efficacy of second-generation DES to BMS. We compared the clinical outcomes between second-generation DES and BMS for primary percutaneous coronary intervention using network meta-analysis.

Methods and Results—Randomized controlled trials comparing stent types (first-generation DES, second-generation DES or BMS) were considered for inclusion. A search strategy used Medline, Embase, Cochrane databases, and proceedings of the international meetings. Information about study design, inclusion criteria, and sample characteristics were extracted. Network meta-analysis was used to pool direct (comparison of second-generation DES to BMS) and indirect evidence (first-generation DES with BMS and second-generation DES) from the randomized trials. Twenty-one trials comparing all stents types, including 12,866 patients randomly assigned to treatment groups, were analyzed. A significantly lower incidence of ST was noted with the use of second-generation DES as early as 30 days (odds ratio [OR], 0.36; 95% confidence interval [CI], 0.15–0.82) and between 31 days and 1 year (OR, 0.49; 95% CI, 0.30–0.79) when compared with BMS. Second-generation DES was associated with significantly lower incidence of definite ST at 1 year (OR, 0.3; 95% CI, 0.11–0.83) and myocardial infarction (OR, 0.3; 95% CI, 0.17–0.54) and target vessel revascularization at 1 year (OR, 0.54; 95% CI, 0.80–0.98) when compared with BMS. There was no difference in mortality at 30 days (OR, 0.84; 95% CI, 0.45–1.59) or 1 year (OR, 0.80; 95% CI, 0.56–1.14) with the use of second-generation DES versus BMS. The small number of events may influence the precision of the analysis.

Conclusions—Network meta-analysis of randomized trials of primary percutaneous coronary intervention demonstrated lower incidence of ST, myocardial infarction, and target vessel revascularization with second-generation DES when compared with BMS. The use of second-generation DES for percutaneous coronary intervention in ST-segment–elevation myocardial infarction was not associated with adverse events when compared with BMS. (Circ Cardiovasc Interv. 2014;7:49-61.)

Key Word: percutaneous coronary intervention

In patients with ST-segment–elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) decreases infarct size, reinfarction, and improves survival when compared with fibrinolysis.¹ Bare-metal stents (BMSs) reduce the risk for reocclusion and reinfarction in primary PCI.² Drug-eluting stents (DESs) extend these benefits over BMS by reducing rates of angiographic restenosis and ischemia-driven target vessel revascularization (TVR) in randomized controlled trials, meta-analysis, and observational studies.³ ⁴ Despite these advantages, early and late stent thrombosis on discontinuation of dual antiplatelet agents, and the ongoing predilection for late stent thrombosis with first-generation DES (Cypher, sirolimus-eluting stents [Cordis, FL] and Taxus, paclitaxel-eluting stents [Boston Scientific, Place Natick, MA]) have raised safety concerns.⁵ To address these issues, new DESs have been developed with novel materials, designs using biocompatible polymers, and newer antiproliferative agents. These second-generation DES were approved in noninferiority trials with first-generation DES, and few studies have compared second-generation DES with each other or with BMS.⁶ ⁷ Only 2 randomized control trials have compared clinical outcomes after implantation of second-generation DES versus BMS in STEMI. The everolimus-eluting stent (EES) versus bare-metal stent in ST-segment–elevation myocardial infarction (EXAMINATION) trial compared EESs (Abbott Vascular, Santa Clara, CA) with BMS in patients with STEMI and showed significantly lower rates of stent thrombosis.⁸ In

Received April 10, 2013; accepted October 7, 2013.
From the Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, OH.
Correspondence to Samir R. Kapadia, MD, Sones Cardiac Catheterization Laboratory, Cleveland Clinic, Cleveland, OH 44195. E-mail kapadis@ccf.org
© 2013 American Heart Association, Inc.
Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org
DOI: 10.1161/CIRCINTERVENTIONS.113.000412

49
WHAT IS KNOWN

• Primary percutaneous coronary intervention improves mortality after ST-segment-elevation myocardial infarction.
• First-generation drug-eluting stents have been evaluated in primary percutaneous coronary intervention, but limited data are available on the safety and efficacy of second-generation drug-eluting stent in this setting.

WHAT THE STUDY ADDS

• When compared with bare-metal stents, second-generation drug-eluting stents in primary percutaneous coronary intervention were associated with significant reductions in risk for stent thrombosis, myocardial infarction, and target vessel revascularization in the first year.
• These data extend the safety of drug-eluting stent in ST-segment–elevation myocardial infarction.

contrast, the Comparison of Biolimus Eluted From a Erodable Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE-AMI) trial compared biodegradable polymer biolimus-eluting stents (Biosensors, Los Angeles, CA) with BMS and failed to demonstrate a significant difference in stent thrombosis.9 Despite its overwhelming relevance to current clinical practice, the pooled analysis of these 2 trials would be fraught with lack of power in several important end points. However, 19 randomized control trials have compared outcomes after implantation of first-generation versus BMS and first-generation DES versus second-generation DES for primary PCI in STEMI.10–28 Using the statistical technique of network meta-analysis, it is possible to create a cyclic network (illustrated in Figure 1B) that would use all these randomized trials to bolster the direct evidence from COMFORTABLE-AMI and EXAMINATION trials.8,9

