Outcomes With Intravascular Ultrasound-Guided Stent Implantation

A Meta-Analysis of Randomized Trials in the Era of Drug-Eluting Stents

Islam Y. Elgendy, MD*; Ahmed N. Mahmoud, MD*; Akram Y. Elgendy, MD; Anthony A. Bavry, MD, MPH

Background—In the era of drug-eluting stents, it is unknown if intravascular ultrasound (IVUS) guidance for percutaneous coronary intervention should be routinely endorsed. This study aimed to determine if IVUS-guided stent implantation is associated with improved outcomes.

Methods and Results—Randomized trials that reported clinical outcomes and compared routine IVUS-guided stent implantation with an angiography-guided approach in the era of drug-eluting stents were included. Summary estimates were constructed primarily using the Peto model. Seven trials with 3192 patients were analyzed. The mean length of the coronary lesions was $32 \text{ mm}$. At a mean of 15 months, routine IVUS-guided percutaneous coronary intervention was associated with a reduction in the risk of major adverse cardiac events ($6.5\%$ versus $10.3\%$; odds ratio, $0.60$; $95\%$ confidence interval, $0.46$–$0.77$; $P<0.0001$), mainly because of reduction in the risk of ischemia-driven target lesion revascularization ($4.1\%$ versus $6.6\%$; odds ratio, $0.60$; $95\%$ confidence interval, $0.43$–$0.84$; $P=0.003$). The risk of cardiovascular mortality ($0.5\%$ versus $1.2\%$; odds ratio, $0.46$; $95\%$ confidence interval, $0.21$–$1.00$; $P=0.05$), and stent thrombosis ($0.6\%$ versus $1.3\%$; odds ratio, $0.49$; $95\%$ confidence interval, $0.24$–$0.99$; $P=0.04$) also appeared to be lower in the IVUS-guided group.

Conclusions—In the era of drug-eluting stents for diffuse coronary lesions, IVUS-guided percutaneous coronary intervention is superior to angiography-guided percutaneous coronary intervention in reducing the risk of major adverse cardiac events. This is primarily because of reduction in the risk of ischemia-driven target lesion revascularization. This analysis also suggests that risk of cardiovascular mortality and stent thrombosis might be lower with an IVUS-guided approach.

(Circ Cardiovasc Interv. 2016;9:e003700. DOI: 10.1161/CIRCINTERVENTIONS.116.003700.)

Key Words: coronary artery disease ■ drug-eluting stents ■ meta-analysis ■ percutaneous coronary intervention ■ ultrasonography, interventional

Intravascular ultrasound (IVUS) is a useful tool for optimization of stent implantation by insuring good stent expansion and apposition.1–5 Despite this benefit, routine IVUS is limited by cost considerations and additional time that is needed to perform the procedure. It is also known which coronary lesion characteristics are best served by IVUS. A meta-analysis of randomized trials in the era of bare-metal stents concluded that IVUS guidance was associated with a reduction in major adverse cardiac events (MACE) and repeat revascularization with a neutral effect on death and myocardial infarction (MI).6 Percutaneous coronary intervention (PCI) is currently performed with drug-eluting stents, which has significantly reduced the risk for restenosis, compared with bare-metal stents.7 A large-scale network meta-analysis demonstrated that all drug-eluting stents (and in particular second generation drug-eluting stents) reduce adverse events compared with bare-metal stents.8 Accordingly, in present day practice, there may be less need for a routine IVUS-guided PCI approach. Meta-analyses in the era of drug-eluting stents were influenced by including observational studies.9–13 Furthermore, the results of additional multicenter randomized trials have become available.14–16 Therefore, we aimed to conduct an updated comprehensive meta-analysis of randomized trials to evaluate clinical outcomes associated with IVUS-guided PCI compared with angiography-guided PCI in the era of drug-eluting stents.

Received February 8, 2016; accepted February 22, 2016.

From the Department of Medicine, University of Florida, Gainesville (I.Y.E., A.N.M., A.Y.E., A.A.B.); and North Florida/South Georgia Veterans Health System, Gainesville (A.A.B.).

