Clinical and research issues regarding chronic advanced coronary artery disease: Part I: Contemporary and emerging therapies

E. Marc Jolicoeur, MD, MSc,a Christopher B. Granger, MD,a Timothy D. Henry, MD,b David J. Holmes, MD,c Carl J. Pepine, MD,d Daniel Mark, MD,a Bernard R. Chaitman, MD,e Bernard J. Gersh, MB, ChB, DPhil,f and E. Magnus Ohman, MDa on behalf of the Working Group Membersg Durham, NC; Rochester, MN; Gainesville, FL; and St. Louis, MO

The following report is based on a working group meeting about advanced coronary artery disease for patients with refractory ischemia who cannot receive revascularization. The aims were to review currently available treatment strategies, define unmet clinical needs, explore clinical trial design issues, and identify promising novel therapeutic targets and approaches for patients with chronic ischemia. The Working Group brought together medical experts in the management of refractory angina with representatives from regulatory agencies, Centers for Medicare and Medicaid Services, and industry. The meeting began with presentations reviewing the limitations of the current medical therapies and revascularization strategies and focused on lessons learned from past therapeutic attempts to optimize outcomes and on what are considered to be the most promising new approaches. Perspectives from clinical experts and from regulatory agencies were juxtaposed against needs and concerns of industry regarding development of new therapeutic strategies. This report presents the considerations and conclusions of the meeting on December 4-5, 2006. This document has been developed as a 2-part article, with contemporary and emerging therapies for advanced coronary artery disease reviewed first. Trial design, end points, and regulatory issues will be discussed in the second part of the article. (Am Heart J 2008;155:418-34.)

Part I. Contemporary and emerging therapies

The population of patients with advanced coronary artery disease (CAD) is growing as a result of the aging of the general population, more extensive use of revascularization, and more effective therapies that have prolonged the survival of patients with severe atherosclerosis. Patients with refractory angina who have exhausted most therapeutic options comprise a growing clinical entity and a therapeutic dilemma. Nonetheless, advanced CAD receives relatively little attention from the medical and research communities. As a result, the scope of the disease is not well defined, its coverage in guidelines from professional associations is scant,1,2 and few new medical options are available.3

This report reviews the current status of advanced CAD, the limits of the contemporary available therapies, and the difficulties encountered in the development of new approaches.

Definition of advanced CAD

Advanced CAD has been recognized under several terms and classifications: intractable angina pectoris, no-option CAD, nonrevascularizable CAD, and end-stage CAD. Truly, refractory angina embodies several chronic coronary artery syndromes that vary in their manifestation and pathophysiology. The syndromes of chronic CAD, their definitions, and suggested pathophysiology are summarized in Table I.

Recently, a European Society of Cardiology Joint Study Group on the Treatment of Refractory Angina proposed the following definition: “A chronic condition (>3 months) characterized by the presence of angina caused by coronary insufficiency in the presence of CAD, which cannot be controlled by a combination of medical therapy, angioplasty, and coronary bypass surgery. The presence of reversible myocardial ischemia should be clinically established to be the cause of the symptoms.”4 Advanced CAD could
be more practically defined as symptomatic multi-vessel CAD in patients who are not candidates for revascularization with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery.

The reasons why a patient may not be revascularizable include unsuitable coronary anatomy, surgery-related issues (previous CABG, lack of surgical conduits, multiple thoracotomies, extensive aortic calcification), extracardiac comorbid illnesses (renal failure, chronic obstructive pulmonary disease), and advanced age (which often combines the above-mentioned features). However, the “nonrevascularization” status also will be influenced by local expertise, operator tolerance to risk, and patient agreeing to the procedure. Likewise, the threshold for revascularization may be modified depending on the clinical context.

Prevalence of advanced CAD

Precise estimates of the prevalence of advanced CAD in a global population are not available. However, rough estimates have been obtained from population surveys and catheterization laboratory registries. In the late 1990s, Mukherjee et al reported that 12% of the patients referred for symptomatic CAD were not amenable to PCI or CABG.