Methods

Search Strategy

We searched for relevant randomized controlled trials for inclusion in this meta-analysis after the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) guidelines.29 We searched for all randomized controlled trials using Medline, the Cochrane Central Register for Controlled Trials (CENTRAL), Embase, TCTMD, ClinicalTrials.gov, Clinical Trial Results, Cardiosource, and abstracts and presentations from major cardiovascular meetings (from their inception of each database until January 2013). Key words used were randomized clinical trial, drug-eluting stent, everolimus-eluting stent, paclitaxel-eluting stent, sirolimus-eluting stent, zotarolimus-eluting stent, biolimus-eluting stent, bare metal stent, primary percutaneous coronary intervention, and ST-segment–elevation myocardial infarction. Citations were screened at the title and abstract level and retrieved if they met our inclusion criteria. Two investigators (F.P. and S.A.) independently reviewed the titles, abstracts, and full-text articles, determined their eligibility in duplicate, and established whether they met the inclusion criteria. No language, publication date, or publication status restrictions were imposed.

DES Definitions

We restricted our analysis to first-generation DES: sirolimus-eluting stent (including the Firebird platform) and paclitaxel-eluting stent (Express and Liberté platforms) and second-generation DES; cobalt-chromium EESs (Xience V or Prime), platinum–chromium EESs (Promus Element, Boston Scientific), phospholipid-based zotarolimus-eluting stents (ZES; Endeavor, Boston Scientific), Biolinx polymer ZESs (ZES-R; Resolute, Medtronic, CA), and biodegradable polymer biolimus-eluting stents (Biosensors).

Inclusion and Exclusion Criteria

Our inclusion criteria were (1) randomized controlled trials comparing different generation DES to BMS or to each other (first-generation DES versus BMS, first-generation DES versus second-generation DES, and second-generation DES versus BMS) in primary PCI; (2) follow-up of ≥26 months; (3) enrollment of ≥50 patients; and (4) ability to report the outcomes of interest. Studies were excluded if any of the following criteria applied: (1) duplicated publication; (2) registries, observational studies, and post hoc analysis; (3) trials using balloon angioplasty, drug-eluting balloons, new BMS platforms or trials done in comparison with coronary artery bypass graft surgery.

Study Outcomes

Safety outcomes were death, MI and stent thrombosis (definite or probable stent thrombosis). TVR was the efficacy outcome.
Definite stent thrombosis was defined as an ischemic syndrome and thrombosis within the stented segment confirmed by angiography or pathology. Probable stent thrombosis was defined as any unexplained death within 30 days after the index procedure or any MI related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis. The definitions for definite or probable stent thrombosis, MI, and TVR were in accordance with the Academic Research Consortium criteria.