*Drs IY Elgendy and Mahmoud contributed equally to this work.


Correspondence to Anthony A. Bavry, MD, MPH, Medical Service, Cardiology Section (111D), North Florida/South Georgia Veterans Health System (Malcom Randall Veterans Administration Medical Center), 1601 SW Archer Rd, Gainesville, FL 32608. E-mail anthony.bavry@va.gov

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Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org

DOI: 10.1161/CIRCINTERVENTIONS.116.003700
WHAT IS KNOWN

- Meta-analysis of randomized trials of bare-metal stents concluded that IVUS guidance was associated with a reduction in major adverse cardiac events (MACE) and repeat revascularization with a neutral effect on death and myocardial infarction but currently percutaneous coronary intervention (PCI) is performed with drug-eluting stents.
- Meta-analyses of IVUS in the era of drug-eluting stents were influenced by including observational studies.

WHAT THE STUDY ADDS

- This meta-analysis of randomized trials using drug-eluting stents demonstrated that IVUS-guided PCI is superior to angiography-guided PCI in reducing the risk of major adverse cardiac events. This is primarily because of reduction in the risk of ischemia-driven target lesion revascularization.

Methods

Data Sources

A computerized search of the Medline database without language restriction was performed from 2005 until February 2016 using the keywords and Medical Subject Heading: coronary, angiography and intravascular ultrasound, limited to clinical trial and human. In addition, the Web of Science, the Cochrane Register of Controlled Trials, major scientific sessions, and clinicaltrial.gov were also searched using the same keywords. The reference lists of the retrieved articles and prior meta-analyses were reviewed. This meta-analysis was registered at the PROSPERO international prospective register of systematic reviews (CRD42015029621).

Selection Criteria and Data Extraction

Clinical trials that randomized patients with obstructive coronary artery disease to either IVUS-guided PCI versus angiography-guided PCI were included. We required that the patients were treated with drug-eluting stents. We preferentially reported the outcomes at the longest reported follow-up time. We communicated with the corresponding authors when further article clarification was necessary. The quality of the included trials was evaluated based on the adequate description of treatment allocation, blinded outcome assessment, and description of loss to follow-up.

Two independent authors (A.N.M. and A.Y.E.) extracted data on study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Extracted data were verified by the first author (I.Y.E.). Discrepancies were resolved by consensus of the authors. For all clinical outcomes, the number of events that occurred in each arm of the trial was tabulated.

Outcomes and Definitions

The interventional angiographic outcomes assessed included postintervention minimum luminal diameter (MLD in millimeter), and postintervention percent diameter stenosis. The clinical outcomes evaluated were MACE as defined per the individual studies, all-cause mortality, cardiovascular mortality, spontaneous nonfatal myocardial infarction, ischemia-driven or clinically driven target lesion revascularization (TLR), ischemia-driven or clinically driven target vessel revascularization, and stent thrombosis. Stent thrombosis was defined as definite or probable according to the Academic Research Consortium.

Table 1. Baseline Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IVUS-XPL</th>
<th>CTO-IVUS</th>
<th>AIR-CTO</th>
<th>Tan et al</th>
<th>Kim et al</th>
<th>AVIO</th>
<th>HOME DES IVUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>700/700</td>
<td>201/201</td>
<td>115/115</td>
<td>61/62</td>
<td>269/274</td>
<td>142/142</td>
<td>105/105</td>
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<td>Second generation</td>
<td>Second generation</td>
<td>First/second generation</td>
<td>First generation</td>
<td>Second generation</td>
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<td>61/61</td>
<td>67/66</td>
<td>77/76</td>
<td>63/64</td>
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<td>59/60</td>
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<td>81/81</td>
<td>89/80</td>
<td>62/69</td>
<td>66/55</td>
<td>82/77</td>
<td>73/71</td>
</tr>
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<td>DM, %</td>
<td>36/37</td>
<td>35/34</td>
<td>30/27</td>
<td>34/30</td>
<td>32/30</td>
<td>24/27</td>
<td>42/45</td>
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<td>Stable angina, %</td>
<td>51/51</td>
<td>100/100</td>
<td>71/76</td>
<td>30/34</td>
<td>53/51</td>
<td>70/64</td>
</tr>
<tr>
<td></td>
<td>Unstable angina, %</td>
<td>35/32</td>
<td>0/0</td>
<td>9/10</td>
<td>70/66</td>
<td>38/39</td>
<td>30/26</td>
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<tr>
<td></td>
<td>ST-elevation MI, %</td>
<td>14/17</td>
<td>0/0</td>
<td>20/15‡</td>
<td>0/0</td>
<td>9/10</td>
<td>0/0</td>
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<td></td>
<td>LVEF, %</td>
<td>63/62</td>
<td>57/57</td>
<td>55/56</td>
<td>55/53</td>
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<td>12</td>
<td>24</td>
<td>24</td>
<td>12</td>
<td>24</td>
<td>18</td>
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</table>

