EDITORIAL COMMENT

“Watchful Waiting” After Thrombolysis

It’s Time for a Re-Evaluation*

William W. O’Neill, MD, FACC
Royal Oak, Michigan

On December 23, 2002, a colleague contacted me for a patient referral. The patient was a 43-year-old male who had presented to an outlying hospital the night before with an evolving inferior ST-elevation myocardial infarction (STEMI). He presented within 2 h of symptom onset and was treated with thrombolytic therapy. Clinically, he promptly reperfused (ST resolution, complete chest-pain relief), and he had only a mild elevation of cardiac enzymes. My colleague and I discussed treatment options. We reasoned that the infarct had largely been aborted and a persistent high-grade obstructive lesion was likely. For this reason, the patient was transferred that day. At catheterization, we found a subtotal occlusion of the distal right coronary artery with TIMI (Thrombolysis In Myocardial Infarction) grade III flow and minimal posterobasal hypokinesia. A 3.5-mm stent was inserted into the right coronary artery with an excellent result. The patient was observed overnight and discharged the next day (Christmas Eve). The patient, his wife and his children were together for this overnight and discharged the next day (Christmas Eve).

Kaplan-Meier curves demonstrate that only 15% of ST-elevation patients are treated with primary PCI, whereas the majority are treated with thrombolytics. Thus, the use and timing of PCI after thrombolytic therapy remain important practice issues. The ACC/AHA guidelines suggest that immediate post-thrombolysis PCI is ineffective or harmful (Class III). These guidelines also suggest that use of PCI hours to days (48 h) after successful thrombolysis is controversial (Class II). Only rescue PCI is considered a Class I indication for use of PCI after thrombolytics. Given the restrictive nature of these recommendations, it is problematic that in the U.S. 71% of patients have catheterization and 58% have revascularization after thrombolytic use (5). On a day-to-day basis clinicians are faced with the ethical, financial, and medicolegal ramifications of recommendations based on randomized trials that are more than a decade old.

It is of interest, then, that Gibson et al. (6) describe the impact of reinfarction in 20,101 thrombolysed-treated patients in this issue of the Journal. Gibson et al. (6) reports that reinfarction occurred in 4.2% of patients treated in the TIMI 4, 9, 10B, and 17 trials. Although reinfarction was relatively infrequent, it was associated with a significantly greater 30-day and two-year mortality. In fact, when revascularization was not used, a 24% hospital mortality occurred for patients suffering reinfarction. Overall mortality appeared to be significantly decreased (6.75% to 2.76%, p < 0.0001) when PCI was used. Risk of reinfarction was also lower when PCI or coronary artery bypass graft (CABG) was used. Reinfarction tended to occur early, a mean of 2.2 days after admission. Kaplan-Meier curves demonstrate that the highest risk of death after reinfarction was during the index admission. A highly predictive model to predict reinfarction risk, based on clinical variables, could not be generated. There are significant limitations to this pooled analysis. Different thrombolytic agents were used in each trial. Definitions of “reinfarction” varied, and in one trial (TIMI 10B) the definition was not centrally adjudicated. In addition, whether PCI was prompted by reinfarction or was the cause of reinfarction could not be retrospectively determined in some patients. Despite these limitations, the detailed analysis of PCI use after thrombolytic therapy in a large contemporaneous practice makes these study results important for discussion. The main findings of this report are that recurrent infarction after thrombolytic therapy occurs early, is unpredictable, is associated with a high mortality, and may be reduced by performance of PCI or CABG during the index admission.

The patient anecdote presented here and the report by Gibson point out major gaps in our current understanding of the proper role of revascularization after thrombolytic therapy. Logistics and patient convenience favor early catheterization and revascularization. The Gibson et al. (6) report furthermore suggests a major safety benefit with PCI or CABG after thrombolysis. Clinicians in the U.S. recognize these advantages and perform catheterization and PCI.

See page 7
in the majority of patients. Unfortunately, the initial randomized trials of routine catheterization and angioplasty suggested a deleterious effect with this approach (7–11). These trials tested the routine strategy of conservative care (also known as “watchful waiting”) compared with immediate catheterization and angioplasty. No benefit, and a disturbing trend toward high mortality, occurred with the aggressive approach (12). Although these trials are more than 15 years old, they still drive treatment (and reimbursement) algorithms.