Data Extraction
We extracted characteristics of the trials, patients, and interventions, including study design, length of follow-up, primary end point,
## Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Stent Type</th>
<th>Sex (M, %)</th>
<th>Age, y</th>
<th>Hpt, %</th>
<th>DM, %</th>
<th>Hpl, %</th>
<th>D-to-B Time (h±SD)</th>
<th>LM, %</th>
<th>LAD, %</th>
<th>LCX, %</th>
<th>RCA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPHOON</strong>&lt;sup&gt;10&lt;/sup&gt;</td>
<td>SES</td>
<td>79</td>
<td>58±12</td>
<td>37</td>
<td>16</td>
<td>41</td>
<td>37 min*</td>
<td>N/A</td>
<td>50</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>BMS</td>
<td>78</td>
<td>61±12</td>
<td>43</td>
<td>17</td>
<td>44</td>
<td>38 min*</td>
<td>41</td>
<td>15</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>STRATEGY</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td>SES</td>
<td>77</td>
<td>62±8</td>
<td>55</td>
<td>17</td>
<td>N/A</td>
<td>70 (55–90) min</td>
<td>N/A</td>
<td>49</td>
<td>17</td>
<td>33</td>
</tr>
<tr>
<td>BMS</td>
<td>69</td>
<td>63±7</td>
<td>50</td>
<td>12</td>
<td>47</td>
<td>67 (53–110) min</td>
<td>41</td>
<td>21</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASSION</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>SES</td>
<td>74</td>
<td>61±12</td>
<td>31</td>
<td>10</td>
<td>23</td>
<td>180±102 min</td>
<td>0.6</td>
<td>50</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>BMS</td>
<td>78</td>
<td>61±13</td>
<td>32</td>
<td>12</td>
<td>28</td>
<td>178±108 min</td>
<td>0.2</td>
<td>49</td>
<td>10</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td><strong>SESAMI</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td>SES</td>
<td>80</td>
<td>63±12</td>
<td>54</td>
<td>18</td>
<td>63</td>
<td>3 (3–7) h</td>
<td>N/A</td>
<td>47</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>BMS</td>
<td>80</td>
<td>62±12</td>
<td>59</td>
<td>24</td>
<td>65</td>
<td>4 (3–6) h</td>
<td>53</td>
<td>13</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MISSION</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>SES</td>
<td>75</td>
<td>59±11</td>
<td>30</td>
<td>13</td>
<td>23</td>
<td>183 (33–258) min</td>
<td>N/A</td>
<td>55</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>BMS</td>
<td>81</td>
<td>59±12</td>
<td>26</td>
<td>7</td>
<td>16</td>
<td>195 (130–198) min</td>
<td>56</td>
<td>12</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASEO</strong>&lt;sup&gt;15&lt;/sup&gt;</td>
<td>SES</td>
<td>71</td>
<td>62±17</td>
<td>27</td>
<td>23</td>
<td>N/A</td>
<td>43±14 min</td>
<td>N/A</td>
<td>51</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>BMS</td>
<td>69</td>
<td>63±15</td>
<td>24</td>
<td>26</td>
<td>N/A</td>
<td>44±14 min</td>
<td>50</td>
<td>23</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gao et al</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td>SES</td>
<td>84</td>
<td>58±12</td>
<td>53</td>
<td>20</td>
<td>27</td>
<td>N/A</td>
<td>N/A</td>
<td>54</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>BMS</td>
<td>42</td>
<td>60±11</td>
<td>50</td>
<td>12</td>
<td>28</td>
<td>41</td>
<td>21</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SELECTION</strong>&lt;sup&gt;24&lt;/sup&gt;</td>
<td>SES</td>
<td>85</td>
<td>59.7*</td>
<td>38</td>
<td>8</td>
<td>33</td>
<td>120±69 min</td>
<td>0</td>
<td>55</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>BMS</td>
<td>85</td>
<td>61.7*</td>
<td>55</td>
<td>18</td>
<td>33</td>
<td>118±100 min</td>
<td>2.5</td>
<td>43</td>
<td>13</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td><strong>MISSON</strong>&lt;sup&gt;16&lt;/sup&gt;</td>
<td>SES</td>
<td>75</td>
<td>59±11</td>
<td>30</td>
<td>13</td>
<td>23</td>
<td>N/A</td>
<td>N/A</td>
<td>55</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>BMS</td>
<td>78</td>
<td>61±12</td>
<td>26</td>
<td>7</td>
<td>16</td>
<td>195 (130–198) min</td>
<td>56</td>
<td>12</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASEO</strong>&lt;sup&gt;25&lt;/sup&gt;</td>
<td>SES</td>
<td>71</td>
<td>62±17</td>
<td>27</td>
<td>23</td>
<td>N/A</td>
<td>43±14 min</td>
<td>N/A</td>
<td>51</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>BMS</td>
<td>69</td>
<td>63±15</td>
<td>24</td>
<td>26</td>
<td>N/A</td>
<td>44±14 min</td>
<td>50</td>
<td>23</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HAAMU-STENT</strong>&lt;sup&gt;19&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>COMFORTABLE-AMI</strong>&lt;sup&gt;9&lt;/sup&gt;</td>
<td>SES</td>
<td>78</td>
<td>60±11</td>
<td>29</td>
<td>9</td>
<td>28</td>
<td>162 min*</td>
<td>N/A</td>
<td>58</td>
<td>17</td>
<td>44</td>
</tr>
<tr>
<td>BMS</td>
<td>75</td>
<td>61±11</td>
<td>29</td>
<td>11</td>
<td>28</td>
<td>164 min*</td>
<td>36</td>
<td>17</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HORIZONS-AMI</strong>&lt;sup&gt;27&lt;/sup&gt;</td>
<td>SES</td>
<td>77</td>
<td>59.9±11</td>
<td>51</td>
<td>16</td>
<td>42</td>
<td>4 (3–6) h</td>
<td>0.6</td>
<td>50</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>BMS</td>
<td>76</td>
<td>59.3±11</td>
<td>52</td>
<td>15</td>
<td>41</td>
<td>4 (3–6) h</td>
<td>0.6</td>
<td>49</td>
<td>10</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td><strong>EXAMINATION</strong>&lt;sup&gt;8&lt;/sup&gt;</td>
<td>SES</td>
<td>61</td>
<td>84±5</td>
<td>46</td>
<td>18</td>
<td>47</td>
<td>N/A</td>
<td>&lt;1</td>
<td>42</td>
<td>14</td>
<td>42</td>
</tr>
<tr>
<td>BMS</td>
<td>82</td>
<td>82±5</td>
<td>51</td>
<td>16</td>
<td>40</td>
<td>N/A</td>
<td>&lt;1</td>
<td>39</td>
<td>15</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td><strong>ZEST-AMI</strong>&lt;sup&gt;11&lt;/sup&gt;</td>
<td>SES</td>
<td>78</td>
<td>61±11</td>
<td>42</td>
<td>28</td>
<td>48</td>
<td>3±3 h</td>
<td>N/A</td>
<td>48</td>
<td>5</td>
<td>47</td>
</tr>
<tr>
<td>BMS</td>
<td>70</td>
<td>68±5</td>
<td>46</td>
<td>16</td>
<td>57</td>
<td>236 (163–400) min</td>
<td>0.2</td>
<td>40</td>
<td>15</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td><strong>KROMER</strong>&lt;sup&gt;14&lt;/sup&gt;</td>
<td>SES</td>
<td>76</td>
<td>60±13</td>
<td>39</td>
<td>20</td>
<td>31</td>
<td>200±189 min</td>
<td>N/A</td>
<td>59</td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>BMS</td>
<td>79</td>
<td>59±12</td>
<td>42</td>
<td>23</td>
<td>31</td>
<td>211±251 min</td>
<td>54</td>
<td>9</td>
<td>37</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEZE</strong>&lt;sup&gt;13&lt;/sup&gt;</td>
<td>SES</td>
<td>49</td>
<td>60±13</td>
<td>48</td>
<td>18</td>
<td>22</td>
<td>120±115 min</td>
<td>N/A</td>
<td>60</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>BMS</td>
<td>69</td>
<td>62±12</td>
<td>54</td>
<td>26</td>
<td>28</td>
<td>94±53 min</td>
<td>56</td>
<td>8</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>XAMI</strong>&lt;sup&gt;12&lt;/sup&gt;</td>
<td>SES</td>
<td>73</td>
<td>61±11</td>
<td>30</td>
<td>8.9</td>
<td>N/A</td>
<td>71 (60–80) min</td>
<td>0.2</td>
<td>39</td>
<td>19</td>
<td>42</td>
</tr>
<tr>
<td>BMS</td>
<td>75</td>
<td>62±11</td>
<td>30</td>
<td>11</td>
<td>N/A</td>
<td>60 (60–70) min</td>
<td>0.5</td>
<td>43</td>
<td>20</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