Data are reported as intravascular ultrasound-guided/angiography-guided strategies. AIR-CTO indicates Study Comparing Angiography- vs. IVUS-Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CTO IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-Eluting Stents; DM, diabetes mellitus; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and NR, not reported.

*76% first generation, and 24% second generation.
†Non-ST-elevation acute coronary syndrome.
‡Acute myocardial infarction >24 hours.
Statistical Analysis

Outcomes were assessed using an intention-to-treat analysis. Standardized mean differences were used for continuous variables. Because we anticipated that some of clinical outcomes are rare; fixed effects summary odds ratios (OR) were performed primarily with a Peto model. Summary risk ratios were also constructed with a DerSimonian and Laird model as a secondary analysis. Statistical heterogeneity was studied using the I² statistic. Egger et al's method was used to estimate publication bias. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. All P values were 2-tailed, with statistical significance set at 0.05, and confidence intervals (CI) were calculated at the 95% level for the overall estimates effect. All analyses were performed using STATA software version 14 (STATA Corporation; College Station, TX).

For the outcome of MACE, a sensitivity analysis was performed: (1) limited to multicenter trials, (2) excluding trials that had any losses to follow-up, (3) excluding trials that exclusively enrolled patients with chronic total occlusions (CTO), and (4) excluding trials that exclusively implanted first generation drug-eluting stents. Random effects meta-regression analyses were prespecified for the outcome of MACE in relation to baseline lesion length, diabetes mellitus, and publication year.

Results

Included Studies

The electronic search yielded 241 articles that were screened by reviewing the title and abstract (Figure I in the Data Supplement). A total of 7 trials (n=3192) were included in the meta-analysis. The measures of the study quality are summarized in Table I in the Data Supplement. All the included studies were conducted in multiple centers except for Tan et al and Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance (HOME DES IVUS), which were single center studies. Two trials enrolled patients with CTO, whereas one trial treated complex lesions. The follow-up time ranged from 12 to 24 months. Overall, the weighted mean follow-up duration was 15 (±5) months. The baseline characteristics of the included studies are summarized in Table 1, whereas Table 2 reports the angiographic characteristics.

Overall, the mean lesion length was 32±5 mm. The baseline diameter stenosis was similar in the IVUS-guided PCI and the angiography-guided PCI (72% versus 73%). At baseline, the MLD was minimally larger in the IVUS-guided PCI group compared with the angiography-guided PCI group (0.92 versus 0.88, P<0.0001 respectively). Postdilation occurred in 63% of the IVUS-guided PCI group versus 47% of the angiography-guided group (P=0.0001). Only 1 study reported postintervention minimal stent cross-sectional area, which was higher in the IVUS-guided PCI group (5.9 versus 4.4 mm). IVUS-guided PCI versus angiography-guided PCI was associated with a larger postintervention MLD (standardized mean differences, 0.18; 95% CI, 0.05–0.36; P=0.04). IVUS-guided PCI was associated with a smaller postprocedural percent diameter stenosis (standardized mean differences, −0.17; 95% CI, −0.29 to −0.05; P=0.005) compared with angiography-guided PCI.

