The Year in Interventional Cardiology

William W. O’Neill, MD, FACC, Simon R. Dixon, BHB, MBCrB, FRACP, Cindy L. Grines, MD, FACC
Royal Oak, Michigan

We are honored to again provide readers of the journal with a comprehensive review of major scientific works related to interventional cardiology published in 2004. Since our original 2003 review, the field of interventional cardiology has continued to expand rapidly. Although this field originally encompassed coronary interventions, we have been asked to include other cardiac (nonvalvular) interventions and peripheral artery interventions. Our goal is not to provide the reader with an exhaustive list of references; rather, we wish to organize all major practice-changing studies and major randomized trials into themes. We believe that noninterventional cardiologists can achieve a thorough understanding of these studies and major randomized trials into themes. We believe that noninterventional cardiologists can achieve a thorough framework for more intensive study. We have reviewed over 300 papers and selected ~100 for inclusion. Although we may have some biases in selection, we believe that these works will move this field forward (Table 1). We hope you enjoy reading about them as much as we enjoyed organizing them for you.

ACUTE MYOCARDIAL INFARCTION (AMI)

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the treatment of AMI were updated in 2004 (1). Although catheter-based reperfusion is now widely accepted as the treatment of choice for ST-segment elevation myocardial infarction (STEMI), many unanswered questions and challenges remain in this field. Key issues and areas of research have included: 1) defining the optimal treatment approach after thrombolysis; 2) evaluating the role of facilitated percutaneous coronary intervention (PCI) to improve clinical outcomes; and 3) identifying new adjunctive therapies to improve myocardial salvage. In addition, there is now tremendous interest in stem-cell therapy to repair infarcted myocardium.

PCI after thrombolysis (rescue and immediate). Two trials of rescue angioplasty after failed thrombolytic therapy were reported this year (Table 2). The Middlesbrough Early Revascularization to Limit INfarction (MERLIN) trial randomized 307 patients treated with streptokinase, who had a lack of ST-segment resolution, to transfer for catheterization versus medical therapy (2). The secondary end point of major adverse cardiac events (MACE) was reduced in the rescue PCI arm (37.3% vs. 50.0%, p = 0.02) due to a reduction in ischemia-driven revascularization. However, stroke and transfusions were more common in the rescue group, and there was no difference in mortality. An accompanying editorial pointed out several reasons why the results of the MERLIN trial conflicted with other studies (3). The larger Rescue Angioplasty Versus Conservative Therapy or Repeat Thrombolysis Trial (REACT) was presented at the 2004 AHA meeting (4). Patients with a lack of ST-segment resolution 90 min after thrombolysis (n = 427) were randomized to three arms: rescue PCI, repeat thrombolysis using tissue-type plasminogen activator (tPA) or recombinant plasminogen activator (rPA), or conservative care. The primary end point of combined death, re-infarction, stroke, or severe heart failure was significantly reduced in the rescue PCI arm (15.3%) compared with the repeat lysis arm (31.0%) and with conservative care (29.8%, p = 0.001). This benefit was due to a reduction in death, re-infarction, and heart failure. Moreover, significantly less ischemia-driven revascularization was required in the rescue PCI arm. Recent data from the Stent or Percutaneous Transluminal Coronary Angioplasty for Occluded Coronary Arteries in Patients With Acute Myocardial Infarction (STOPAMI) investigators indicate that stenting after failed thrombolysis is associated with greater myocardial salvage than balloon angioplasty alone (5). In aggregate, these studies suggest that patients with failed thrombolysis should undergo rescue stenting.

Previous clinical guidelines discouraged routine angioplasty after thrombolysis because of historical (but outdated) studies suggesting an excess risk of complications in these patients. Since then, significant advances in mechanical and pharmacologic therapy have occurred. In the Combined Angioplasty and Pharmacological Intervention versus Thrombolytics Alone in Acute Myocardial Infarction (CAPITAL AMI) study, tenecteplase (TNK) plus immediate angioplasty was found to be superior to tenecteplase alone (6) in 170 high-risk STEMI patients. Also, MACE was significantly reduced at 30 days (9.3% vs. 22.0%, p = 0.03) and six months in the TNK-PCI group, due to reductions in recurrent unstable ischemia and re-infarction. There was no increase in the incidence of major bleeding. In
the GRACIA-1 trial, 500 patients treated with tPA were randomized to an early invasive strategy (stenting within 24 h) or to a conservative (ischemia-guided) approach (7). The invasive group had a reduction in in-hospital ischemia-driven revascularization (2% vs. 12%, p < 0.0001) and a shorter hospital stay (7.1% vs. 10.5%, p = 0.0001), with no increase in bleeding. At one year, the combined end point of death, re-infarction, or ischemia-driven revascularization was lower in the invasive group (9% vs. 21%, p = 0.0008).

Taken together, these studies indicate that in the era of stents and newer antiplatelet agents, routine PCI after thrombolysis is not only safe but also improves outcomes and thus may be preferable to “watchful waiting.”

Facilitated PCI. Prognosis is favorable in AMI patients referred for primary PCI who are found to have Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 on baseline angiography, compared with TIMI flow grade 0 to 2. Based on this observation, several studies have attempted to
pharmacologically facilitate reperfusion before primary PCI. The Bavarian Reperfusion Alternatives Evaluation (BRAVE) trial randomized 253 patients with STEMI to facilitated PCI with half-dose reteplase plus abciximab, versus abciximab alone (8). Despite the delay in PCI (74% of patients had to be transferred), infarct size measured by technetium (Tc)–sestamibi was similar between the two groups. Major bleeding tended to be higher in the facilitated group (5.6% vs. 1.6%, p = 0.16), and MACE at six months was similar. The Ongoing Tirofiban in Myocardial Infarction Evaluation (ON-TIME) trial randomized 507 patients with STEMI who required transfer for PCI to receive prehospital tirofiban (facilitated) versus primary PCI (9). There was no difference in post-PCI perfusion, as assessed by final TIMI flow grade, blush score, or corrected TIMI frame counts. Moreover, there was a trend toward increased MACE in the facilitated group at 30 days (8.6% vs. 4.4%, p = 0.06). Thus, to date, no trial has shown that facilitated PCI is superior to primary PCI alone.

**Primary PCI.** The Primary Angioplasty in Myocardial Infarction (PAMI)–No cardiac Surgery On-Site (No SOS) Registry prospectively enrolled and performed primary PCI in 500 consecutive, high-risk, thrombolytic-eligible AMI patients who presented to hospitals with No SOS (10). No SOS patients were compared with similar high-risk patients who were randomized to transfer for primary PCI. Patients who received primary PCI with no SOS were treated 67 min earlier and had a higher rate of final TIMI flow grade 3 (96% vs. 86%, p = 0.004) and trend toward improved MACE.

Management of the thrombolytic-ineligible patient remains uncertain. The STOPAMI-3 trial randomized 611 thrombolytic-ineligible patients to stent versus percutaneous

<table>
<thead>
<tr>
<th>Study Design</th>
<th>n</th>
<th>Primary Study End Point</th>
<th>Principal Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCI after thrombolysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAVE (8)</td>
<td>253</td>
<td>Infarct size by SPECT imaging</td>
<td>Higher incidence of initial TIMI flow grade 3 in reteplase + abciximab group, but no difference in final infarct size (13% vs. 11.5%, p = NS)</td>
</tr>
<tr>
<td>CAPITAL AMI* (6)</td>
<td>170</td>
<td>Death, MI, recurrent angina, stroke at 30 days</td>
<td>Significant reduction in primary end point in the TNK + PCI group (9.3% vs. 22.0%); no difference in bleeding between groups</td>
</tr>
<tr>
<td>MERLIN (2)</td>
<td>307</td>
<td>All-cause mortality at 30 days</td>
<td>Mortality similar in study groups; less revascularization in the rescue group (6.5% vs. 20.1%, p &lt; 0.01)</td>
</tr>
<tr>
<td>REACT (4)</td>
<td>427</td>
<td>Composite of death, nonfatal MI, stroke, or significant heart failure</td>
<td>Significant reduction in primary end point in rescue PCI group (15.3%) compared with conservative therapy (29.8%) or repeat lysis (31.0%)</td>
</tr>
</tbody>
</table>