*BMS indicates bare metal stent; COMFORTABLE-AMI, Comparison of Biolimus Eluted From a Erodable Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction; D-to-B, door-to-balloon time; DEBATER, Comparison of Drug Eluting and Bare Metal stents With or Without Abciximab in ST-Elevation Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; DM, diabetes mellitus; EES, everolimus-eluting stent; EXAMINATION, Clinical Evaluation of the Xience V stent in Acute Myocardial InfarcTion; GRACIA-3, Role Of The Paclitaxel-eluting Stent and Tirofiban in Patients With ST-Elevation Myocardial Infarction Undergoing Postfibrinolysis Angioplasty; HAAMU-STENT, Comparison Of Paclitaxel-Eluting with Bare Metal Stents in Acute Myocardial Infarction; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; Hpl, hyperlipidemia; Hpt, hypertension; KROMER, Korean Multicenter Endeavor acute myocardial infarction trial; LAB, left anterior descending artery; LCC, left circumflex artery; LM, left main coronary artery; MISSION, MISSION! Intervention Study; MULTISTRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; N/A, not applicable; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting vs Conventional Stent in Myocardial Infarction with ST-Segment Elevation; PES, paclitaxel-eluting stent; RCA, right coronary artery; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Stent vs Conventional Stent in Acute Myocardial Infarction; SESAMI, Sirolimus-Eluting Stent vs Bare-Metal Stent in Acute Myocardial Infarction; SEZE, Sirolimus eluting and Zotarolimus eluting stent in acute myocardial infarction; STRATEGY, Tirofiban and Sirolimus-Eluting Stent vs Abciximab With Bare-Metal Stent for Acute Myocardial Infarction; TYPHOON, Trial to Assess the Use of Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty; XAMI, Xience V vs Cypher Stent in Primary PCI for Acute Myocardial Infarction; ZES, zotarolimus-eluting stent; and ZEST-AMI, Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent vs Sirolimus-Eluting Stent vs Paclitaxel-Eluting Stent for Acute Myocardial Infarction.

*Median time.
components of methodological quality, and source of funding, sex, hypertension status, diabetes mellitus status, hyperlipidemia status, stent type, and the recommended dual antiplatelet duration per protocol as shown in Tables 1 and 2. As components of the methodological quality, we assessed the source of funding, concealment of allocation, blinding of investigators adjudicating clinical events, and the inclusion of all the individuals in the analysis according to the intention-to-treat principle. Concealment of allocation was considered adequate if investigators responsible for the selection of patients did not know before allocation which treatment was next in line (central randomization, sealed, opaque, sequentially numbered assignment envelopes, etc.). The analysis was considered according to the intention-to-treat principle if all the randomized patients were analyzed in the group they were assigned to regardless of which treatments were received. The methodological characteristics of the clinical trials used are not clearly shown in Table 3. Briefly, 11 trials reported use of a concealed allocation method; 12 trials had blinded adjudication; all studies reported the number of patients; if there were any, lost-to-follow-up and analysis were performed on the intention-to-treat principle in 13 studies. A drug or device company sponsored 6 studies, and in 8 studies the funding source was unclear. Figure 1 shows the schematic of network used in this meta-analysis.