Table 2. Angiographic Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>IVUS-XPL14</th>
<th>CTO-IVUS15</th>
<th>AIR-CTO16</th>
<th>Tan et al16</th>
<th>Kim et al27</th>
<th>AVIO28</th>
<th>HOME DES IVUS29</th>
</tr>
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<tbody>
<tr>
<td>Coronary arteries</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD, %</td>
<td>65/60</td>
<td>42/47</td>
<td>44/37</td>
<td>NA*</td>
<td>62/68</td>
<td>53/49</td>
<td>56/54</td>
</tr>
<tr>
<td>LCX, %</td>
<td>14/15</td>
<td>14/16</td>
<td>21/15</td>
<td>NA*</td>
<td>15/13</td>
<td>NR</td>
<td>11/15</td>
</tr>
<tr>
<td>RCA, %</td>
<td>21/25</td>
<td>44/37</td>
<td>35/46</td>
<td>NA*</td>
<td>23/20</td>
<td>NR</td>
<td>29/24</td>
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<tr>
<td>Multivessel disease, %</td>
<td>67/70</td>
<td>NA</td>
<td>NA</td>
<td>NA*</td>
<td>41/38</td>
<td>NR</td>
<td>15/17</td>
</tr>
<tr>
<td>Bifurcating lesions, %</td>
<td>NR</td>
<td>NA</td>
<td>NA</td>
<td>NA*</td>
<td>0/0</td>
<td>23/27</td>
<td>NR</td>
</tr>
<tr>
<td>Chronic total occlusions, %</td>
<td>NR</td>
<td>100/100</td>
<td>100/100</td>
<td>NA*</td>
<td>0/0</td>
<td>14/18</td>
<td>NR</td>
</tr>
<tr>
<td>Reference vessel diameter, mm‡</td>
<td>2.9(0.5)/2.9(0.5)</td>
<td>2.7(0.4)/2.6(0.6)</td>
<td>2.7(0.4)/2.6(0.3)</td>
<td>NR</td>
<td>2.8/2.8†</td>
<td>2.7(0.5)/2.6(0.4)</td>
<td>3.2(0.6)/3.0(0.3)</td>
</tr>
<tr>
<td>Preintervention MLD, mm‡</td>
<td>0.8(0.4)/0.8(0.4)</td>
<td>NR</td>
<td>NR</td>
<td>1.9(0.2)/1.9(0.2)</td>
<td>1.0/0.9†</td>
<td>0.8(0.5)/0.7(0.5)</td>
<td>1.1(0.4)/1.0(0.4)</td>
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<tr>
<td>Preintervention diameter stenosis, %</td>
<td>71(14)/71(14)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>72(16)/76(16)</td>
<td>82(8)/79(9)</td>
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<tr>
<td>Lesion length, mm‡</td>
<td>35(11)/35(11)</td>
<td>36(17)/36(17)</td>
<td>28(18)/29(19)</td>
<td>NR</td>
<td>30/30†</td>
<td>27(16)/26(15)</td>
<td>18(7)/18(7)</td>
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<tr>
<td>Total stented length, mm‡</td>
<td>39(13)/39(12)</td>
<td>44(19)/42(18)</td>
<td>55(23)/52(25)</td>
<td>21(6)/18(5)</td>
<td>33/31†</td>
<td>24(7)/23(7)</td>
<td>24/22</td>
</tr>
<tr>
<td>Post-dilation, %</td>
<td>76/57</td>
<td>51/41</td>
<td>NR</td>
<td>23/9</td>
<td>48/43</td>
<td>88/68</td>
<td>24/0</td>
</tr>
</tbody>
</table>

Data are reported as intravascular ultrasound-guided/angiography-guided strategies. AIR-CTO indicates Study Comparing Angiography- vs. IVUS- Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CTO IVUS, Impact of Intravascular Ultrasound-Guided Chronic Total Occlusion Intervention With Drug-Eluting Stents; HOME DES IVUS, Long-Term Health Outcome and Mortality Evaluation After Invasive Coronary Treatment Using Drug Eluting Stents With or Without the IVUS Guidance; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; LAD, left anterior descending artery; LCX, left circumflex artery; MLD, minimum luminal diameter; NR, not reported; RCA, right coronary artery; and SD, standard deviation.