Adjunctive therapies and devices to enhance myocardial salvage

<table>
<thead>
<tr>
<th>Study Design</th>
<th>n</th>
<th>Primary Study End Point</th>
<th>Principal Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIMI* (22)</td>
<td>480</td>
<td>Infarct size by SPECT imaging</td>
<td>No reduction in infarct size with rheolytic thrombectomy; higher mortality in thrombectomy group.</td>
</tr>
<tr>
<td>AMIHOT* (24)</td>
<td>269</td>
<td>RWM of infarct zone at 3 months; ST-segment resolution; infarct size at 14 days</td>
<td>No difference in study end points with AO, but trend toward improved RWM in overall group In patients &lt;6 h, reduced infarct size and improved RWM</td>
</tr>
<tr>
<td>CASTEMI* (25)</td>
<td>387</td>
<td>Infarct size at 7 days</td>
<td>Overall, no difference in infarct size</td>
</tr>
<tr>
<td>EMERALD* (23)</td>
<td>501</td>
<td>Infarct size by SPECT imaging</td>
<td>No difference in infarct size or ST-segment resolution with GuardWire</td>
</tr>
<tr>
<td>ICE-IT* (27)</td>
<td>228</td>
<td>Infarct size by SPECT imaging</td>
<td>Overall, no difference in primary end point, but reduction of infarct size in anterior MI group</td>
</tr>
</tbody>
</table>

**Table 2. Interventional Trials in Acute Myocardial Infarction in 2004**

*Note: Trial presented at scientific meetings but not yet published.

AMI = acute myocardial infarction; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; RWM = regional wall motion; STR = ST-segment resolution.
transluminal coronary angioplasty (PTCA) (11). Patients were immediately injected with Tc-sestamibi and scanned to determine the initial perfusion defect size, and follow-up scintigraphy was performed at 7 to 14 days. The salvage index was substantial in both the stent and PTCA groups (0.54 and 0.50, p = 0.20), suggesting that either primary PCI strategy would greatly benefit thrombolytic-ineligible patients.

Some have questioned whether performance of primary PCI during “off-hours” is harmful to AMI patients. In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial of 2,082 patients undergoing primary PCI, 49% of patients presented during the evening or weekend (12). Although time-to-treatment was delayed an additional 21 min, this did not influence procedural success, myocardial recovery, or survival after PCI.

In pooled PAMI trials of 3,065 patients undergoing primary PCI, sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) in the catheterization laboratory was noted in 4.3% (13). Independent predictors of VT/VF included smoking, shorter time-to-treatment, initial TIMI flow grade 0, right coronary infarct vessel, and lack of procedural beta-blockers. Although the initial catheterization laboratory course was more complicated, the in-hospital and one-year adverse events were similar to those in patients without these arrhythmias.

Predicting the risk of patients undergoing primary PCI was the subject of multiple publications. The PAMI risk score found that procedural clinical criteria were useful (14), but PCI success was a more important determinant (15). The CADILLAC study group found that death, major bleeding, and stroke rates continued to be high in elderly patients undergoing primary PCI, and that these outcomes were not affected by stents or glycoprotein IIb/IIIa receptor inhibitors (16). Additional risk factors of poor outcome after primary PCI included baseline anemia (17), any degree of mitral regurgitation (18), lack of myocardial blush (19), or ST-segment resolution (20). Early re-occlusion after primary PCI occurred more frequently in vessels that were aneurysmal, involved bifurcations, were treated with smaller balloons, and did not received abciximab (21).

Therapies and devices to enhance myocardial salvage.

Six clinical trials evaluating new adjuncts to mechanical reperfusion were reported in 2004 (Table 2). Two of these trials (AngioJet in Acute Myocardial Infarction [AIMI] and Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris [EMERALD]) investigated methods to reduce distal embolization, whereas the other four explored adjunctive therapies to limit reperfusion injury (Acute Myocardial Infarction With Hyperoxemic Therapy [AMIHOT], Calderet in ST-Elevation Myocardial Infarction [CASTEMI], Clinical Trial of Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation—Estudios Cardiológicos Latinoamérica [CREATE-ECLA], and Intravascular Cooling Adjunctive to Primary Coronary Intervention [ICE-IT]).

In the AIMI and EMERALD trials, it was hypothesized that use of the AngioJet (Possis Medical Inc., Minneapolis, Minnesota) or GuardWire (Medtronic, Santa Rosa, California) devices, respectively, would prevent distal embolization, improve microcirculatory flow, and thus reduce final infarct size (22,23). In the AIMI trial, patients were randomized to primary PCI with or without rheolytic thrombectomy using the AngioJet device before stent implantation (22). Surprisingly, the primary end point (infarct size by single-photon emission computed tomographic [SPECT] imaging) was higher in the thrombectomy group (12.1% vs. 10.9%, p < 0.02), and there was no difference in final TIMI flow grade, myocardial blush, TIMI frame count, or ST-segment resolution between the study groups. Moreover, there was a significantly higher incidence of MACE at 30 days in the thrombectomy arm (6.7% vs. 1.7%, p < 0.01). In the EMERALD trial, the GuardWire balloon occlusion and aspiration system (Medtronic) was used for embolic protection during the angioplasty procedure (23). Although visible debris was retrieved in 70% of cases treated with the protection device, this was not associated with any improvement in final TIMI flow grade, myocardial perfusion, infarct size, or clinical events. Taken together, these data do not support the routine use of either the AngioJet or GuardWire during mechanical reperfusion.

Whether these devices are useful in patients with a large thrombus burden needs further investigation.

The AMIHOT trial investigated the use of hyperoxemic reperfusion with Aqueous Oxygen (AO) during AMI (24). After stent implantation, patients in the AO group received a 90-min intracoronary infusion of blood supersaturated with oxygen. One important difference in study design, compared with previous reperfusion trials, was that patients were eligible for enrollment up to 24 h from symptom onset. Hyperoxemic reperfusion was safe and well tolerated; however, there was no significant improvement in the primary study end points (ST-segment resolution, regional wall motion by serial echocardiography, and SPECT infarct size). In a secondary analysis, there did appear to be a treatment benefit in patients presenting within 6 h, and a further trial is being planned to confirm these observations.

In the CASTEMI trial, 387 AMI patients were treated with intravenous caldaret (an agent that reduces intracellular calcium levels by inhibiting the Na/Ca exchanger and increasing uptake into the sarcoplasmic reticulum) (25). In the treatment arm, two doses of caldaret were studied (low dose of 57.5 mg and high dose of 172.5 mg). There was no difference in the primary end point (infarct size at day 7) between the study groups; however, a benefit was seen in anterior myocardial infarction (MI) patients in the high-dose group. A larger clinical trial with caldaret (EVOLVE) is currently in progress in the U.S.

The results of the recently presented CREATE-ECLA trial have now settled the question of whether glucose-
insulin-potassium (GIK) improves mortality in AMI patients (26). In this trial (the largest study of GIK therapy), 20,201 patients with STEMI presenting within 12 h from symptom onset were randomized to receive high-dose GIK infusion for 24 h or usual care. Approximately 1,800 patients in the trial were treated with primary PCI. At 30 days, there was no difference in all-cause mortality (control 9.7% vs. GIK 10.0%, p = 0.45) or any secondary outcome measures, including cardiac arrest, cardiogenic shock, or re-infarction.

Finally, results of the ICE-IT study, the second trial to investigate hypothermia during AMI, were also reported this year (27). Patients randomized to receive hypothermia were cooled with an endovascular cooling catheter for 6 h (Innercool Inc., San Diego, California). The trial was discontinued after 228 patients were enrolled. There was no difference in final infarct size (the primary end point) in the hypothermia group. In post-hoc analysis, anterior MI patients who received sufficient cooling before reperfusion appeared to have a reduction in infarct size—an observation concordant with the previously reported Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients With Acute Myocardial Infarction (COOL MI) trial.

Cell-based cardiac repair. Cell therapy for myocardial regeneration has received enormous attention due to the potential for stem cells to potentially differentiate into multiple cell types, as well as the ready availability of autologous cells (using the patient’s own bone marrow-derived stem cells or skeletal myoblasts).