**Statistical Analysis**

Meta-analysis was performed using the metan function in Stata version 12.1 (Stata Corp, College Station, TX). Fixed effects modeling was primarily used to conduct outcomes meta-analysis from the included studies. Random effect modeling was used in instances of significant statistical heterogeneity (I²<50% with P<0.05). Publication biases were assessed using the funnel plot method and Egger regression asymmetry testing. Separate analyses were performed for each of the treatment comparisons (BMS versus first-generation DES, BMS versus second-generation DES, and first-generation DES versus second-generation DES) using standard meta-analytic techniques described above. For the purposes of this analysis, the comparison between second-generation DES and BMS contributed to the direct evidence, and the other 2 comparisons contributed to the indirect evidence.
evidence. Network meta-analysis was used to combine all the available trial evidence into an internally consistent set of estimates although still respecting the randomization in the evidence. In addition, we used the network meta-analysis to pool the relative treatment effect using direct and indirect evidences and provide treatment effect of each intervention relative to every other whether they had been directly compared in trials. The event rates from the indirect comparisons (BMS versus first-generation DES or first-generation DES versus second-generation DES) and direct comparisons (second-generation DES versus BMS) were used to perform the network meta-analysis. Indirect comparisons were undertaken by performing separate pooled analyses on the individual randomized trial comparisons. Each comparison yielded discrete odds ratios (ORs) and SEs. The log-transformed ORs from the 2 indirect comparisons were used to estimate the pooled log-transformed ORs. The SE of the pooled log-transformed OR was estimated from the square root of the sum of squared SEs of individual comparisons. Subsequently, a weighted combination of the results from the indirect and the direct comparisons was computed as an inverse variance weighted average.

Results

We screened the title or abstract of 2357 potentially eligible abstracts or publications, and 2287 articles did not meet the inclusion criteria and were excluded. We chose 70 articles for detailed review of the abstract and article, and 21 trials met our inclusion criteria as shown in Figure 1. The main characteristics of the 12866 patients enrolled in 21 trials are shown in Table 1. A loading dose of 300 to 600 mg of clopidogrel was administered before PCI, and the shortest and longest durations of dual antiplatelet therapy (DAPT) were 3 and 12 months, respectively. Patient baseline clinical characteristics are described in Table 2. Most patients were middle-aged males with a high incidence of cardiovascular risk factors. The most common infarct-related vessel was the left anterior descending artery, followed by the right coronary and left circumflex arteries.

Mortality

Seventeen studies (15 with indirect evidence and 2 with direct evidence) included 4767 patients contributed to the analysis for 30 days, and 11316 patients contributed to the analysis at 1 year for mortality. There was no difference in cardiac mortality with the use of second-generation DES when compared with BMS at 30 days or 1 year in primary PCI as shown in Figures 2 and 3.

Myocardial Infarction

Twelve studies (10 with indirect evidence and 2 with direct evidence) including 4050 patients contributed to the analysis for 30 days, and 10757 patients contributed to the analysis for 1 year for MI. There was no difference in the 30-day incidence of MI with second-generation DES when compared with BMS. However, the use of second-generation DES was associated with 70% reduction in the incidence of MI at 1 year follow-up as shown in Figures 2 and 4.

Stent Thrombosis

Ten studies (9 studies with indirect evidence and 1 with direct evidence) with 5668 patients contributed to the analysis of 30-day stent thrombosis. Seventeen studies (15 studies with indirect evidence and 2 with direct evidence) with 10991 patients contributed to the analysis of 1-year stent thrombosis. The use of second-generation DES was associated with significant reduction in the incidence of definite (OR, 0.3; 95% confidence interval, 0.11–0.83) and definite and probable stent thrombosis as shown in Figures 2 and 5. Moreover, there was a significant 64% reduction in the incidence of early stent thrombosis and a 51% reduction in the incidence of late stent thrombosis with the use of second-generation DES when compared with BMS as shown in Figure 5II. In addition, after exclusion of patients from Asia (where reported rates of stent thrombosis are low) and the COMFORTABLE-AMI trial (not a federal drug administration approved stent), there was still a significantly lower incidence of stent thrombosis with second-generation DES when compared with BMS (OR, 0.20; 95% confidence interval, 0.34–0.78). We excluded the EXAMINATION trial and noted a nonsignificant 43% reduction in the incidence of stent thrombosis (OR, 0.57; 95% confidence interval, 0.30–1.0) at 1 year.

Target Vessel Revascularization

Twenty-one studies (19 with indirect evidence and 2 with direct evidence) with 3510 patients contributed to the analysis...
### MORTALITY