*This trial evaluated left main lesions.
†Median is reported.
‡Mean and standard deviation is reported.
Major Adverse Cardiac Events
All the included studies reported the incidence of MACE. The definition of MACE per the individual studies is reported in Table II in the Data Supplement. Compared with angiography-guided PCI, IVUS-guided PCI strategy was associated with a lower risk of MACE (6.5% versus 10.3%; OR, 0.60; 95% CI, 0.46–0.77; P=0.0001; I²=0%; Figure 1). There was no evidence of publication bias with Egger test (P=0.49). The sensitivity analyses yielded similar results: (1) limited to multicenter trials (OR, 0.60; 95% CI, 0.45–0.79; P<0.0001; I²=0%), (2) excluding trials with any losses to follow-up (OR, 0.55; 95% CI, 0.36–0.84; P=0.005; I²=0%), (3) excluding trials with exclusively enrolled patients with CTO (OR, 0.58; 95% CI, 0.43–0.79; P<0.0001; I²=0%), and (4) excluding trials that exclusively implanted first generation drug-eluting stents (OR, 0.57; 95% CI, 0.41–0.79; P=0.001; I²=0%).

To account for the possibility of a variable treatment effect with a longer follow-up time, we performed a subgroup analysis at 12 and 24 months, which demonstrated a similar effect (OR12 months=0.56; 95% CI, 0.40–0.77; P<0.0001; I²=0% and OR24 months=0.67; 95% CI, 0.46–0.97; P=0.03; I²=0%, respectively). Meta-regression analyses did not identify a difference in treatment effect based on lesion length, diabetes mellitus, or publication year (P=0.30, 0.74, and 0.17, respectively).

Other Outcomes
IVUS-guided PCI was associated with a significant reduction in the risk of TLR (4.1% versus 6.6%; OR, 0.60; 95% CI, 0.43–0.84; P=0.003, I²=0%). IVUS-guided PCI appeared to be associated with a lower risk of cardiovascular mortality (0.5% versus 1.2%; OR, 0.46; 95% CI, 0.21–1.00; P=0.05; I²=0%), and stent thrombosis (0.6% versus 1.3%; OR, 0.49; 95% CI, 0.24–0.99; P=0.04; I²=0%). The risk of myocardial infarction was nonsignificantly lower with IVUS-guided PCI (0.8% versus 1.5%; OR, 0.52; 95% CI, 0.26–1.02; P=0.06; I²=0%). Figure 2 demonstrates the forest plot for cardiovascular mortality, myocardial infarction, TLR, and stent thrombosis, whereas Table 3 summarizes the summary estimates for the outcomes of interest using Peto and DerSimonain Laird methods.

Discussion
This meta-analysis of 7 randomized trials in the era of drug-eluting stents with 3192 patients demonstrated that IVUS-guided PCI was associated with a significantly larger postintervention MLD, as well as a greater reduction in the diameter stenosis. IVUS-guided PCI was associated with a reduction in the risk of MACE (number needed to treat=26), primarily because of a reduction in ischemia or clinically driven TLR (number needed to treat=40) at a mean follow-up of 15 months. IVUS-guided PCI also appeared to be associated with a borderline lower risk of stent thrombosis and cardiovascular mortality. Although improved stent apposition might be expected to decrease
both of these outcomes, these were secondary outcomes with limited number of events, which reduced the power to detect a difference.

Prior meta-analyses in the era of drug-eluting stents were limited by inclusion of observational studies.9–13 The data analyzed from randomized trials in the earlier meta-analyses had failed to demonstrate the superiority of an IVUS-guided PCI approach because of limited number of randomized trials. By including the totality of data to date, this analysis showed the superiority of IVUS-guided PCI compared with angiography-guided PCI in the drug-eluting stent era. These results are applicable to the studied patient population, of which the most salient characteristic was diffuse coronary artery disease (mean lesion length of 32 mm).