Skeletal muscle contains precursor cells (satellite cells/myoblasts), which are able to divide and repopulate the myocardium. At the ACC meeting in March 2004, Siminiak (28) reported a new method of myoblast transplantation via a catheter in the cardiac vein, which allows transvenous needle puncture of the myocardium. In a series of 10 patients, the injections were successfully delivered in nine, and one patient was noted to develop VT. Dib et al. (29) reported myoblast transplant during coronary artery bypass graft surgery (CABG) in 22 patients. Subsequent positron emission tomography (PET) scanning confirmed improved viability. Four patients were noted to have VT in this series. Arrhythmias have been a persistent concern in clinical trials of myoblast transplantation and have resulted in trials being stopped and/or modified to require automatic implantable cardioverter-defibrillator (AICD). The increase in arrhythmias is thought to be due to needle injections (puncture sites showing disordered growth, delayed differentiation, and surrounded by fibrous tissue), as well as failure to form electromechanical coupling with native myocytes. Injection of myoblasts rather than stem cells (which can potentially differentiate into myocardium, capillaries, as well as the conduction system) may also predispose to arrhythmias.

Use of stem cells for myocardial regeneration has been the subject of multiple recent investigations. The Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration (BOOST) trial randomized 60 patients to control (n = 30) or intracoronary bone marrow-derived cell (BMC) infusion 4.8 days after PCI (n = 30) (30). At six months, the global ejection fraction increased only 0.7% in the control group and 6.7% in the BMC group (p = 0.003). No proarrhythmic events or increase in restenosis were noted. Although these results are promising, it is important to point out that baseline ejection fraction was high (51.3% in the control group), and the benefit of cell transplantation was magnified due to the unexpected lack of improvement in the control group. Furthermore, this was a very heterogeneous population, with 40% of patients receiving thrombolytic therapy, and PCI was performed between 2 and 120 h from symptom onset. This suggests that spontaneous improvement may have occurred (and would be expected) in some patients. Alternatively, the TECAM pilot study (31) enrolled 20 patients with a large MI and no viability by low-dose dobutamine echocardiography, all of whom received intracoronary infusion of bone marrow-derived stem cells. At magnetic resonance imaging (MRI) follow-up, improved wall thickness, wall motion, and ejection fraction were noted in the BMC group, which appeared to be superior to the results in a nonrandomized control group. Conversely, Kuethe et al. (32) treated five patients with a large anterior MI with intracoronary BMC and found no improvement at three months in ejection fraction, regional wall motion, contractility index, coronary flow reserve, or maximum oxygen uptake. The authors suggest the “euphoria” created by small studies may be premature.

Use of circulating stem cells provides an attractive alternative to performing multiple bone marrow aspirations. The TOPCARE-AMI trial (33) reported one-year follow-up in 59 patients randomized to receive intracoronary circulating stem cells versus bone marrow cells 4.9 days after AMI. No late deaths or arrhythmias were noted, and both groups had similar improvements in ejection fraction and a reduction in infarct size. These data suggest that circulating stem cells are as safe and effective as BMCs. However, stem cells circulate in the peripheral blood in very low numbers. Granulocyte colony-stimulating factor (GCSF) has been used clinically in patients with immunosuppression or pancytopenia and to harvest cells for bone marrow transplantation. The GCSF has recently been used in AMI patients to mobilize stem cells into peripheral blood, both for harvesting cells for intracoronary infusion and in studies utilizing GCSF alone. The latter technique assumes signaling factors released during myonecrosis promote homing, engraftment, and differentiation of passively circulating stem cells in the myocardium. However, induction of leukocytosis shortly after AMI is controversial. Numerous studies have shown that even a slight elevation in leukocytes is associated with worse outcomes. Some animal studies have suggested greater infarct expansion and mortality (34). To date, six small clinical studies have been reported and demonstrate mixed results (Table 3). The largest of these small series are MAGIC Cell and FIRSTLINE-AMI.
The MAGIC Cell trial (35) randomized 27 patients with AMI to usual care, GCSF alone, or GCSF followed by apheresis to harvest the cells followed by intracoronary infusion. PCI was performed four days after randomization, and follow-up angiography in 10 patients demonstrated a 70% restenosis rate. Because peak GCSF-induced leukocytosis occurs at day 4, performing PCI in this milieu may have contributed to high restenosis rates. Alternatively, the FIRSTLINE-AMI trial enrolled 30 patients with a large MI and successful PCI to control versus GCSF (starting after PCI) (36). With this approach, restenosis occurred in only 13%, and GCSF-treated patients were noted to have better ejection fraction and left ventricular volumes.

In aggregate, these pilot studies are promising but have not shown improvement in clinical outcome. Once cell type and delivery technique are optimized, pivotal multicenter, controlled trials in high-risk patients must be performed.

### Factors influencing clinical outcomes after primary PCI

#### PERIPROCEDURAL BETA-BLOCKADE

Two studies reported this year emphasized the prognostic importance of beta-blocker therapy in patients treated with mechanical reperfusion (37,38). In a report from the CADILLAC trial, Halkin et al. (37) found that administration of intravenous beta-blockers before primary PCI was associated with improved 30-day survival and myocardial recovery at seven months. Kernis et al. (38) analyzed outcomes in 2,442 patients from the PAMI trials and found that patients receiving oral beta-blockers after successful primary PCI had a threefold lower incidence of death at six months. The greatest benefit of beta-blocker therapy was seen in patients with multivessel disease or a low ejection fraction.

#### TIME TO TREATMENT ISSUES

As we previously stated, 2004 was the year when infarct angioplasty left the realm of clinical research and became mainstay therapy for STEMI. The ACC/AHA STEMI guidelines have attempted to place primary PCI into the context of community practice (1). Many of these updated recommendations involve issues such as access to mechanical reperfusion and time delays inherent in this approach. The STEMI Committee was greatly influenced by the report from Nallamothu et al. (39), which suggested little benefit for primary PCI if the delay for door-to-balloon time versus door-to-needle time was >60 min. Therefore, the Committee promoted a 90-min door-to-balloon time as an optimal target. However, older and sicker patients have longer delays. In a pooled analysis of all the randomized trials of thrombolysis versus PCI, thrombolysis was never superior to PCI, regardless of the time delay (40). De Luca et al. (41,42) reviewed the Zwolle experience from 1997 to 2001. They found that a delay to treatment significantly impacted ST-segment resolution, myocardial blush grade, and one-year survival. Data regarding off-hours PCI remain conflicting. It is clear that door-to-balloon time is prolonged off-hours. Sadeghi et al. (12) reported that no

### Table 3. Clinical Trials of Stem-Cell Therapy After Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>Cell Type</th>
<th>Delivery</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOOST (30)</td>
<td>Primary PCI for AMI; randomized to BMSC or control</td>
<td>60</td>
<td>BMSC</td>
<td>Intracoronary infusion</td>
<td>At 6 months, improved EF in bone marrow cell group (6.7% change vs. 0.7% change in controls, p = 0.0026); no difference in risk of restenosis, arrhythmia, or adverse clinical events</td>
</tr>
<tr>
<td>FIRSTLINE (36)</td>
<td>Primary PCI for AMI; randomized to G-CSF vs. control</td>
<td>30</td>
<td>Bone marrow stimulation with G-CSF</td>
<td>Passive from circulation</td>
<td>Improved EF and LV volume with G-CSF. Restenosis in only 13%</td>
</tr>
<tr>
<td>MAGIC Cell (35)</td>
<td>Primary PCI for AMI; randomized to 3 groups: cell infusion, G-CSF alone, or control</td>
<td>27</td>
<td>PBSC after G-CSF mobilization</td>
<td>Intracoronary infusion</td>
<td>Improved myocardial perfusion, EF, and exercise capacity in patients who received cell infusion, but high rate of in-stent restenosis in patients who received G-CSF</td>
</tr>
<tr>
<td>POZNAN (28)</td>
<td>Phase I trial of percutaneous delivery of autologous skeletal myoblasts</td>
<td>10</td>
<td>Autologous myoblasts</td>
<td>Intramyocardial injection from cardiac veins</td>
<td>Percutaneous cell delivery safe and feasible</td>
</tr>
<tr>
<td>TOPCARE (33)</td>
<td>Primary PCI for AMI; randomized to BMSC or PBSC</td>
<td>59</td>
<td>BMSC and PBSC</td>
<td>Intracoronary infusion</td>
<td>Stem cell infusion safe and feasible; compared with historical controls, patients treated with cell infusion had improved EF and regional wall motion in infarct zone</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; BMSC = bone marrow stem cell; EF = ejection fraction; G-CSF = granulocyte colony–stimulating factor; PBSC = peripheral blood stem cell; PCI = percutaneous coronary intervention.
deleterious effect occurred during off-hours PCI in the 2,082 CADILLAC patients. Conversely, Saleem et al. (43) found in a single-center experience that mortality was higher (5.8% vs. 3.2%, p < 0.05) for 1,050 patients treated from 1998 to 2002. Furthermore, Bradley et al. (44) found that disparities in time to treatment in racial subgroups related more to type of hospital rather than racial bias in treatment. In summary, the year 2004 started the important process of how practical issues such as catheterization laboratory volume, staff availability, and treatment delay might impact on the routine use of PCI for STEMI in the community.