In absolute numbers, this would represent more than 100,000 patients per year in the United States. This proportion is somewhat similar to Swedish surveys in which 10% of the patients did not undergo revascularization despite severe angina symptoms. Inferences from catheterization laboratory registries should be interpreted with caution, however, because referrals for angiography are generally biased by patients initially deemed by their physicians to be candidates for revascularization. This referral bias likely leads to an underestimate of the true prevalence of chronic refractory angina because the most morbid patients are probably not included in the denominator. Using the same logic, this referral bias may lead to an overrepresentation of unsuitable anatomy (or lack of graft material) as a reason for revascularization ineligibility.

Mortality associated with advanced CAD

In patients with chronic stable angina, the annual mortality rate is approximately 1.5%. For advanced CAD, few mortality and morbidity data have been
<table>
<thead>
<tr>
<th>Study therapy, year</th>
<th>Design (n)</th>
<th>Relevant inclusion/exclusion criteria</th>
<th>Mortality and morbidity in control group</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schofield et al15 TMR, 1999 Control: medical</td>
<td>E: LVEF &gt;30%, unable to do treadmill, life expectancy &lt;12 mo</td>
<td>Death: 4% at 12 mo ACS: 63% at 12 mo</td>
<td>Medical therapy not detailed ACS expressed as 0.8 per patient-year (n = 83)</td>
<td></td>
</tr>
<tr>
<td>ATLANTIC11 TMR, 1999 Control: medical</td>
<td>I: At least one protected vascular territory E: LVEF &lt;30%, unable to do treadmill</td>
<td>Death: 10% at 12 mo ACS: 77% at 12 mo CHF: 10% at 12 mo</td>
<td>Protected region defined as unobstructed blood flow (lesion &lt;50%) or patent CABG: 65% had a protected LAD</td>
<td></td>
</tr>
<tr>
<td>Frazier et al12 TMR, 1999 Control: medical</td>
<td>E: LVEF &lt;20%, concurrent major illness</td>
<td>Death: 21% ACS: 69% at 12 mo</td>
<td>18 patients underwent revascularization procedure despite being nonrevascularizable initially. At 5 y; the number goes up to 35</td>
<td></td>
</tr>
<tr>
<td>Allen et al10 TMR, 1999 Control: medical</td>
<td>I: Class IV angina only E: LVEF &lt;25%, severe COPD</td>
<td>Death: 11% at 12 mo ACS: 69% at 12 mo</td>
<td>The incapacity to undergo a stress test was not an inclusion criterion.</td>
<td></td>
</tr>
<tr>
<td>PACIFIC14 TMR, 2000 Control: medical</td>
<td>E: LVEF &lt;30%, unable to do treadmill, symptomatic heart failure, renal insufficiency, moderate AS, severe PAD</td>
<td>Death: 3% at 12 mo ACS: 53% at 12 mo CHF: 10% at 12 mo</td>
<td>24 patients had PTCA/CABG or TMR during follow-up. Nonrevascularization assessment poorly defined</td>
<td></td>
</tr>
<tr>
<td>Aaberge et al9 TMR, 2000 Control: medical</td>
<td>E: age &gt;75 y, LVEF &lt;30%, overt heart failure</td>
<td>Death: 8% at 12 mo ACS: 40% at 12 mo</td>
<td>Medical therapy is optimal with rate of administration higher than 80%</td>
<td></td>
</tr>
<tr>
<td>Leon et al13 TMR, 2005 Control: placebo</td>
<td>E: unable to do treadmill, chronic AF</td>
<td>Death: 5% at 12 mo ACS: 3% at 12 mo MACE: 11% at 12 mo</td>
<td>Medical therapy group underwent sham invasive procedure (may affect survival)</td>
<td></td>
</tr>
<tr>
<td>FIRST19 rFGF-2, 2002 Control: placebo</td>
<td>E: LVEF &lt;30%, unstable cardiac condition or revascularization within the past 3 mo, renal dysfunction</td>
<td>Death: 1% at 6 mo ACS: 15% at 6 mo MACE: 6%</td>
<td>Placebo patients underwent intracoronary placebo injection with no complication. Hypotension associated with dosing was reported</td>
<td></td>
</tr>
<tr>
<td>VIVA16 rhVEGF, 2003 Control: placebo</td>
<td>I: age 40-75 y E: LVEF &lt;25%, previous TMR, unable to do treadmill, history cancer/proliferative diabetic retinopathy, renal dysfunction</td>
<td>Death: 3% at 4 mo ACS: 11% at 4 mo</td>
<td>Placebo patients underwent intracoronary placebo injection with no complication</td>
<td></td>
</tr>
<tr>
<td>Euroinject One17 phVEGF-A65, 2005 Control: placebo</td>
<td>E: LVEF &lt;45%, history of cancer, proliferative diabetic retinopathy, premenopausal women</td>
<td>Death: 3% at 6 mo ACS: 15% at 6 mo</td>
<td>Placebo patients underwent sham injections (2 procedural complications reported. STEMI and complete AV block)</td>
<td></td>
</tr>
<tr>
<td>REVASC18 Ad-VEGF121, 2006 Control: medical</td>
<td>I: Angina CCS II-IV E: age &gt;80 y, LVEF &lt;25%, unprotected proximal LAD stenosis/left main equivalent, ICD, severe CHF, anemia unable to do treadmill, renal dysfunction</td>
<td>Death: 3% at 6 mo MACE: 26% at 6 mo</td>
<td>Several exclusion criteria, including past history of cancer</td>
<td></td>
</tr>
<tr>
<td>AGENT III and IV21 Control: placebo</td>
<td>I: age 30-75 y, angina CCS II-IV</td>
<td>MACE: 22% at 12 mo</td>
<td>Mortality rates not provided</td>
<td></td>
</tr>
</tbody>
</table>
reported. In recent years, several controlled trials have explored the efficacy of alternative therapies including laser transmyocardial revascularization and therapeutic angiogenesis. In general, these trials enrolled patients with refractory angina despite optimal medical therapy, so that the outcomes experienced by the patients randomized to the control arm of these trials may give a fair representation of the outcomes experienced by patients with advanced CAD (Table II). In the control arm of these alternative therapy trials, annual mortality rates varied from 3% to 21%, whereas coronary events rates (including hospitalization for decompensated angina and acute coronary syndromes [ACSs]) varied from 11% to 69%. Of note, most of these trials excluded patients unable to perform an exercise treadmill test (ETT) or patients with left ventricular ejection fraction (LVEF) <30% (detailed in Table II). Thus, these exclusion criteria are biased toward a less severe picture than what may actually be the case in an unselected population of advanced CAD because inability to perform an exercise test is associated with increased mortality.