One mechanism by which IVUS is beneficial is that IVUS guidance results in larger postintervention diameters mainly as a result of angiography-guided postdilatation. This was observed in the Assessment of Dual Antiplatelet Therapy with Drug-Eluting Stents (ADAPT-DES) study. In that large study, IVUS-guided PCI resulted in additional optimization of the procedure that otherwise would not have been performed. The most common changes (in decreasing frequency) were selection of larger size stents/balloons, higher inflation pressures, longer stents, and additional postdilatation.9–13 The relative size of the data analyzed from randomized trials in the earlier meta-analyses was limited by inclusion of observational studies.9–13

Figure 2. Summary plot for cardiovascular mortality, myocardial infarction, target lesion revascularization, and stent thrombosis. Trials were listed in the forest plot for the individual outcome only if the outcome was reported by the trial.14–15,26–29 The relative size of the data markers indicates the weight of the sample size from each study. In IVUS-XPL, myocardial infarction was defined as target lesion myocardial infarction. AIR-CTO indicates Study Comparing Angiography- vs. IVUS- Guided Stent Implantation for Chronic Total Occlusion in Coronary Artery; AVIO, Angiography vs IVUS Optimisation; CI, confidence interval; CTO IVUS, intravascular ultrasound; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime Stents in Long Lesions; OR, odds ratio; and PCI, percutaneous coronary intervention.
The American College of Cardiology/American Heart Association guideline gives a class IIb recommendation for IVUS utilization in left main coronary artery stenting and for assessment of nonleft main intermediate coronary stenosis. An analysis from the National Cardiovascular Data Registry (NCDR) data showed that IVUS was used in ≈20% of total PCI procedures. A potential explanation for infrequent use could be perceived lack of benefit from this technology because some operators may think that visual assessment of the coronary lesions is sufficient. However, it is well known that physician’s assessment of the severity of coronary lesions is variable and poorly correlates with myocardial ischemia. Alternatively, the cost of the equipment and lack of reimbursement are considerations for underutilization. However, a previous study had suggested that IVUS guidance was not only cost-effective, but may be cost-saving among patients who are at increased risk of restenosis (eg, diabetics, chronic kidney disease, and acute coronary syndromes). The results of this analysis support the recommendation to expand the routine use of IVUS for revascularization of diffuse lesions (ie, >30 mm).

Although we demonstrated that an IVUS-guided approach was associated with a reduction in MACE, primarily because of reduction in ischemia or clinically driven TLR, the magnitude of the reduction was small (absolute risk reduction=2.5%). Most of the included studies demonstrated a reduction in TLR with an IVUS-guided approach except for HOME DES IVUS, which showed a neutral effect on TLR. One potential explanation is that this trial mainly treated focal lesions (mean, 18 mm).

This analysis has some limitations. First, the definition of MACE was different among the trials; however, there was a clear benefit from IVUS on the outcome of TLR. Furthermore, we observed no evidence of heterogeneity for the outcome of MACE. Second, lack of access to patient level data precluded a full evaluation to identify patient characteristics (ie, stable angina versus acute coronary syndromes) associated with the maximal clinical benefits. Third, because of the way individuals trials were designed, we were not able to assess the impact of IVUS guidance on postinterventional cross-sectional area. Most trials reported postinterventional MLD and percent diameter stenosis, which are crude measures to gauge final stent size. Moreover, preintervention MLD was only reported by 5 of the included studies. Fourth, 3 of the included studies did not have 100% follow-up. The losses to follow-up were small (ranged from 2% to 5%) and likely not a meaningful source of bias. However, we performed a sensitivity analysis excluding these 3 trials and demonstrated a similar treatment effect. Finally, the included studies cannot generalize IVUS usage for all lesions but is most applicable to diffuse lesions.

**Conclusions**

In the era of drug-eluting stents, IVUS-guided PCI is superior to angiography-guided PCI in reducing the risk of major adverse cardiac events. This is primarily because of reduction in the risk of ischemia-driven target vessel revascularization. The risk of stent thrombosis and cardiovascular mortality may also be reduced with an IVUS-guided approach. The routine use of IVUS for revascularization of diffuse coronary lesions should be considered.