ACUTE CORONARY SYNDROMES (ACS)

To determine the benefit of routine invasive procedures in patients who present with ACS, a meta-analysis was performed of five trials, which randomized 6,766 patients in the era of stents and glycoprotein IIb/IIIa antagonists (45). The invasive strategy was superior to conservative care, with a significant reduction in the composite end point of death or MI at all periods of follow-up, as well as a reduction in mortality at 24 months (relative risk 0.77, 95% confidence interval [CI] 0.60 to 0.99). The greatest benefit was seen in men and troponin-positive patients. Moreover, the meta-analysis would have lent even greater support to the invasive approach if it had included the ISAR COOL study (46).

Conversely, the more recent Invasive Versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS) trial (47) randomized 1,200 patients with ACS to an early versus “selective invasive” approach and found no difference in the composite end point of death, MI, or re-hospitalization for ACS at one year. The lack of benefit was thought to be largely due to the aggressive approach in the selective invasive group, with 67% receiving catheterization (mean 142 h) and 47% undergoing revascularization. The routine invasive strategy did reduce re-admission (7.0% vs. 10.9%, p = 0.017), but this was offset by a higher rate of periprocedural MI.

Earlier studies of ACS demonstrated that enoxaparin was superior to unfractionated heparin (UFH) at reducing combined death and MI; however, its use in combination with glycoprotein IIb/IIIa agents or invasive procedures was unknown. Phase A of the Aggrastat to Zocor (A to Z) trial enrolled 3,987 patients who were receiving tirofiban and aspirin and randomized them to enoxaparin versus UFH (48). A nonsignificant improvement in MACE was observed in the enoxaparin group (8.4% vs. 9.4%). The Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial enrolled 10,027 patients with high-risk ACS expected to undergo early invasive therapy and randomized them to enoxaparin versus UFH (49). Overall, death or MI at 30 days was similar in the enoxaparin and UFH groups (14.0% vs. 14.5%), but a significant increase in bleeding was observed with enoxaparin. Increased bleeding was confined to patients who crossed over and received both treatments; patients who received only enoxaparin had good clinical outcomes with minimal bleeding.

PCI FOR CHRONIC CORONARY ARTERY DISEASE

PCI versus medical therapy or CABG. In the 1990s, 11 randomized trials of PCI versus CABG were completed. In aggregate, these trials demonstrated that patients treated with PCI had a shorter length of stay and less in-hospital costs. Conversely, CABG-treated patients had better relief of angina and fewer repeat revascularization procedures. In 2004, a number of studies tried to shed further light on the relative benefits of these two revascularization options. Legrand et al. (50) published the three-year follow-up of the Arterial Revascularization Therapy Study (ARTS). They showed that mortality was similar in both groups, but repeat revascularization rates were higher in PCI patients compared with CABG patients (26.7% vs. 6.6%). This advantage of CABG may be lessened in the drug-eluting stent (DES) era. Serruys (51) recently presented the six-month outcome for the ARTS-II trial. In this trial, 600 patients were treated in a registry with the Cypher (Johnson and Johnson, Cordis Corp., Warren, New Jersey) sirolimus DES, and these patients were compared with the original stent cohort in the ARTS-I trial, as well as the CABG cohort in the ARTS-II trial (Table 4). Although this type of retrospective comparison is not conclusive, it lends support for the conduct of two prospective CABG versus DES trials (Syntax and Freedom).

Although CABG provides superior anginal relief, a potential major drawback in quality of life exists. Neurocognitive dysfunction is now recognized as a major risk of CABG. This year, Wahrborg et al. (52) first reported a substudy of the Surgery or Stent (SoS) trial in which neuropsychological outcomes were evaluated. A total of 145 patients were randomized to CABG or PCI. A very low incidence of neurologic dysfunction occurred in both groups, and no differences were detected between the groups. The large difference in the incidence of neurocognitive dysfunction between this study and the Duke study (53) suggests that testing methodology needs to be standardized. Hopefully, the Syntax or Freedom trial will explore this area further.

<table>
<thead>
<tr>
<th>Table 4. Clinical Outcomes in the ARTS-I and ARTS-II Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARTS-I PCI</td>
</tr>
<tr>
<td>Death (%)</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
</tr>
<tr>
<td>Repeat PCI (%)</td>
</tr>
<tr>
<td>Repeat CABG (%)</td>
</tr>
<tr>
<td>Stroke (%)</td>
</tr>
<tr>
<td>MACE (%)</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft surgery; DES = drug-eluting stent; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention.
Although medical therapy is often forgotten or ignored in patients eligible for revascularization, interest in alternatives to revascularization has re-emerged in 2004. Medical therapy appears particularly attractive in younger patients with mild angina and well-preserved systolic function. Hambrecht et al. (54) randomized 101 such individuals to PCI or medical therapy. They found that patients assigned to medical therapy and regular exercise had superior event-free survival (88% vs. 70%, p = 0.023) and greater exercise capacity than those assigned to PCI. Hueb et al. (55) reported the results of the Medicine, Angioplasty, or Surgery Study (MASS-II). In this trial, 611 patients with multivessel disease, 79% of whom had Canadian Cardiovascular Society (CCS) class II or III angina, were assigned to medical therapy (n = 203), PCI (n = 205), or CABG (n = 203). At one-year, a trend toward higher mortality (4.5% vs. 4.0% vs. 1.5%) was observed for angioplasty or surgery versus medical therapy. Event-free survival was greater for CABG (94%) compared with medicine (89%) or PCI (76%). Persistent class II or III angina occurred in 64% medicine, 45% PCI, and 39% CABG patients (p < 0.001). These two studies suggest that intensive medical therapy is safe in younger patients with stable angina. The same may not be true in elderly patients. Pfisterer (56) reported the long-term outcome of the Trial of Invasive vs. Medical Therapy in Elderly Patients With Chronic Coronary Artery Disease (TIME) trial, which compared invasive versus medical therapy in the elderly. In this trial, 301 patients ≥75 years old were randomized to revascularization (CABG or PCI) or optimized medical therapy (47% of patients had CCS angina class III and 35% had CCS angina class IV). On an intention-to-treat basis, no difference in four-year survival was seen between the groups. This analysis was confounded because 45% of medically treated patients had late revascularization. Mortality was higher at four years in patients not revascularized (85% vs. 40%, p = 0.0027). Patients treated with revascularization had less angina and were taking fewer medications. These trials suggest that older and more symptomatic patients are more likely to have symptomatic and survival benefits from revascularization.

The Bypass Angioplasty Revascularization Investigation (BARI) trial provides further argument for optimized medical therapy, even in patients undergoing revascularization (57). They reported a five-year angiographic substudy of the BARI trial. Recurrent angina at five years occurred in 42% PCI-treated patients and 51% of CABG-treated patients. Importantly, two-thirds of these recurrences were related to disease progression of nontreated arteries. This trial is a timely reminder that intense risk factor modification is required regardless of the revascularization strategy chosen. An even more potent argument for aggressive medical therapy is provided by the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial (58). In this study, patients with ACS who were randomized to high-dose atorvastatin had a significantly lower incidence of adverse cardiovascular events at two-year follow-up (22.4% vs. 26.3%, p = 0.005).