Registries provide additional but variable information. The Mediators of Social Support Study reported mortality and myocardial rates of 38% and 10%, respectively, after a median of 2.2 years of follow-up for patients with medically treated advanced CAD (defined as significant 3-vessel or left main disease and either LVEF <50% or severe angina). Hospitalization occurred in 89% of patients. In the Options In Myocardial Ischemic Syndrome Therapy Program (Minneapolis Heart Institute, Minneapolis, MN), the largest reported prospective series of patients with refractory angina reported, total mortality was 11.7% after an average follow-up of 5.4 years. Despite the presence of extensive CAD, cardiovascular mortality was low (6.2%)—an annualized death rate of only 1%. Of note, 8.3% of all the patients experienced myocardial infarction (MI). Patients who died were more likely to have diabetes, peripheral arterial disease, chronic renal disease, valvular disease, history of congestive heart failure (CHF), lower ejection fraction, and more angina at baseline.

In aggregate, these data suggest that mortality associated with advanced CAD is variable and depends on multiple factors including associated comorbidities. In addition to improving mortality and cardiovascular events, newer therapies directed at advanced CAD should also improve functional status and health-related quality of life.

### Contemporary treatments of advanced CAD

Current pharmacological and nonpharmacological therapies are outlined in Tables III and IV. Most antianginal medications currently in use decrease myocardial oxygen demand either by limiting heart rate, lowering systolic pressure, or by decreasing contractility. Additional lusitropic and vasodilatory properties also contribute significantly.

Combination of antianginal medication is often needed to relieve refractory angina. Simple principles may be used to enhance the efficacy of these possible combinations. For instance, the circadian variation of ischemic episodes shows 2 peaks (one in the early morning and one in the late evening). An appropriate chronopharmacological strategy using different preparations of extended-release nitrates or long-acting calcium antagonists may help achieve a significantly better therapeutic response in these critical periods of the day. Orthostatic hypotension frequently limits the total dose of antianginal medication that can be administered to a patient. Likewise, orthostatic hypotension by itself may beget angina due to a decrease of the coronary perfusion pressure. Simplification of the drug regimen should be attempted whenever possible to enhance medical adherence.