A number of trials of interventional therapy of acute coronary syndromes (ACS) and post-lytic PCI have been performed (Table 1) (13–18). Ruptured or fissured coronary plaques with superimposed intraluminal thrombus are believed to cause both STEMI and ACS/NSTEMI. Timely, successful thrombolysis removes the thrombotic occlusion and leaves coronary architecture similar to that found in ACS/NSTEMI. It is difficult to understand why randomized trials of post-lytic PCI appear to give such discordant results when used after successful thrombolytic therapy compared with ACS (7–11,19–21). Can these discordant results be reconciled?

First, it must be understood that the original randomized post-thrombolytic trials were done in an early era of angioplasty. Heparin dosage was excessive; large bore arterial and venous sheaths were employed. The deleterious local harm caused by thrombolytic therapy was not understood (19). Furthermore, the role of thrombin-mediated platelet activation was unknown at that time. Interventionists were operating in a hostile environment with primitive equipment. Today—armed with low-profile guiding catheters, superb X-ray equipment, potent antiplatelet agents, thrombin inhibitors, and especially, flexible, deliverable stents—angioplasty results have dramatically improved (22).

The more recent ACS trials have routinely used newer generation stents and glycoprotein receptor blockers. The TIMI-TACTICS (Treat Angina with Aggrastat and determine the Cost of Therapy with Invasive or Conservative Strategy) investigators have demonstrated that with these modern techniques, the early hazard of PCI in ACS has been largely eliminated (14). In addition, the use of thrombectomy devices (23) and distal protection devices (24) may further decrease the risk of reinfarction due to distal embolization. Finally, as Yarlagadda and Boden (25) have suggested, pharmacologic interventions with statins (26) and thienopyridines (27) have further improved the outcomes after PCI in ACS.

There is no doubt that thrombolytic therapy will remain a widely applied treatment of STEMI worldwide. What lessons can be gleaned from the modern ACS trials and the report of Gibson et al. (6)? We must recognize that reinfarction after successful thrombolytic therapy occurs early, is unpredictable, and has lethal consequences if PCI or CABG is not performed. Thus “watchful waiting” means exactly that. Clinicians must carefully watch for signs of recurrent ischemia or reinfarction. They must also have a well-organized triage and transfer program set up so that PCI or CABG can be promptly performed. If patients develop recurrent ischemia, further attempts at medical stabilization are pointless because, as Gibson notes, patients have a one in four chance of dying unless PCI or CABG is performed.

The expanded use of PCI beyond rescue PCI or for recurrent ischemia is not currently supported by the randomized trials. Gibson has suggested, and I strongly concur, that re-evaluation of the strategy of routine catheterization and PCI after thrombolytic therapy is warranted. This re-evaluation would incorporate advances in pharmacotherapy and employ modern interventional techniques and clinical risk stratification. It is likely that such a trial would have outcomes similar to those of the modern ACS trials. Until these data are available, clinicians will be left with conflicting and outdated trial data with which to make crucial decisions about post-thrombolytic care.

**Reprint requests and correspondence:** Dr. William W. O’Neill, Division of Cardiology, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, Michigan 48073. E-mail: wonieill@beaumont.edu.

---

**Table 1. Interventional Therapy Versus Conservative Care**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Better</th>
<th>Same</th>
<th>Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACS/NSTEMI</td>
<td>MATE (13)</td>
<td>TIMI IIIB (17)</td>
<td>VANQUISH (18)</td>
</tr>
<tr>
<td></td>
<td>TIMI TACTICS (14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRISC II (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RITA 3 (16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-lytic PCI</td>
<td>DANAMI I (20)</td>
<td>PACT (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FRISC II (15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TAMI I (7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TIMI IIA (8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ECGS (9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Barbash et al. (11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SWIFT (10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SAMI (19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All patients had inducible ischemia prior to randomization. Trial names are defined in text.

ACS = acute coronary syndrome; NSTEMI = non–ST-segment elevation myocardial infarction.
REFERENCES