#### A DES-I and BMS

<table>
<thead>
<tr>
<th>Study</th>
<th>DES-I Mortality</th>
<th>BMS Mortality</th>
<th>OR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>TYPHOON</td>
<td>12/355</td>
<td>17/357</td>
<td>0.70 (0.33, 1.49)</td>
<td>12.81</td>
</tr>
<tr>
<td>DEBATER</td>
<td>11/424</td>
<td>10/446</td>
<td>1.16 (0.46, 2.76)</td>
<td>7.42</td>
</tr>
<tr>
<td>HORIZONS-AMI</td>
<td>78/2257</td>
<td>26/749</td>
<td>1.00 (0.63, 1.56)</td>
<td>29.48</td>
</tr>
<tr>
<td>STRATEGY</td>
<td>7/87</td>
<td>8/88</td>
<td>0.88 (0.30, 2.53)</td>
<td>5.72</td>
</tr>
<tr>
<td>PASSION</td>
<td>14/310</td>
<td>20/309</td>
<td>0.69 (0.34, 1.38)</td>
<td>14.99</td>
</tr>
<tr>
<td>GRACIA-3</td>
<td>21/217</td>
<td>15/216</td>
<td>1.44 (0.72, 2.87)</td>
<td>10.62</td>
</tr>
<tr>
<td>L Llora et al</td>
<td>2/60</td>
<td>2/54</td>
<td>1.37 (0.22, 8.52)</td>
<td>1.56</td>
</tr>
<tr>
<td>HAAMU-STENT</td>
<td>8/70</td>
<td>4/75</td>
<td>1.97 (0.75, 6.88)</td>
<td>2.89</td>
</tr>
<tr>
<td>SESAMI</td>
<td>3/160</td>
<td>7/160</td>
<td>0.82 (0.41, 1.64)</td>
<td>5.37</td>
</tr>
<tr>
<td>MISSION</td>
<td>2/158</td>
<td>4/152</td>
<td>0.47 (0.09, 2.63)</td>
<td>3.15</td>
</tr>
<tr>
<td>PASEO</td>
<td>8/180</td>
<td>6/90</td>
<td>0.57 (0.18, 1.74)</td>
<td>6.01</td>
</tr>
<tr>
<td>Overall (I² sq: 0%, p&lt;0.09)</td>
<td></td>
<td></td>
<td>0.92 (0.72, 1.19)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

#### Odds Ratio

**Favours DES-I**

**Favours BMS**

- A
- B
- C

### Figure 3

Figure 3. Odds ratio (OR) of overall 1-year mortality of all the randomized trials in this network meta-analysis. **A**, Randomized trials comparing drug-eluting stent (DES-I) to bare-metal stent (BMS). **B**, Randomized trials comparing DES-II and DES-I. **C**, Randomized trials comparing DES-II to BMS. CI indicates confidence interval; COMFORTABLE-AMI, Comparison of Biolimus Eluted From a Erodable Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction; DEBATER, Comparison of Drug Eluting and Bare Metal stents With or Without Abciximab in ST-Elevation Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; EXAMINATION, Clinical Evaluation of the Xience V stent in Acute Myocardial Infarction; GRACIA-3, Role Of The Paclitaxel-Eluting Stent and Tirofiban in Patients With ST-Elevation Myocardial Infarction Undergoing Postfibrinolysis Angioplasty; HAAMU-STENT, Comparison Of Paclitaxel-Eluting with Bare Metal Stents in Acute Myocardial Infarction; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; KROMER, Korean Multicenter Endeavor acute myocardial infarction trial; MISSION, MISSION! Intervention Study; MULTISTRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting vs Conventional Stent in Myocardial Infarction with ST-Egment Elavation; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Stent vs Conventional Stent in Acute Myocardial Infarction; SESAMI, Sirolimus-Eluting Stent vs Bare-Metal Stent in Acute Myocardial Infarction; SEIZE, Sirolimus eluting and Zotarolimus eluting stent in acute myocardial infarction; STRATEGY, Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare-Metal Stent for Acute Myocardial Infarction; TYPHOON, Trial to Assess the Use of Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty; XAMI, Xience V vs Cypher Stent in Primary PCI for Acute Myocardial Infarction; and ZEST-AMI, Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent vs Sirolimus-Eluting Stent vs Paclitaxel-Eluting Stent for Acute Myocardial Infarction.
Figure 4. Odds ratio (OR) of overall 1-year myocardial infarction of all the randomized trials in this network meta-analysis. A, Randomized trials comparing drug-eluting stent (DES)-I to bare-metal stent (BMS). B, Randomized trials comparing DES-II and DES-I. C, Randomized trials comparing DES-II to BMS. CI indicates confidence interval; COMFORTABLE-AMI, Comparison of Biolimus Eluted From a Erodable Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction; DEBATER, Comparison of Drug Eluting and Bare Metal stents With or Without Abciximab in ST-Elevation Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; EXAMINATION, Clinical Evaluation of the Xience V stent in Acute Myocardial Infarction; GRACIA-3, Role Of The Paclitaxel-Eluting Stent and Tirofiban in Patients With ST-Elevation Myocardial Infarction Undergoing Postfibrinolysis Angioplasty; HAAMU-STENT, Comparison Of Paclitaxel-Eluting with Bare Metal Stents in Acute Myocardial Infarction; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; KROMER, Korean Multicenter Endeavor acute myocardial infarction trial; MISSION, MISSION! Intervention Study; MULTISTRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting vs Conventional Stent in Myocardial Infarction with ST-Segment Elevation; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Stent vs Conventional Stent in Acute Myocardial
Discussion

This is the first network meta-analysis comparing the safety and efficacy outcomes between second-generation DES and BMS for the treatment of STEMI in primary PCI. During the first year, the use of second-generation DES was associated with significantly lower risk for 30-day and 31–365-day TVR compared with BMS. These risk reductions were substantial at 64% at 30 days and 51% between 31 days and 1 year with the use of second-generation DES when compared with BMS. In addition, there were significantly lower rates of TVR and MI at 1 year with the use of second-generation DES when compared with BMS. There were no differences in the overall mortality at 30 days or 1 year with the use of either stent platform for primary PCI.

An important finding of this study is the significantly lower risk of stent thrombosis with second-generation DES when compared with BMS in ST-segment–elevation myocardial infarction. Although DES are more effective at reducing restenosis, their safety has continued to be questioned in view of the ongoing propensity of first-generation DES for late stent thrombosis.33 Polymer hypersensitivity reactions, positive remodeling with late acquired mal-apposition, delayed endothelial healing and endothelial dysfunction seem to be the possible causes for stent thrombosis with first-generation DES.34 Awareness of these safety concerns resulted in a decrease in the use of first-generation DES, especially in the treatment of STEMI since 2006. In most randomized comparisons, second-generation DES have been compared with one another or rarely with BMS, restricting a full comparative understanding of their outcomes.9 In this regard, the EXAMINATION trial was the first trial to compare a second-generation DES with BMS during primary PCI and reported lower rates of stent thrombosis. However, with only 1504 randomized patients, this trial was not powered to detect differences in stent thrombosis.8 This large-scale, comprehensive network meta-analysis included 21 trials, including 12,866 patients and was capable of revealing important safety and efficacy differences between second-generation DES and BMS. Specifically, second-generation DES emerged as the device with significantly lower incidence of stent thrombus and MI in comparison with BMS. In addition, second-generation DES resulted in a significant reduction in TVR at 1 year. These findings suggest that second-generation DES are safer and more effective and may be the stent of choice for primary PCI for STEMI.

Patients with STEMI are at increased risk of stent thrombosis when compared with patients with stable coronary artery disease after both DES and BMS implantation. The observed differential timing of stent thrombosis suggests differences in the underlying pathophysiological pathways. Early stent thrombosis is related to pronounced activation of platelets and the coagulation cascade in the milieu of acute coronary thrombosis. In this context, the permanent polymers of first-generation DES (Cypher sirolimus-eluting stent and Taxus paclitaxel-eluting stent) are noted to induce granulomas, hypersensitivity reactions, fibrin deposition, and resulting thrombogenic reactions.35 Second-generation DES (Xience [EES], Endeavor [ZES], Resolute [ZES-R], and Biolimus A9 [biolimus-eluting stent]) have a biodegradable polymer (biolimus-eluting stent) or polymers that induce less inflammation because they are biomimetic containing phosphatidyl choline (ZES and ZES-R), a component of the cell wall or biocompatible containing acrylic and fluorinated polymers (Xience V and EES). In addition, DES-II have a much thinner coating of permanent polymer and strut thickness than DES-I making them much more deliverable and allowing for complete endothelial coverage.36 These changes in polymer may be most beneficial in patients at the highest risk for stent thrombosis (like ST-segment–elevation MI), and similar reduction in stent thrombosis may be seen in stable syndromes when a large enough number of patients are studied.

Late stent thrombosis is thought to be a chronic process because of delayed arterial healing and vessel remodeling resulting from continual local inflammation from persistence of durable polymers and long-term effects of eluted drugs.37,38 In patients with STEMI, certain anatomic and pathophysiologic peculiarities increase risk for stent thrombosis. Furthermore, autopsy data suggest a differential healing response of first-generation DES when compared with BMS when implanted into the plaques of patients with STEMI.39 In addition, incomplete stent apposition has also been recognized as an important morphological substrate for late stent thrombosis.39 Incomplete stent apposition is frequently observed in patients with STEMI treated with DES and may be related to jailed thrombus with subsequent resolution or vessel remodeling in response to the drug or polymer as seen on intravascular ultrasound and optical coherence tomographic imaging.40 All of these factors may be of particular relevance on discontinuation of DAPT during long-term follow-up. The lower rates of stent thrombosis with the second-generation DES could be attributed to advances in the permanent polymers used to enhance drug delivery and still provide an opportunity for endothelial coverage. Interestingly, optical coherence tomography have shown greater endothelial coverage of stents with second-generation DES (EES and ZES) with a 3-month mean stent strut coverage of 99.9% when comparable with that observed at 3 months with BMS.41 These benefits can even be extended to apposed or overlapping stents incompletely, which is particularly relevant in STEMI where eventual dissolution of the thrombus behind the struts might lead to a high incidence of late acquired mal-apposition.42 In addition, different antiproliferative agents used in second-generation DES (zotarolimus, everolimus, and biolimus) allow more rapid endothelialization resulting in less exposure of blood to exposed thrombogenic
Figure 5. Odds ratio (OR) of overall 30-day (I) and 31-day to 1-year (II) stent thrombosis of all the randomized trials in this network meta-analysis. A, Randomized trials comparing drug-eluting stents (DES-I) to bare-metal stents (BMS). B, Randomized trials comparing DES-II and DES-I. C, Randomized trials comparing DES-II to BMS. COMFORTABLE-AMI indicates Comparison of Biolimus Eluted From a Erodable Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction; DEBATER, Comparison of Drug Eluting and Bare Metal stents With or Without Abciximab in ST-Elevation Myocardial Infarction; DEDICATION, Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; EXAMINATION, Clinical Evaluation of the Xience V stent in Acute Myocardial INfArcTion; GRACIA-3, Role Of The Paclitaxel-Eluting Stent and Tirofiban in Patients with ST-Elevation Myocardial Infarction Undergoing Postfibrinolysis Angioplasty; HAAMU-STENT, Comparison Of Paclitaxel-Eluting with Bare Metal Stents in Acute Myocardial Infarction; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; KROMER, Korean Multicenter Endeavor acute myocardial infarction trial; MISSION, MISSION! Intervention Study; MULTISTRATEGY, Multicenter Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting vs Conventional Stent in Myocardial Infarction; SEZAM, Sirolimus-Eluting Stent vs Bare-Metal Stent in Acute Myocardial Infarction; SIEMENS, Sirolimus-Eluting Stent vs Bare-Metal Stent in Acute Myocardial Infarction; TYPHOON, Trial to Assess the Use of Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty; XAMI, Xience V vs Cypher Stent in Primary PCI for Acute Myocardial Infarction; and ZEST-AMI, Comparison of the Efficacy and Safety of Zotarolimus-Eluting Stent vs Sirolimus-Eluting Stent vs Paclitaxel-Eluting Stent for Acute Myocardial Infarction.
stent struts, which can potentially precipitate stent thrombosis.43 Furthermore, in vivo optical coherence tomography studies have noted significantly lower rates of uncovered stent struts and near-complete strut coverage (95%) in a stents with a biodegradable polymer when compared with a stents with a durable polymer (first-generation DES).40,46

We used a network meta-analysis to answer the clinical question “Should a BMS or second-generation DES be used for primary PCI”. This statistical method is particularly relevant when there are multiple treatment evidence structures with limited direct evidence addressing the research question at hand.45 A network meta-analysis allows us to create a cyclic evidence network where indirect evidence can augment evidence from direct comparisons. Although, the current American College of Cardiology/American Heart Association guidelines recommend the continuation of DAPT for 1 year when either a DES or BMS is implanted in primary PCI.10 It is well established that DAPT compliance is a significant predictor of stent thrombosis within the first 6 months.47 In addition, chronic DAPT use has been associated with bleeding complications, which adversely affect compliance. Recent studies have shown bleeding events occurring in 32.2% patients leading to a discontinuation of DAPT in ≤50% cases.48 In addition, patients who have acute coronary syndromes and particularly ST-segment–elevation MI are at a 3-fold increased risk for stent thrombosis.49 We think that the type of stent implanted matters in mitigating this risk, and our data provide some evidence for safety and efficacy in this setting.

This meta-analysis has some limitations. First, as with any meta-analysis, our report shares the limitations of the original studies. Moreover, network meta-analysis assumes that patients enrolled in individual studies could be sampled from the same theoretical population, and similar comparators between different trials have a consistent risk–benefit ratio. However, the robustness of our findings is evident in view of the strong clinical and statistical findings obtained from the analysis. Second, many of the end points had a small number of events that may reduce the overall precision of the analysis. This may explain the discrepancy between individual end points likely to contribute to mortality, and the lack of difference in mortality is seen. Third, we include trials using BMSs using different geometries and strut thickness, which may be associated with different rates of stent thrombosis. Fourth, different durations of DAPT in patients treated with DES versus BMS are a possible confounding factor in this study. Fifth, some of the trials included in this study have not been published in peer-reviewed journals; therefore, data for the primary and secondary end points were obtained from presentations at international meetings. Sixth, we do not have any data beyond 1 year in the direct comparison groups, and we are not able to ascertain the rates of late stent thrombosis with either stent groups. Finally, evolving interventional techniques and newer antithrombotic agents might have affected risk of stent thrombosis over time.

In conclusion, the use of second-generation DES in primary PCI for STEMI is associated with significant reductions in risk for stent thrombosis, MI and TVR in the first year. The use of second-generation DES in primary PCI for STEMI was not associated with adverse events when compared with BMS.

Disclosures

None.

References


Stent Thrombosis With Second-Generation Drug-Eluting Stents Compared With Bare-Metal Stents: Network Meta-Analysis of Primary Percutaneous Coronary Intervention Trials in ST-Segment–Elevation Myocardial Infarction

Femi Philip, Shikhar Agarwal, Matthew C. Bunte, Sachin S. Goel, E. Murat Tuzcu, Stephen Ellis and Samir R. Kapadia

Circ Cardiovasc Interv. 2014;7:49-61; originally published online November 26, 2013; doi: 10.1161/CIRCINTERVENTIONS.113.000412

An erratum has been published regarding this article. Please see the attached page for:
/content/7/1/132.full.pdf
Correction


Title “Stent Thrombosis With Second-Generation Drug-Eluting Stents Compared With Bare-Metal Stents: Network Meta-Analysis of Primary Percutaneous Coronary Intervention Trials in ST-Segment–Elevation Myocardial Infarction” was changed to “Stent Thrombosis With Second-Generation Drug-Eluting Stents Compared With Bare-Metal Stents: Network Meta-Analysis of Primary Percutaneous Coronary Intervention Trials in ST-Segment–Elevation Myocardial Infarction.”

Dr Bunte appeared as Matthew Bunte, MD in the author byline. This has been corrected to Matthew C. Bunte, MD.

Figures 3–5 were replaced. The original published figures contained errors in the headings.

This has been corrected in the current version of the article.