Secondary causes of angina, like anemia, poorly controlled hypertension, thyroid dysfunction, or atrial fibrillation with rapid ventricular rate response, should be identified and treated accordingly.
Rationale for the administration of β-blockers, calcium antagonists, and nitrates in refractory angina relates to the evidence for their use in the wider population of patients with chronic stable angina (Table III). In addition to this traditional pharmacopeia, newer anti-anginal drugs like ranolazine are now available. Antiplatelet agents and intensive dyslipidemia management should be part of a comprehensive approach to risk factor modification.

### Table III. Contemporary treatments for chronic refractory angina: pharmacological therapies

<table>
<thead>
<tr>
<th>Pharmacological therapy</th>
<th>Proposed mechanisms of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin and clopidogrel</td>
<td>No known antianginal effect: prevention of thrombotic events</td>
<td>Warfarin may be substituted in case of AF or decreased LVEF</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1. Coronary vasodilatation 2. Ventricular wall stress reduction (i.e., both pre- and postcharge) 3. Antithrombotic effect</td>
<td>Tachyphylaxis development: nitrate-free periods required</td>
</tr>
<tr>
<td>Dihydropiridine calcium antagonists</td>
<td>1. Coronary vasodilatation 2. Afterload reduction (anti-HTN)</td>
<td>May cause reflex tachycardia: should be used in combination to a β-blockers. Aggravation of angina possible if severe fixed coronary obstruction</td>
</tr>
<tr>
<td>Ranolazine</td>
<td>1. Partial inhibition of late Na+ current (I\textsubscript{Na}) 2. Partial inhibition of fatty acid metabolism</td>
<td>Doubt have been emitted about action of ranolazine on fatty acid oxidation</td>
</tr>
<tr>
<td>Statins</td>
<td>1. Unknown: improved endothelial function of epicardial conductance vessels 2. ↓ coronary events 3. Plaque burden regression</td>
<td>Prolonged use required before therapeutic effect</td>
</tr>
<tr>
<td>Opioids</td>
<td>1. Direct analgesia 2. Possible decrease in adrenergic tone with epidural analgesia</td>
<td>Reserved for selected patients, often as a palliative solution. Frequent adverse events. Epidural analgesia hampered by several side effects</td>
</tr>
</tbody>
</table>

AF, Atrial fibrillation; HTN, hypertension.

**Pharmacological treatments**

Rationale for the administration of β-blockers, calcium antagonists, and nitrates in refractory angina relates to the evidence for their use in the wider population of patients with chronic stable angina (Table III). In addition to this traditional pharmacopeia, newer anti-anginal drugs like ranolazine are now available. Antiplatelet agents and intensive dyslipidemia management should be part of a comprehensive approach to risk factor modification.

**Antiplatelet agents combination: aspirin and clopidogrel.** Neither aspirin nor clopidogrel has intrinsic antiangiinal properties. Aspirin is a mandatory component of the treatment of CAD because of its ability to prevent atherothrombotic events. Several trials have assessed whether the combination of aspirin with clopidogrel would result in a further reduction of coronary events. The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events trial showed that clopidogrel was slightly better than aspirin in preventing vascular complications in a population of patients with stable vascular disease. The Clopidogrel in Unstable Angina to Prevent Recurrent Events trial demonstrated a 20% relative reduction of cardiovascular events when clopidogrel was added to aspirin in patients with ACS.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance trial assessed whether the addition of clopidogrel (75 mg, daily) to aspirin (75-162 mg, daily) was superior to aspirin alone in reducing adverse cardiovascular events in high-risk stable patients for over 4 years. The combination led to a nonsignificant reduction of the composite end point (cardiovascular death/MI/stroke) from 7.3% in the placebo plus aspirin arm to 6.8% in the clopidogrel plus aspirin arm ($P = .22$). However, aspirin plus clopidogrel significantly increased moderate bleeding (2.1% vs 1.3%, $P < .001$). In a prespecified subgroup analysis, patients with documented atherothrombotic disease at baseline did derive benefit from clopidogrel (6.9% vs 7.9% in the placebo group, $P = .046$). However, there is currently no strong evidence for routinely combining antiplatelet therapy...
**Table IV.** Contemporary treatments for chronic refractory angina: mechanical treatments and advances