**Disclosures**

Dr Anthony A. Bavry discloses the following relationship: Honorarium from American College of Cardiology. The other authors report no conflicts.

**References**


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doi: 10.1161/CIRCINTERVENTIONS.116.003700

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**Supplemental Material:**

Supplemental Table 1: Measures of study quality

Supplemental Table 2: Definition of MACE per the individual studies

Supplemental Figure 1: Study Selection Flow Diagram

Supplemental References
Supplemental Table 1: Measures of study quality

<table>
<thead>
<tr>
<th>Study (reference#)</th>
<th>Single/Multicenter</th>
<th>Blinded end point</th>
<th>Generation of treatment assignment</th>
<th>Follow up completion%</th>
<th>Primary outcome</th>
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<td>Yes</td>
<td>Interactive web-based response system</td>
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<td>MACE</td>
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<td>Yes</td>
<td>Interactive web-based response system</td>
<td>100</td>
<td>Cardiovascular mortality</td>
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<tr>
<td>AIR-CTO #3</td>
<td>Multicenter</td>
<td>Yes</td>
<td>Central computer</td>
<td>98</td>
<td>In-stent late lumen loss</td>
</tr>
<tr>
<td>Tan et al #4</td>
<td>Single center</td>
<td>No</td>
<td>NR</td>
<td>100</td>
<td>MACE</td>
</tr>
<tr>
<td>Kim et al #5</td>
<td>Multicenter</td>
<td>No</td>
<td>Interactive web-based response system</td>
<td>100</td>
<td>MACE</td>
</tr>
<tr>
<td>AVIO #6</td>
<td>Multicenter</td>
<td>No</td>
<td>Sealed opaque envelopes</td>
<td>97</td>
<td>Post-intervention MLD</td>
</tr>
<tr>
<td>HOME DES IVUS #7</td>
<td>Single center</td>
<td>No</td>
<td>Sealed opaque envelopes</td>
<td>100</td>
<td>MACE</td>
</tr>
</tbody>
</table>

*Follow up completion reported at 12 months
MACE= major adverse cardiac events
MLD= minimum luminal diameter
TLR= target lesion revascularization
NR= not reported
Supplemental Table 2: Definition of major adverse cardiac events per the individual studies

<table>
<thead>
<tr>
<th>Study (reference#)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVUS-XPL #1</td>
<td>Composite of cardiovascular mortality, target-lesion related MI, or TLR</td>
</tr>
<tr>
<td>CTO-IVUS #2</td>
<td>Composite of cardiovascular mortality, MI, or TVR</td>
</tr>
<tr>
<td>AIR-CTO #3</td>
<td>NR</td>
</tr>
<tr>
<td>Tan et al #4</td>
<td>Composite of all-cause mortality, MI, or TLR</td>
</tr>
<tr>
<td>Kim et al #5</td>
<td>Composite of cardiovascular mortality, MI, stent thrombosis, or TLR</td>
</tr>
<tr>
<td>AVIO #6</td>
<td>Composite of cardiovascular mortality, MI, or TVR</td>
</tr>
<tr>
<td>HOME DES IVUS #7</td>
<td>Composite of all-cause mortality, MI, or TLR</td>
</tr>
</tbody>
</table>

MI= myocardial infarction  
NR= not reported  
TLR= target lesion revascularization  
TVR= target vessel revascularization
Records identified through database search using keywords “coronary”, “angiography”, and “intravascular ultrasound” (n=2,695)

Limited to “humans” and “clinical trials” from 2005 onwards (n=241)

Articles deleted based on the title review (n=187)

Relevant articles retrieved from detailed assessment (n=54)

- Topic not relevant (n=27)
- Retrospective/non randomized studies (n=10)
- Trial design (n=7)
- Trials evaluating bare metal stents (n=3)

Studies included in the final meta-analysis (n=7)
References:


