Rescue Angioplasty or Repeat Fibrinolysis After Failed Fibrinolytic Therapy for ST-Segment Myocardial Infarction
A Meta-Analysis of Randomized Trials

Harindra C. Wijeysundera, MD,* Ram Vijayaraghavan, MD,* Brahmajee K. Nallamothu, MD, MPH,† JoAnne M. Foody, MD,‡§ Harlan M. Krumholz, MD, SM,‡| Christopher O. Phillips, MD, MPH,¶ Amir Kashani, MD, MS,‡ John J. You, MD,##†† Jack V. Tu, MD, PtID,**†† Dennis T. Ko, MD, MSC*††
Ontario, Canada; Ann Arbor, Michigan; New Haven and West Haven, Connecticut; and Cleveland, Ohio

Objectives
We sought to best estimate the benefits and risks associated with rescue percutaneous coronary intervention (PCI) and repeat fibrinolytic therapy as compared with conservative management in patients with failed fibrinolytic therapy for ST-segment myocardial infarction (STEMI).

Background
Fibrinolytic therapy is the most common treatment for STEMI; however, the best therapy in patients who fail to achieve reperfusion after fibrinolytic therapy remains uncertain.

Methods
We performed a meta-analysis of randomized trials using a fixed-effects model. We included 8 trials enrolling 1,177 patients with follow-up duration ranging from hospital discharge to 6 months.

Results
Rescue PCI was associated with no significant reduction in all-cause mortality (relative risk [RR] 0.69; 95% confidence interval [CI] 0.46 to 1.05), but was associated with significant risk reductions in heart failure (RR 0.73; 95% CI 0.54 to 1.00) and reinfarction (RR 0.58; 95% CI 0.35 to 0.97) when compared with conservative treatment. Rescue PCI was associated with an increased risk of stroke (RR 4.98; 95% CI 1.10 to 22.5) and minor bleeding (RR 4.58; 95% CI 2.46 to 8.55). Repeat fibrinolytic therapy was not associated with significant improvements in all-cause mortality (RR 0.68; 95% CI 0.41 to 1.14) or reinfarction (RR 1.79; 95% CI 0.92 to 3.48), but was associated with an increased risk for minor bleeding (RR 1.84; 95% CI 1.06 to 3.18).

Conclusions
Rescue PCI is associated with improved clinical outcomes for STEMI patients after failed fibrinolytic therapy, but these benefits must be interpreted in the context of potential risks. On the other hand, repeat fibrinolytic therapy is not associated with significant clinical improvement and may be associated with increased harm. (J Am Coll Cardiol 2007;49:422–30) © 2007 by the American College of Cardiology Foundation

Clinical outcomes of patients with ST-segment elevation myocardial infarction (STEMI) are strongly dependent on the patency in the infarct-related artery after reperfusion therapy (1,2). Despite potential advantages of primary percutaneous coronary intervention (PCI), fibrinolytic therapy remains the most common therapy for STEMI in the U.S. and worldwide (3–5). Fibrinolytic therapy restores normal flow in only one-half of STEMI patients, as assessed angiographically at 90 min, with even less success in elderly patients and in those with cardiogenic shock (6–9). Given that one-half of the 500,000 STEMI patients treated annually in the U.S. receive fibrinolytic therapy, almost 125,000 patients a year will have suboptimal reperfusion and poorer outcomes (4,10).
The most appropriate treatment strategy for STEMI patients who fail fibrinolytic therapy is uncertain. Recent practice guidelines for STEMI recommend rescue PCI as a potential therapy for patients who fail fibrinolytic therapy; however, this recommendation is based primarily on expert opinions and consensus (10,11). The lack of convincing data on how to treat STEMI patients who fail fibrinolytic therapy is reflected by the inconsistency in clinical practice where conservative therapy with no further reperfusion treatment, repeat fibrinolytic therapy, and rescue PCI are all being used commonly (12).

Two recent studies have provided new insights into the treatment strategies for STEMI patients who fail fibrinolytic therapy (13). The REACT (Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis) trial demonstrated that rescue PCI is associated with an improvement in the composite end point of death, reinfarction, stroke, or severe heart failure, when compared with repeat fibrinolytic therapy or conservative management (13). However, this benefit was driven predominantly by a reduction in reinfarction, with no difference in survival between treatment strategies. Moreover, this trial was terminated prematurely, before complete enrollment, raising concerns about the true estimate of benefits (13,15). A second contemporary study, the MERLIN (Middlesbrough Early Revascularization to Limit Infarction) trial did not show significant reduction of the primary end point of all-cause mortality associated with rescue PCI when compared with conservative therapy (14). Furthermore, in both trials, patients treated with rescue PCI had increased bleeding, an important predictor of poor long-term outcome (13,14,16).

We designed a meta-analysis of randomized trials comparing rescue PCI or repeat fibrinolytic therapy with conservative therapy to provide the best estimate of benefits and risks associated with these competing rescue strategies.

Methods

Study identification. Relevant published studies were identified through a computerized literature search of the Cochrane library, EMBASE, and MEDLINE electronic databases from January 1966 to February 2006, using the terms angioplasty, percutaneous coronary intervention, myocardial infarction, thrombolytic therapy, fibrinolytic therapy, and treatment failure. OVID search software (OVID, New York, New York) was utilized using the “exploded” search feature (17). In addition, bibliographies of journal articles, and relevant reviews were extensively hand-searched to locate additional studies. No attempt was made to contact authors for primary or missing data. Relevance for inclusion in the systematic review for both English and non-English publications was determined using a hierarchical approach based on title, abstract, and the published manuscript (18).

Study selection. Two investigators (H.C.W. and R.V.) independently evaluated studies for possible inclusion. Any disagreements were resolved by consensus. We included randomized trials that enrolled STEMI patients who had failed fibrinolytic therapy and compared a strategy of either rescue PCI or repeat fibrinolytic therapy with conservative therapy. Conservative therapy was defined as no further immediate reperfusion therapy. We accepted either angiographic or clinical definitions for failed fibrinolytic therapy. Angiographic failure was defined by the Thrombolysis In Myocardial Infarction (TIMI) perfusion grade in the infarct-related epicardial artery at the time of angiography. The presence of either an occluded infarct related artery (TIMI flow grade 0 or 1) or an artery with impaired flow (TIMI flow grade 2) was accepted as evidence of failed fibrinolytic therapy (19–22). Clinical failure was defined by the lack of ST-segment resolution at a set time after fibrinolytic therapy (13,14). Although definitions of reperfusion varied slightly between trials, each trial ascertained the failure of fibrinolytic therapy in an identical fashion for its participants.

Study quality was evaluated based on the 5-point scale outlined by Jadad et al. (23), with criteria for: randomization with proper concealment of the allocation sequence, blinding of the patient and investigator to treatment allocation with description of the blinding method, and completeness of follow-up (23).

Outcomes. Clinical efficacy outcomes of interest included all-cause mortality, heart failure, and reinfarction. Safety outcomes abstracted included stroke, major bleeding, and minor bleeding. We accepted the original study definitions for all efficacy and safety end points. Although the assessment of clinical outcomes among the trials was not standardized, within each trial the same criteria were applied equally to the treatment groups.

Statistical analysis. A fixed-effects model based on the Mantel-Haenszel method for combining results from the individual trials was used. Summary relative risk (RR) ratios and 95% confidence intervals (CI) were calculated, as was the pooled estimate of absolute risk reduction. Number needed to treat (NNT) and number needed to harm were derived from the latter. Tests of heterogeneity were calculated by the Mantel-Haenszel method. Statistically significant heterogeneity was not detected in any of the efficacy or safety end points for either rescue PCI or repeat fibrinolytic therapy.

Sensitivity analyses were conducted to examine the robustness of our results. For mortality, we eliminated 1 study at a time from the analysis to determine if the pooled estimates were disproportionately influenced by a particular trial. In addition, we explored the efficacy of rescue PCI in studies where failed fibrinolytic therapy was defined by ST-segment resolution alone. Statistical significance was set
Results

Study selection. The process of study selection and exclusion is outlined in Figure 1. We excluded 2 randomized studies of rescue PCI because they were not restricted to STEMI patients who failed fibrinolytic therapy (24,25). We also excluded 1 trial of repeat fibrinolytic therapy, because it did not report any clinical endpoints (26). Therefore, our meta-analysis included 8 trials with 1,177 patients, of which there were 6 trials that randomized 908 patients to rescue PCI or conservative therapy and 3 trials that randomized 410 patients to repeat fibrinolysis or conservative therapy (13,14,19–22,27,28).

Rescue PCI versus conservative therapy. STUDY DESIGN AND QUALITY. Table 1 summarizes the study designs of the 6 rescue PCI trials. Time from initial fibrinolytic administration to rescue PCI ranged from 77 min to 274 min. The

Table 1

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Year</th>
<th>Randomized, n</th>
<th>Inclusion Criteria</th>
<th>Follow-Up</th>
<th>Mean Age, yrs</th>
<th>Women, %</th>
<th>Anterior Wall, %</th>
<th>Symptom Onset to Lytic, min*</th>
<th>Symptom Onset to Rescue PCI, min*</th>
<th>Jadad Score†</th>
</tr>
</thead>
<tbody>
<tr>
<td>REACT (13)</td>
<td>2005</td>
<td>285</td>
<td>&lt;50% ST-segment resolution at 90 min and TIMI 3</td>
<td>6-month</td>
<td>61</td>
<td>22</td>
<td>43</td>
<td>140 (95-220)†</td>
<td>414 (350-505)†</td>
<td>4</td>
</tr>
<tr>
<td>MERLIN (14)</td>
<td>2004</td>
<td>307</td>
<td>&lt;50% ST-segment resolution at 60 min</td>
<td>30-day</td>
<td>63</td>
<td>28</td>
<td>44</td>
<td>180 ± 120</td>
<td>327 ± 121</td>
<td>3</td>
</tr>
<tr>
<td>RESCUE II (22)</td>
<td>2000</td>
<td>29</td>
<td>TIMI 2</td>
<td>30-day</td>
<td>63</td>
<td>7</td>
<td>59</td>
<td>210 ± 156</td>
<td>294 ± 252</td>
<td>3</td>
</tr>
<tr>
<td>RESCUE (20)</td>
<td>1994</td>
<td>151</td>
<td>TIMI 0/1</td>
<td>30-day</td>
<td>59</td>
<td>18</td>
<td>100</td>
<td>N/A</td>
<td>270 ± 110</td>
<td>3</td>
</tr>
<tr>
<td>TAMI (21)</td>
<td>1994</td>
<td>108</td>
<td>TIMI 2</td>
<td>In-hospital</td>
<td>57</td>
<td>19</td>
<td>41</td>
<td>176 ± 62</td>
<td>268 ± 71</td>
<td>2</td>
</tr>
<tr>
<td>Belenkie et al. (19)</td>
<td>1992</td>
<td>28</td>
<td>TIMI 0</td>
<td>In-hospital</td>
<td>58</td>
<td>56</td>
<td>56</td>
<td>&lt;180</td>
<td>257 ± 57</td>
<td>2</td>
</tr>
</tbody>
</table>

*Only data for treatment arm shown; †Jadad score rates study quality to a maximum of 5, based on randomization method, blinding, and completeness of follow-up; ‡Interquartile range.

MERLIN = Middlesbrough Early Revascularization to Limit Infarction trial; PCI = percutaneous coronary intervention; REACT = Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis Trial; RESCUE = Randomized Comparison of Rescue Angioplasty with Conservative Management of Patients with Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction trial; TAMI = Thrombolysis and Angioplasty in Myocardial Infarction Study; TIMI = Thrombolysis in Myocardial Infarction perfusion grade.
The REACT trial defined clinical reperfusion as 50% ST-segment resolution at 90 min after initial fibrinolytic administration (13). The MERLIN trial defined clinical reperfusion using the same criteria at 60 min (14). Median time from symptom onset to rescue PCI was 414 min in the MERLIN trial and 327 min in the REACT trial; both studies enrolled patients at non-interventional facilities and required transfer for rescue PCI (13,14). There were 4 trials that used angiographic TIMI perfusion grade for inclusion (19–22). Follow-up durations in the trials ranged from hospital discharge to 6 months.

The 5-point quality score of the included studies are presented in Table 1. Follow-up was complete in all 6 trials. CLINICAL AND ADVERSE OUTCOMES OF RESCUE PCI. Rescue PCI was associated with no significant improvement in all-cause mortality compared with conservative therapy, defined as no additional immediate reperfusion treatment (RR 0.69; 95% CI 0.46 to 1.05; p = 0.09) (Fig. 2). For heart failure, rescue PCI was associated with an RR reduction of 27% (RR 0.73; 95% CI 0.54 to 1.00; p = 0.05) and an absolute risk reduction of 5% (95% CI 0% to 9%; p = 0.05). Similarly, the risk of reinfarction was significantly reduced with rescue PCI (RR 0.58; 95% CI 0.35 to 0.97; p = 0.04; absolute risk reduction 4%; 95% CI 0% to 9%; p = 0.03) (Fig. 2).

In 3 trials (13,14,21) enrolling 700 patients that reported the composite end point of all-cause mortality, reinfarction, and heart failure (Fig. 2).
and heart failure, rescue PCI was associated with a significant RR reduction of 28% (RR 0.72; 95% CI 0.59 to 0.88; p = 0.001). Furthermore, there was an 11% absolute risk reduction (95% CI 5% to 18%; p < 0.001) in this composite end point with an incidence of 29.2% in the PCI arm and 41.0% in the conservative arm, leading to a NNT of 9.

Table 2 Sensitivity Analysis of the Effect of Rescue PCI or Repeat Fibrinolytic Therapy on Mortality

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Trials (n)</th>
<th>Patients Analyzed (n)</th>
<th>Mortality RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue PCI</td>
<td>All trials</td>
<td>6</td>
<td>908</td>
</tr>
<tr>
<td></td>
<td>Restricted to trials that assessed clinical reperfusion (REACT and MERLIN)</td>
<td>2</td>
<td>592</td>
</tr>
<tr>
<td></td>
<td>Analysis of all studies except</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REACT</td>
<td>5</td>
<td>623</td>
<td>0.82 (0.49–1.35)</td>
</tr>
<tr>
<td>MERLIN</td>
<td>5</td>
<td>601</td>
<td>0.59 (0.34–1.02)</td>
</tr>
<tr>
<td>RESCUE</td>
<td>5</td>
<td>757</td>
<td>0.72 (0.46–1.13)</td>
</tr>
<tr>
<td>RESCUE II</td>
<td>5</td>
<td>879</td>
<td>0.67 (0.44–1.02)</td>
</tr>
<tr>
<td>TAMI</td>
<td>5</td>
<td>800</td>
<td>0.64 (0.41–0.98)</td>
</tr>
<tr>
<td>Belenkie et al.</td>
<td>5</td>
<td>880</td>
<td>0.75 (0.48–1.15)</td>
</tr>
<tr>
<td>All trials</td>
<td>3</td>
<td>410</td>
<td>0.69 (0.41–1.14)</td>
</tr>
</tbody>
</table>

CI = confidence interval; PCI = percutaneous coronary intervention; RR = relative risk; other abbreviations as in Table 1.

In the 2 trials enrolling 592 patients that assessed stroke as an outcome, the incidence of stroke was 3.4% (10 of 297) in the rescue PCI arm and 0.7% (2 of 295) in the conservative arm (absolute risk increase 2.7%; 95% CI 0% to 5%; p = 0.02) (Fig. 3). This corresponded to an increased RR of 4.98 (95% CI 1.10 to 22.5; p = 0.04) for stroke associated with rescue PCI. Information was reported on the severity of stroke for 7 of the 10 events in the rescue PCI arm; 1 stroke was fatal, and 2 resulted in long-term disability (13,14,21). None of the strokes in the conservative arm resulted in death or long-term disability.

Only the REACT trial reported the incidence of major bleeding, which was 2.7% in the rescue PCI arm and 3.5% in the conservative arm (RR 0.78; 95% CI 0.21 to 2.86; p = 0.65) (13). Among the 620 patients for which minor bleeding data were available, the incidence of minor bleeding was 16.6% in the PCI arm and 3.6% in the conservative arm (absolute risk increase 13%; 95% CI 8% to 18%; p < 0.001) (13,14,19). Rescue PCI was associated with a significantly increased risk of minor bleeding (RR 4.58; 95% CI 2.46 to 8.55; p < 0.001) compared with conservative therapy (Fig. 3).

SENSITIVITY ANALYSES FOR MORTALITY IN RESCUE PCI. In the REACT and MERLIN trials, which enrolled patients using only clinical reperfusion criteria, rescue PCI was associated with a similar estimate for all-cause mortality (RR 0.68; 95% CI 0.42 to 1.12) as compared with our overall pooled estimate (RR 0.69; 95% CI 0.46 to 1.05) (Table 2). Furthermore, the point estimate for all-cause
mortality associated with rescue PCI versus conservative therapy was not disproportionately influenced by any of the 6 trials included in the meta-analysis (Table 2).

**Repeat fibrinolytic therapy versus conservative therapy.** The 3 trials included in the repeat fibrinolytic therapy analysis are shown in Table 3. The agent used for repeat fibrinolytic therapy was tissue-type plasminogen activator in all 3 trials (13,27,28). Information on the method of random allocation generation was provided in all of the trials (Table 3) (13,27,28). Two trials had a double-blinded design; the REACT trial had only blinding of end-point adjudication. All 3 trials had complete follow-up, ranging from hospital discharge to 6 months.

**CLINICAL AND ADVERSE OUTCOMES OF REPEAT FIBRINOLYTIC THERAPY.** We only analyzed all-cause mortality and reinfarction as our clinical outcomes because heart failure was only reported in 1 trial. Repeat fibrinolytic therapy was not associated with significant risk reduction in all-cause mortality (RR 0.68; 95% CI 0.41 to 1.14; p = 0.14) or reinfarction (RR 1.79; 95% CI 0.92 to 3.48; p = 0.09) (Fig. 4). The incidence of heart failure in the REACT trial was 7% in the repeat fibrinolytic therapy arm and 7.8% in the conservative arm.

Stroke was reported only in the REACT trial with 1 event in the conservative arm and 1 event in the repeat fibrinolytic therapy arm. Minor bleeding was significantly increased with repeat fibrinolytic therapy versus conservative therapy (RR 1.84; 95% CI 1.06 to 3.18; p = 0.03), but no significant difference in the risk of major bleeding was observed (RR 1.54; 95% CI 0.54 to 4.4; p = 0.42) (Fig. 5).

**SENSITIVITY ANALYSES FOR MORTALITY IN REPEAT FIBRINOLYTIC THERAPY.** The results of sensitivity analyses evaluating the impact of individual studies on the pooled estimate of all-cause mortality are shown in Table 2. This estimate was strongly influenced by the study of Sarullo et al. (28); with elimination of this trial that enrolled 90 patients, the RR for all-cause mortality was 0.99 (95% CI 0.55 to 1.8).

### Discussion

This meta-analysis, which systematically reviewed the existing literature on treatment strategies for STEMI patients who fail fibrinolytic therapy, found that rescue PCI was associated with significant risk reductions for heart failure and reinfarction. In addition, the overall absolute reduction in the composite endpoint of all-cause mortality, heart failure, or reinfarction was substantial, requiring only 9 patients to be treated for benefit. Conversely, there was insufficient evidence to suggest that a strategy of repeat fibrinolytic therapy was efficacious. Nonetheless, rescue PCI was also associated with an increased risk of stroke and minor bleeding. Our study lends support to the recommendation of rescue PCI as the treatment of choice for STEMI patients who fail fibrinolytic therapy, but cannot advocate the use of repeat fibrinolytic therapy. The potential benefits
of rescue PCI, however, must be interpreted in the context of its risks.

Due to limited evidence regarding the best management of STEMI patients who fail fibrinolytic therapy, practice guidelines do not strongly support any particular rescue strategy as the treatment of choice (10,11). This has translated into significant diversity in the management of these patients (12). In a 1996 survey of European physicians, 45% of respondents favored conservative management of patients who fail fibrinolytic therapy, 16% favored rescue PCI, 20% favored administration of an alternative fibrinolytic agent, and 16% favored a combination strategy (12). Our study has addressed this gap in knowledge by rigorously pooling all available evidence in a meta-analysis. Although
our conclusions are based on <1,000 enrolled patients, this is the most comprehensive assessment to date of treatment strategies for STEMI patients who fail fibrinolytic therapy. Among patients who fail fibrinolytic therapy, rescue PCI was associated with consistent improvements in clinical outcomes despite time delays from symptom onset to treatment that ranged from 4.3 to 6.9 h. Moreover, these benefits were observed in the MERLIN and REACT trials, which included patients that required transfer to institutions with interventional capacities (13,14). Median transfer time was 85 min in the REACT trial (13). In contrast, Nallamothu et al. (29) found a door-to-door time of 120 min among transfer patients undergoing primary PCI in the U.S. This supports the fact that improved systems are urgently needed if full benefits of rescue PCI are to be realized in transferred patients (30).

We also observed a significant 3% increase in the absolute risk of stroke associated with rescue PCI. However, the estimate had relatively wide CIs because it was based on only 10 events in the rescue PCI arm and 2 events in the conservative therapy arm. Moreover, the pooled estimate was driven predominantly by the MERLIN trial, in which 7 events (4.6%) occurred in patients randomized to rescue PCI. Interestingly, the majority of strokes in that trial were thromboembolic rather than hemorrhagic, opposite to what one would expect given the heightened degree of anticoagulation associated with rescue PCI (14). To place these figures in proper context, the rate of stroke was 1.1% in the recent meta-analysis on facilitated PCI, and 0.3% in primary PCI (31). Further understanding of stroke risk associated with rescue PCI is necessary in order to improve patient safety.

We evaluated bleeding as a safety end point because it has been demonstrated to be an important predictor of adverse outcomes after PCI (16). Given the systemic fibrinolytic state, and the additional antplatelet and antithrombin use with rescue PCI, it was reassuring that there was no excess major bleeding. Instead, most bleeding associated with rescue PCI was minor and localized to the arterial puncture site. Regardless, the increase in the risk of minor bleeding associated with rescue PCI was substantial, with an absolute risk increase of 13%. These adverse outcomes underscore the importance of vigilant monitoring of hemostasis and the need for experienced operators.

In contrast with the clinical benefits of rescue PCI, we observed no significant benefits of repeat fibrinolytic therapy on all-cause mortality, reinfarction, or stroke. The point estimate for mortality associated with repeat fibrinolytic therapy was 0.69, but was disproportionately influenced by 1 study in which the mortality rate in the conservative arm was excessively high at 28.8% (compared with mortality rates of 12.7% in the REACT trial) (28). The lack of substantial benefit is consistent with the properties of fibrinolytic therapy in which achieving arterial patency is attenuated with time due to organization of the epicardial artery thrombus, making it more resistant to the fibrinolytic agent (32). As such, current evidence cannot advocate repeat fibrinolytic therapy for the treatment of STEMI patients who have failed fibrinolytic therapy.

This study has several important limitations. First, despite the absence of statistically significant heterogeneity, there are substantial differences in the entrance criteria of the included trials. This heterogeneity reflects the difficulty in evaluating the degree of reperfusion without recourse to angiography, a major barrier to the adoption of a standardized rescue policy for management of failed fibrinolytic therapy (14). As a non-invasive surrogate of angiographic reperfusion, ST-segment resolution has varying sensitivity to predict clinical reperfusion (1,33,34). Despite uncertainty as to the optimal means of assessing reperfusion, our study suggests that there is an improvement in clinical outcome if a rescue PCI strategy is employed.

Second, our pooled estimates are based on <500 patients randomized per arm reflecting the difficulty in recruiting patients for trials in this area (13,35). The lack of power to detect a statistically significant difference (calculated power of 0.48 to detect 30% RR reduction) is the most likely explanation for why we did not find any improvement in all-cause mortality. Despite this, the trend for reduced all-cause mortality with rescue PCI is compelling given its consistency across varying assumptions in the sensitivity analysis. In addition, our estimates of benefit and harm across other clinical outcomes are robust and relevant as a means of guiding therapy.

In summary, this meta-analysis of randomized trials lends support to the use of rescue PCI for failed fibrinolytic therapy in patients with STEMI. In contrast, repeat fibrinolysis cannot be recommended based on the available evidence. In order to further improve outcomes and minimize risks, randomized trials should be performed to determine the most appropriate adjunctive pharmacotherapy in patients undergoing rescue PCI.

Reprint requests and correspondence: Dr. Dennis T. Ko, Room G1-06, 2075 Bayview Avenue, Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada, M4N 3M5. E-mail: dennis.ko@ices.on.ca.

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APPENDIX

For the efficacy and safety end point definitions, please see the online version of this article.