Factors influencing clinical outcomes after elective PCI. HOSPITAL VOLUME AND ON-SITE SURGERY. In 2004, two important studies were published that addressed the relationship between different PCI centers and clinical outcomes (59,60). In the first study, Wennberg et al. (59) examined outcomes in Medicare patients treated with PCI at institutions with and without on-site cardiac surgery. Patients undergoing PCI without on-site surgery were more likely to have primary/rescue PCI for AMI, but after adjustment for baseline differences, these patients were found to have a mortality similar to AMI patients treated at sites with on-site surgery. In contrast, patients undergoing nonemergent PCI had a significantly higher mortality in hospitals without on-site surgery (adjusted odds ratio [OR] 1.38, 95% CI 1.14 to 1.67, p = 0.001), particularly in hospitals performing <50 Medicare PCI procedures per year. In the second study, Epstein et al. (60) reported that PCI-related mortality was significantly higher in low-volume centers (<200 cases/year) than medium- or high-volume centers (OR 1.21, 95% CI 1.06 to 1.28).

IMPACT OF RENAL DYSFUNCTION, DIABETES, AND ANEMIA. With dramatic advances in interventional technology, PCI success rates are higher. Therefore, patient clinical factors have taken a dominant role in predicting adverse outcomes after PCI (61). Numerous studies published in 2004 dealt with diabetes, chronic kidney disease (CKD), and anemia. The adverse consequences of radiographic contrast nephropathy (RCN) are well known. Marenzi et al. (62) described the magnitude of this problem in patients undergoing primary PCI. They found that RCN occurred in 19% of patients and was associated with 31% in-hospital mortality. Using two large angioplasty data bases, Mehran et al. (63) and Bartholomew et al. (64) have developed models that predict RCN. Both groups found that the presence of CKD, diabetes, age >75 years, intra-aortic balloon pump use, congestive heart failure, and total contrast volume predicted RCN. These studies can be used to predict RCN and, in the future, can be used to design prophylactic strategies in high-risk patients.

A second major comorbidity in the PCI patient is diabetes mellitus. Norhammar et al. (65) described worsened survival in diabetic patients treated with either early invasive or early conservative strategies in the Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) trial. The relative value of early invasive therapy was greater in diabetic than nondiabetic patients. Even when adjusted for the extent of CAD, diabetes remained a strong independent predictor of mortality (RR 5.43, 95% CI 2.09 to 14.12, p = 0.001). Diabetes and CKD often co-exist in PCI patients. Nikolsky et al. (66) found this combination is associated with an explosive increase in one-year mortality. Diabetic patients without CKD had a 5% one-year mortality rate, whereas those with CKD had...
16.5% mortality and those on dialysis had 44% mortality (p < 0.001). Corpus et al. (67) suggested that close attention to glycemic control must occur in PCI patients with diabetes. These authors followed 175 patients with diabetes and found that target vessel revascularization (TVR) occurred in 34% of patients with glycosylated hemoglobin (HbA1c) >7% versus 15% for those with HbA1c <7% (p = 0.02). Because obesity and adult-onset diabetes co-exist, it is intuitive that obese patients may have worsened outcomes after PCI. It is therefore surprising that when Minutella et al. (68) queried the New York State Angioplasty Registry, they found that mild to moderate obesity (body mass index [BMI] 30 to 39 kg/m²) had a mild protective effect. Only cases of extreme obesity (BMI >40 kg/m²) had an increased risk of death.

Like obesity and diabetes, preprocedural anemia and the need for blood transfusions co-exist. Again, it seems intuitive that patients with severe coronary disease would benefit from optimizing the oxygen-carrying capacity of blood by normalizing the hematocrit. Lee et al. (69) found a striking increase in postoperative creatine kinase-MB fraction (CK-MB) and troponin release, as well as one-year mortality, for anemic PCI patients (hemoglobin [Hg] <10). Clinical outcome was also worse for patients with mild anemia (Hg 10 to 12). Similarly, McKechnie et al. (70) found a higher in-hospital mortality for PCI patients with anemia, regardless of gender. The risk of preoperative anemia appears magnified in the AMI population. Nikolsky et al. (17) found a strikingly higher in-hospital mortality (4.6% vs. 1.1%, p < 0.001), a higher risk of stroke (0.8% vs. 0.1%, p = 0.005), and higher one-year mortality (9.4% vs. 3.5%, p < 0.0001) for patients treated in the CADILLAC trial who had baseline anemia. These alarming data have led some to suggest that preprocedural transfusions may be indicated (69). In this regard, the report of Rao et al. (71) is sobering. These authors describe an association of blood transfusions with increased mortality in three large trials of ACS, which enrolled 24,112 patients, 10% of whom underwent blood transfusions. Unadjusted 30-day mortality was higher for transfused patients (8% vs. 3.08%, p < 0.0001). A hazard ratio of 3.94 (95% CI 3.26 to 4.75) existed after adjustment for baseline variables.

In summary, close attention to patient comorbidities is essential to minimize the risk of PCI. The presence of CKD, diabetes, severe obesity, and baseline anemia identifies individuals with greatly enhanced procedural risk and worsened one-year survival. We hope that 2005 will provide further studies that shed light on new RCN preventative strategies, a systematic approach to glycemic control and answers to the pressing question of whether blood transfusions are necessary or harmful to anemic PCI patients.

**Therapeutic angiogenesis.** Studies utilizing gene therapy (modifying a disease by introducing the deoxyribonucleic acid [DNA] or ribonucleic acid [RNA] of a specific gene into cells) have reported disappointing results. Despite promising initial data from the Angiogenic Gene Therapy (AGENT)-1 and -2 studies utilizing adenovirus-mediated fibroblast growth factor-4 to induce angiogenesis, the larger pivotal AGENT-3 study was stopped early. Although there were no safety concerns, the Data and Safety Monitoring Board recommended that the trial be terminated due to futility. Preliminary data were reported on 360 patients with chronic angina randomized to receive intracoronary low-dose adenovirus 5 fibroblast growth factor-4 (Ad5FGF-4), high-dose Ad5FGF-4, or placebo (72). All three groups had improvement in exercise duration at 12 weeks; however, there were no differences between treatment arms. Interestingly, sicker patients (≥55 years of age with CCS angina class III to IV or a baseline exercise duration of ≤300 s) were noted to have a greater exercise time with gene therapy, suggesting some therapeutic benefit. Therefore, gene therapy for angiogenesis appears to show subtle improvements in symptoms, but objective measures of ischemia have not been convincing. Larger trials are clearly needed, perhaps with larger doses or different modes of administration. Moreover, because angiogenesis involves multiple growth factors, a combination of growth factors and/or cell therapy may be necessary. In this regard, a report of 11 patients who received endocardial injection of autologous bone marrow cells, compared with nine patients receiving usual care, demonstrated improvement in myocardial perfusion and exercise capacity (73). However, because this study was not randomized or blinded, investigator or patient bias may have influenced the results.

**THERAPIES FOR THE PREVENTION OF RESTENOSIS**

**DES.** The year 2004 continued to provide trial data demonstrating the superiority of DES over bare-metal stents in limiting restenosis. We have summarized the currently available data on the impact of different DES types on target lesion revascularization (TLR) in Figure 1. We have included all major randomized trials, as well as large registries that employed repeat angiography on a prospective, systematic basis. Because the main value of DES is to decrease fibrointimal hyperplasia, the efficacy of various stents can be determined by the amount of angiographic late loss that occurs. Fortunately, most of these trials included short, simple lesions in medium to large arteries. It is apparent that both sirolimus- and paclitaxel-eluting stents significantly decrease late loss and lessen the risk of TLR compared with controls. Although sirolimus appears to be more potent than paclitaxel in limiting late loss, TLR appears equally low. A threshold of late loss of 0.5 to 0.6 mm appears to exist. Above this value there is no advantage over bare-metal stents. Numerous prospective, comparative trials are being conducted and will be reported in 2005. These trials will continue to shed light on whether different stent types or drug platforms will perform better. Until then, cost, availability, and deliverability of stents will drive usage patterns.

**NONAPPROVED DES.** The majority of the data on DES is derived from trials using sirolimus and paclitaxel; however,
studies investigating different drugs, doses, and polymers are now available (74–80).

The First Use to Underscore Restenosis Reduction with Everolimus (FUTURE-1) trial randomized 42 patients to receive the everolimus–coated stent (n = 27) versus bare-metal stent (n = 15) (74). Late loss was 0.11 mm; the restenosis rate was 0% with everolimus; and intravascular ultrasound (IVUS) follow-up confirmed preservation of efficacy (82). One-year follow-up of the SIRIUS trial, in which 1,058 patients were randomized to a sirolimus-eluting versus bare-metal stent, demonstrated continued benefit (83). Target lesion revascularization was 4.9% versus 20% (p < 0.001), and there was no difference in death or MI. In high-risk subsets (long lesions, small vessels, diabetes), a 70% to 80% reduction in TVR was observed. Furthermore, subsets that traditionally have the greatest benefit from bypass surgery did well with implantation of a Cypher stent. In fact, TLR was reduced from 22.3% to 6.9% (p < 0.001) in diabetics (84), and restenosis after stenting of the left anterior descending coronary artery was reduced from 41.6% to 2% (p < 0.001) (85).

NEW LESION SUBSETS. The pivotal trials required for FDA approval of DES generally enrolled low-risk lesions. Therefore, “real-world” registries and additional randomized trials are needed. The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital Registry (RESEARCH) treated 508 consecutive patients with Cypher DES and compared them with 450 consecutive patients who received bare-metal stents (86). Although the group treated with Cypher had more complex lesions (more type C lesions, bifurcation, multivessel) and received more stents, one-year MACE was reduced (9.7% vs. 14.8%, p = 0.008), as well as TVR (3.7% vs. 10.9%, p < 0.001).

Virtually all lesion subsets appear to benefit from DES. The RESEARCH registry treated 102 very long lesions with Cypher stents (mean length 61.2 mm [range 41 to 134 mm]) and demonstrated low MACE, restenosis of 11.9%, and late implantation of a Cypher stent. In fact, TLR was reduced from 22.3% to 6.9% (p < 0.001) in diabetics (84), and restenosis after stenting of the left anterior descending coronary artery was reduced from 41.6% to 2% (p < 0.001) (85).

Figure 1. Relationship between late loss and target lesion revascularization (TLR) in clinical trials evaluating bare-metal stent and drug-eluting stent (DES) platforms. Squares = sirolimus/everolimus DES; diamonds = paclitaxel DES system; circles = bare-metal stent. Target lesion revascularization is at nine months unless indicated (*TLR at six months; †TLR at 12 months). Drug-eluting stents: 1 = FUTURE-I; 2 = C-SIRIUS; 3 = SIRIUS; 4 = E-SIRIUS; 5 = TAXUS-IV; 6 = TAXUS-II (slow-release group); 7 = TAXUS-II (moderate-release group); 8 = TAXUS-VI; 9 = DELIVER. Bare-metal stents: 10 = TAXUS-IV; 11 = BENESTENT (stent group); 12 = STRESS (stent group); 13 = TAXUS-II (moderate-release group); 14 = TAXUS-II (slow-release group); 15 = FUTURE-I; 16 = DELIVER; 17 = SIRIUS; 18 = C-SIRIUS; 19 = TXUS-VI; 20 = E-SIRIUS.

FOOD AND DRUG ADMINISTRATION (FDA)-APPROVED DES. The TAXUS-IV study randomized 1,314 patients undergoing single-vessel de novo PCI to receive a polymer-based paclitaxel stent versus a bare-metal stent (81). Mean lesion length was 13.4 mm, and 1.08 stents were implanted per patient. Ischemia-driven TVR at nine months was reduced in the paclitaxel stent arm (4.7% vs. 12.0%, p < 0.001). Cardiac death or MI at nine months was similar between the two groups. An additional three months of follow-up confirmed preservation of efficacy (82). One-year follow-up of the SIRIUS trial, in which 1,058 patients were randomized to a sirolimus-eluting versus bare-metal stent, demonstrated continued benefit (83). The pivotal trials required for FDA approval of DES generally enrolled low-risk lesions. Therefore, “real-world” registries and additional randomized trials are needed. The Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital Registry (RESEARCH) treated 508 consecutive patients with Cypher DES and compared them with 450 consecutive patients who received bare-metal stents (86). Although the group treated with Cypher had more complex lesions (more type C lesions, bifurcation, multivessel) and received more stents, one-year MACE was reduced (9.7% vs. 14.8%, p = 0.008), as well as TVR (3.7% vs. 10.9%, p < 0.001).

Virtually all lesion subsets appear to benefit from DES. The RESEARCH registry treated 102 very long lesions with Cypher stents (mean length 61.2 mm [range 41 to 134 mm]) and demonstrated low MACE, restenosis of 11.9%, and late
loss of 0.13 mm (87). At the Transcatheter Cardiovascular Therapeutics meeting in 2004, Park (88) reported a study in which 739 long (>24 mm) lesions were treated based on operator preference to receive a Cypher stent (n = 344), Taxus stent (Boston Scientific, Maple Grove, Minnesota) (n = 194), or bare-metal stent. As expected, in-segment restenosis was greatest in the bare-metal stent group (42.5%). Surprisingly, despite a smaller baseline reference vessel size (which should increase restenosis rates), the Cypher-treated lesions had a significant reduction in restenosis compared with Taxus-treated lesions (7.4% vs. 21.3%, p < 0.001). Finally, the Canadian Sirolimus-Eluting Stent in Coronary Lesions (C-SIRIUS) trial showed a marked reduction in restenosis in long lesions treated with the Cypher stent compared with the bare-metal stent (89).

Two registries using DES for chronic total occlusion (CTO) have been reported. Hoye et al. (90) reported the use of Cypher stents in 56 CTOs (one month duration) that were 2.35 mm in diameter, using 45.2 mm of the stent. Event-free survival at one-year was 96.4%, and restenosis occurred in 9.1%. Werner et al. (91) reported 48 patients with total occlusion >2 weeks’ duration, who were treated with a Taxus stent (mean 40 mm) in vessels 2.57 mm in diameter. Event-free survival was 87.5%, and restenosis occurred in 8.3%.

Additional lesion subsets that have shown good clinical outcomes and low restenosis rates in Cypher registries and randomized trials include saphenous vein grafts (92), AMI (93), aorto-ostial lesions (94), multivessel disease (95), unprotected left main lesions (96,97), small vessels (98), and stenting of the parent vessel of a bifurcation lesion (99). However, similar to bare-metal stent studies, stenting the side branch of the bifurcation appears to be associated with higher subacute thrombosis and a nonsignificant increase in branch vessel restenosis. Finally, the Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) randomized trial showed lower rates of restenosis were observed with Cypher compared with Taxus (14% vs. 22%), both of which were superior to PTCA (45%, p < 0.001) when used to treat in-stent restenosis (100).

PREDICTORS AND TREATMENT OF DES RESTENOSIS. Restenosis is an uncommon problem after implantation of DES and is generally focal rather than diffuse in nature. In 2004, Lemos et al. (101) reported on predictors of restenosis after sirolimus-eluting stent implantation. Angiographic restenosis was found to be predominantly associated with lesion-based characteristics, including aorto-ostial location, treatment of restenosis, long lesions, small vessels, as well as diabetes. The optimal treatment strategy for patients with restenosis in DES is not well defined. Data from the RESEARCH registry suggest that implantation of a second DES is safe and may be associated with a lower recurrence rate than treatment with a bare-metal stent or balloon dilation alone (102). Further investigation is required in this area.

STENT THROMBOSIS WITH DES. The year 2004 also brought forth reports of stent thrombosis in DES, initially raising widespread concern about the magnitude of this problem. These concerns were alleviated with data from several series that showed the incidence of stent thrombosis with sirolimus-eluting stents to be similar to the incidence of thrombosis with bare-metal stenting (103,104). However, in another report, McFadden et al. (105) presented four cases of late, angiographically confirmed thrombotic occlusion approximately one year after implantation of sirolimus- or paclitaxel-eluting stents. All four cases arose soon after aspirin or clopidogrel was interrupted, thus highlighting the importance of prolonged antiplatelet therapy in these patients.

Other devices for restenosis. CUTTING BALLOON. Based on promising data from retrospective studies, the cutting balloon has frequently been employed to treat in-stent restenosis. The RESCUT trial prospectively evaluated the efficacy of this device compared with conventional balloon dilation in 428 patients with focal and diffuse in-stent restenosis (106). The investigators observed less slippage with the cutting balloon, with a trend toward a lower rate of additional stenting in the cutting balloon group; however, there was no difference in angiographic restenosis (primary end point) at seven months (cutting balloon 29.8% vs. PTCA 31.4%, p = 0.82) or clinical events.

BRACHYTHERAPY. Two trials of intracoronary brachytherapy for the treatment of de novo lesions brought mixed results (107,108). These studies were designed to study the effect of beta-radiation after stenting to prevent restenosis. Both trials demonstrated a significant reduction in in-stent neointimal proliferation with beta-radiation (assessed by angiographic late loss in the Beta-Radiation Investigation With Direct Stenting and Galileo in Europe (BRIDGE) trial; neointimal volume by IVUS in the Sabate et al. [108] study). However, this benefit was offset by an edge effect in the vessels treated with beta-radiation. Although neither trial was powered to detect a difference in clinical events, the investigators in both studies also observed a higher rate of late stent thrombosis in patients treated with brachytherapy compared with the control groups.

Adjunctive drug therapy to limit restenosis. Although DES have greatly reduced restenosis, there are situations where DES may be cost prohibitive (multiple lesions) or vessels may be too small or tortuous to accommodate a DES. Therefore, oral medications to reduce restenosis may be of benefit.

The VESPA trial randomized 700 patients with successful PCI (83% of whom received stents) to verapamil 240 mg twice a day versus placebo (109). A significant reduction in TVR was noted (19.3% vs. 29.3%, p = 0.002). However, this may have been due to the anti-anginal effects of verapamil, as there was no difference in minimal lumen diameter or percent stenosis, and only a trend toward a reduction in restenosis (25.7% vs. 32.3%, p = 0.06).
Sirolimus-coated stents have nearly eliminated restenosis, and systemic oral sirolimus has prevented intimal hyperplasia in animal models. Two small trials have evaluated this class of oral drugs in patients treated with bare-metal stents (110,111). The Oral Sirolimus to Inhibit Recurrent In-Stent Stenosis (OSIRIS) trial randomized 300 patients with in-stent restenosis to placebo, usual-dose or high-dose sirolimus for 10 days, starting two days before PCI (110). Significant reductions in angiographic restenosis were seen in the high-dose sirolimus group compared with placebo (22.1% vs. 42.2%). Low-dose sirolimus had little effect. Another trial gave open-label rapamycin 2 mg (n = 30) versus 5 mg (n = 30) for 30 days (111). The 5-mg dose had more side effects, and 30% of patients did not complete the course. Late loss (0.6 mm) and restenosis rates (7%) were low in both groups, suggesting a possible benefit.

Although earlier small trials using folic acid suggested a reduction in restenosis, Lange et al. (112) reported a negative trial of 636 patients randomized to folic acid, with B6 and B12 versus placebo. In fact, folate and B-complex vitamins appeared to increase the risk of restenosis (34.5% vs. 26.5%, p = 0.05) and TVR (15.8% vs. 10.6%, p = 0.05).

**OTHER CORONARY DEVICES**

**Embolic protection devices.** The treatment of saphenous vein graft disease remains a challenge in interventional cardiology. The results of two clinical trials investigating new embolic protection devices were reported in 2004 (Table 5) (113,114).

The Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization (PRIDE) trial compared the efficacy of the TriActiv distal balloon occlusion system (Kensey Nash, Exton, Pennsylvania) with either the GuardWire or FilterWire EX (Boston Scientific) devices (113). After PCI, there was no significant difference in the incidence of final TIMI flow grade 3 between the study groups (TriActiv 99.1% vs. control 97.8%, p = 0.057). A modified intent-to-treat analysis was also performed, excluding patients in whom the randomization strategy was not attempted or patients treated without protection. In this analysis, the EmboShield was found to be noninferior to the GuardWire (10.1% vs. 8.8%, p = 0.022).

**Covered stents.** An alternative approach to treatment of saphenous vein graft disease has been the use of membrane-covered stents. It was proposed that the polytetrafluoroethylene (PTFE) membrane would reduce distal embolization and also reduce neointimal proliferation through the stent struts. The Prospective, Randomized Trial of a Self-expanding PTFE Stent Graft During SVG Intervention (SYMBIOT-III) compared the Symbiot self-expanding PTFE-covered nitinol stent (Boston Scientific, Minneapolis, Minnesota) with bare-metal stents in saphenous vein graft intervention (115). Patients who received the Symbiot stent had a slightly higher incidence of MACE (30.6% vs. 26.5%, p = 0.43), and there was no difference in the primary end point (diameter stenosis by angiography at eight months) between the study groups. These data suggest that use of the Symbiot stent does not confer any additional

<table>
<thead>
<tr>
<th>Study Design</th>
<th>n</th>
<th>Primary End Point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Embolic protection device</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAPTIVE (114)</td>
<td>849</td>
<td>MACE at 30 days</td>
<td>MACE 11.4% vs. 9.1% (p = 0.057 for noninferiority). In a modified ITT analysis (excluding patients not treated with protection), the CardioShield was noninferior to GW (10.1% vs. 8.8%, p = 0.022)</td>
</tr>
<tr>
<td>PRIDE (113)</td>
<td>894</td>
<td>MACE at 30 days</td>
<td>In the noninferiority arm, PCI with the TriActiv system resulted in a similar incidence of MACE to the active control group (11.2% vs 10.1%)</td>
</tr>
<tr>
<td><strong>Covered stents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYMBIOT III (115)</td>
<td>400</td>
<td>Percent diameter stenosis at 8 months</td>
<td>No reduction in restenosis with the Symbiot stent</td>
</tr>
</tbody>
</table>

MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; SVG = saphenous vein graft.
benefit over bare-metal stents in saphenous vein graft lesions.

CAROTID ARTERY AND AORTIC DISEASE

Given the enormous controversy and bitter turf battles raging about noncoronary percutaneous endoluminal repair, the year 2004 finally provided scientific data. Clinicians can now begin to make rationale decisions about the choice of surgical or percutaneous repair for carotid lesions and abdominal aneurysm.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial is the first trial of carotid stenting with distal protection versus surgical endarterectomy (116). In this trial, 334 patients with carotid lesions and major co-morbidities (severe pulmonary disease, congestive heart failure, ≥80 years of age) were enrolled. The primary end point—MACE at one year—was lower in the stent group (12.2% vs. 20.1%, \( p = 0.053 \)). This was largely driven by a lower risk of MI in the stent group (2.5% vs. 8.1%, \( p = 0.03 \)). On the basis of this trial and the Guidant Corporation-sponsored ARCHER registry (117), both the FDA and Centers for Medicare and Medicaid Services have approved carotid stenting. Promising outcome data were also reported from registries evaluating newer generation carotid stents and embolic protection devices (118,119). Major challenges persist in this field, including training and credentialing issues, turf issues, and a lack of prospective data concerning lower risk patients who are currently being treated surgically.

The other major field—endoluminal stent grafting for abdominal aortic aneurysms—had important trial data published in 2004. Prinssen et al. (120) randomized 345 patients with aneurysms ≥5 cm in diameter, who were eligible for surgical or stent graft repair. Perioperative mortality (4.6% vs. 1.2%, \( p = 0.10 \)) and 30-day MACE tended to be lower in the stent graft group. Although this trial is the first to scientifically compare these techniques, an argument can be made that a 30-day end point does not deal with the major limitation of stent grafting (late endoluminal leak). Until a trial shows mortality reduction, controversy will still exist about surgical or stent graft repair.

A final trial involving peripheral vascular disease patients performed in 2004 that needs mention is the Coronary Artery Revascularization Prophylaxis (CARP) trial (121). To determine the value of preoperative revascularization, 510 patients scheduled to undergo noncardiac vascular surgery who had stable symptoms, preserved left ventricular function, and anatomy suitable for CABG or PCI were randomized to a strategy of preoperative coronary revascularization or medical therapy. At 2.7-year follow-up, no difference in mortality or postoperative MI existed. Although only 9% of all patients were randomized, this trial should change the practice of cardiology concerning preoperative assessment and preoperative revascularization in stable peripheral vascular disease patients who require noncardiac surgery.

ADJUNCTIVE PHARMACOTHERAPY

Antiplatelet therapy. The Intracoronary Stenting and Antithrombotic Regimen (ISAR) investigators continue to redefine antiplatelet regimens. The Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment (ISAR-REACT) trial enrolled 2,159 patients who were pretreated with 600 mg of clopidogrel ≥2 h before elective PCI (122). Patients with recent AMI, unstable angina (with positive troponin, or electrocardiographic changes), or angiographic evidence of thrombus were excluded. Patients were randomized to abciximab with low-dose heparin (70 ìg/kg) versus placebo with high-dose heparin (140 ìg/kg). The abciximab group had more profound thrombocytopenia (1% vs. 0%, \( p = 0.002 \)) and transfusions (2% vs. 1%, \( p = 0.007 \)). The primary end point of combined death, MI, or urgent TVR at 30 days was identical between the two groups, as was the rate of TVR, MI, large MI, or any combinations of ischemic end points. The Intracoronary Stenting and Antithrombotic Regimen-Is Abciximab a Superior Way to Eliminate Elevated Thrombotic Risk in Diabetics (ISAR-SWEET) study was designed to specifically address whether the benefit of clopidogrel could be extended to diabetic patients. The trial randomized 701 diabetic patients undergoing PCI who were pretreated with 600 mg clopidogrel to receive abciximab versus placebo (123). The majority of patients (80%) were treated with bare-metal stents (10% received DES and 10% PTCA). The primary end point of death or MI at one year was similar between the abciximab and placebo groups (8.3% vs. 8.6%, \( p = 0.91 \)). Interestingly, angiographic restenosis was significantly reduced in the abciximab group (28.9% vs. 37.8%, \( p = 0.01 \)). Therefore, the two ISAR trials suggest that glycoprotein IIb/IIa receptor inhibitors may be safely withheld in elective patients if they are pretreated with 600 mg clopidogrel (given a mean of 6 h before PCI) and high-dose heparin.

There has been growing interest in resistance to antiplatelet therapy, which appears to occur more frequently than expected. Chen et al. (124) used a rapid platelet function assay to determine aspirin responsiveness in 151 patients pretreated with 300 mg clopidogrel versus placebo (125). The majority of patients (80%) were treated with bare-metal stents (10% received DES and 10% PTCA). The primary end point of death or MI at one year was similar between the abciximab and placebo groups (8.3% vs. 8.6%, \( p = 0.91 \)). Interestingly, angiographic restenosis was significantly reduced in the abciximab group (28.9% vs. 37.8%, \( p = 0.01 \)). Therefore, the two ISAR trials suggest that glycoprotein IIb/IIa receptor inhibitors may be safely withheld in elective patients if they are pretreated with 600 mg clopidogrel (given a mean of 6 h before PCI) and high-dose heparin.

There has been growing interest in resistance to antiplatelet therapy, which appears to occur more frequently than expected. Chen et al. (124) used a rapid platelet function assay to determine aspirin responsiveness in 151 patients pretreated with 300 mg clopidogrel versus placebo (125). The majority of patients (80%) were treated with bare-metal stents (10% received DES and 10% PTCA). The primary end point of death or MI at one year was similar between the abciximab and placebo groups (8.3% vs. 8.6%, \( p = 0.91 \)). Interestingly, angiographic restenosis was significantly reduced in the abciximab group (28.9% vs. 37.8%, \( p = 0.01 \)). Therefore, the two ISAR trials suggest that glycoprotein IIb/IIa receptor inhibitors may be safely withheld in elective patients if they are pretreated with 600 mg clopidogrel (given a mean of 6 h before PCI) and high-dose heparin.

There has been growing interest in resistance to antiplatelet therapy, which appears to occur more frequently than expected. Chen et al. (124) used a rapid platelet function assay to determine aspirin responsiveness in 151 patients pretreated with 300 mg clopidogrel versus placebo (125). The majority of patients (80%) were treated with bare-metal stents (10% received DES and 10% PTCA). The primary end point of death or MI at one year was similar between the abciximab and placebo groups (8.3% vs. 8.6%, \( p = 0.91 \)). Interestingly, angiographic restenosis was significantly reduced in the abciximab group (28.9% vs. 37.8%, \( p = 0.01 \)). Therefore, the two ISAR trials suggest that glycoprotein IIb/IIa receptor inhibitors may be safely withheld in elective patients if they are pretreated with 600 mg clopidogrel (given a mean of 6 h before PCI) and high-dose heparin.
**CONCLUSIONS**

We have provided a list of what we consider to be the 10 most influential original articles published in 2004 (Table 6). Although such lists are subjective, we believe that these trials will stand the test of time with respect to their impact on the field. The SYNERGY and REPLACE trials further advance the science of periprocedural antithrombotic therapy. The ISAR trials further advance the science of periprocedural antiplatelet therapy. The BRAVE trial is the first in a series of trials of facilitated angioplasty and may foreshadow the results of large reperfusion trials. The SAPPHIRE and CARP trials begin scientific evaluation by the cardiology community of issues related to noncoronary vascular disease. The TAXUS-IV trial is the seminal study of the drug elution of paclitaxel. The Merten study provides a new, easily used method of prophylaxis for contrast nephropathy. Finally, the BOOST trial opens the field of regenerative medicine for repair of myocardial damage. We believe that each of these trials require detailed study and analysis by students of the field. We look forward to an equally daunting task of collating and summarizing the trials of 2005.

**REFERENCES**


---

**Table 6. Top Ten “Must-Read” Published Studies in Interventional Cardiology 2004**

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOOST (30)</td>
<td>Intracoronary autologous bone marrow cell transfer after myocardial infarction: the BOOST randomized, controlled trial</td>
</tr>
<tr>
<td>BRAVE (8)</td>
<td>Early administration of reteplase plus abciximab vs. abciximab alone in patients with acute myocardial infarction referred for percutaneous coronary intervention: a randomized trial</td>
</tr>
<tr>
<td>CARP (121)</td>
<td>Coronary artery revascularization before elective major vascular surgery</td>
</tr>
<tr>
<td>ISAR-REACT (122)</td>
<td>A clinical trial of abciximab in elective percutaneous coronary intervention after pretreatment with clopidogrel</td>
</tr>
<tr>
<td>ISAR-SWEET (123)</td>
<td>Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel</td>
</tr>
<tr>
<td>Merten et al. (129)</td>
<td>Prevention of contrast-induced nephropathy with sodium bicarbonate: a randomized, controlled trial</td>
</tr>
<tr>
<td>REPLACE-2 (128)</td>
<td>Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs. heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization</td>
</tr>
<tr>
<td>SAPPHIRE (116)</td>
<td>Protected carotid artery stenting versus endarterectomy in high-risk patients</td>
</tr>
<tr>
<td>SYNERGY (49)</td>
<td>A prospective, randomized trial of enoxaparin vs. unfractionated heparin in high-risk patients with non–ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy</td>
</tr>
<tr>
<td>TAXUS-IV (81)</td>
<td>A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease</td>
</tr>
</tbody>
</table>

**Antithrombin therapy.** On the basis of the REPLACE-2 trial, bivalirudin has become a widely accepted alternative to unfractionated heparin for patients undergoing PCI. Long-term clinical outcome data from the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial were reported in 2004 (128). At six months and one year, the incidence of death and MI was similar in both study groups, suggesting that the efficacy of bivalirudin remains comparable to that of heparin plus glycoprotein IIb/IIIa inhibition at late follow-up.

**Agents to prevent RCN.** Apart from preprocedural hydration, measures to prevent RCN have proven disappointing. In this regard, the report from Merten et al. (129) provides hope that sodium bicarbonate administration may be of value to prevent this complication. These authors randomized 119 patients with mild chronic kidney disease (creatinine $\geq$1.1 mg/dl) to sodium chloride or sodium bicarbonate administered during procedures, where on average of 370 ml of iopomiodol was used. They found that RCN developed in 1.7% of sodium bicarbonate–treated and 13.6% of sodium chloride–treated patients. A follow-up registry of 191 similar patients treated with sodium bicarbonate yielded RCN in 1.6% of patients. In another study, Spargias et al. (130) found that prophylactic oral ascorbic acid may also protect against RCN in high-risk patients. Although these studies provide important steps forward, RCN remains a challenging and difficult problem in clinical practice and will be an important area for ongoing investigation in 2005.