<table>
<thead>
<tr>
<th>Nonpharmacological therapy</th>
<th>Proposed mechanisms of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTO recanalization</td>
<td>1. Restoration of epicardial blood flow</td>
<td>Success depends on technical skills and technology used</td>
</tr>
<tr>
<td>EECP</td>
<td>1. Diastolic augmentation + enhanced coronary perfusion pressure</td>
<td>Contraindications: impossible ECG gating, decompensated heart failure, severe AI, uncontrolled systemic hypertension, severe pulmonary hypertension, severe lower extremity PAD, aortic aneurysm, recent DVT</td>
</tr>
<tr>
<td></td>
<td>2. ↓ LV afterload</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Release of growth factors, mobilization of progenitor cells, ↑ NO and ↓ intraendothelial pressure</td>
<td></td>
</tr>
<tr>
<td>Spinal cord stimulation</td>
<td>1. Pain inhibition: gate control theory</td>
<td>Class A therapeutic option for refractory angina according to ESC Joint Study Group</td>
</tr>
<tr>
<td></td>
<td>2. Anti-ischemia:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. ↓ myocardial oxygen consumption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Redistribution of coronary flow</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. ↓ sympathetic tone</td>
<td></td>
</tr>
<tr>
<td>Heart transplantation</td>
<td>Organ replacement</td>
<td>Described indication: few cases reported</td>
</tr>
</tbody>
</table>

*AI, Aortic insufficiency; DVT, deep vein thrombosis; ECG, echocardiogram; ESC, European Society of Cardiology; LV, left ventricle; NO, nitric oxide; PAD, peripheral arterial disease.*

In patients who remain symptomatic despite optimal medical therapy.

**Statin and dyslipidemia management.** Intensive statin therapy reduces death and vascular events in patients with established CAD. Whether statins have a true anti-ischemic effect on top of usual therapy is unknown. Statin-related improvement in endothelial function provides a rationale for how angina could be improved. The regression of atherosclerotic plaque burden observed with intensive statin therapy or with reconstituted high-density lipoprotein (HDL) ApoA-1 Milano or with recombinant HDL has generated hope for a reversal of symptoms in patients with advanced CAD.

Fueled by the observational studies suggesting protection by elevated HDL, modulation of HDL intermediate metabolism has been considered a promising target for halting progression of atherosclerosis. In the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events trial, however, the experimental HDL-raising drug torcetrapid (a cholesteryl-ester-transfer-protein [CETP] inhibitor) in combination with atorvastatin was associated with an increased risk of death. Aside from the significant increase in the blood pressure associated with the drug, it has been speculated that the type of HDL produced by CETP inhibition may be proatherogenic rather than antiatherosclerotic.

**Ranolazine.** Ranolazine (Ranexa) is the first drug in more than 20 years to be approved by the United States Food and Drug Administration (FDA) for the treatment of chronic angina. The antianginal mechanisms of action of ranolazine are not entirely known. It had been postulated that ranolazine acted as a partial inhibitor of fatty acid oxidation, which would facilitate energy production in hypoxic cardiomyocytes by partially shifting cardiac lipid oxidation to glucose oxidation. More recent studies in human cardiac myocytes indicate this is an unlikely explanation for the antianginal/anti-ischemic properties because the pFOX inhibitory effect is small at the concentrations of ranolazine used to treat chronic angina.

More recently, ranolazine has been found to have electrophysiological properties similar to amiodarone, which could explain its anti-ischemic and antianginal properties. At the cardiomyocytes level, ranolazine inhibits the late Na⁺ current, which is found to be abnormally increased during hypoxia or in the presence of reactive oxygen species and ischemic metabolites. In experimental hypoxic conditions, this inhibition of the Na⁺ current leads to an intracellular Na⁺ overload, which activates several exchangers to maintain cellular Na⁺ homeostasis. One of the most important exchangers is the Na⁺/Ca⁺ exchanger that transports excess Na⁺ out of the cell in exchange for Ca⁺, resulting in abnormal intramyocyte Ca⁺ concentration. This abnormal Ca⁺ overload impairs both the contraction-relaxation coupling and as a consequence increases diastolic tension, thereby reducing coronary perfusion. Ranolazine, through a partial inhibition of the late Na⁺ current, could limit this pathological process and attenuate the abnormal increase in intracellular Ca⁺.

The Monotherapy Assessment of Ranolazine in Stable Angina (MARISA) study was the first placebo-controlled crossover trial with the sustained release preparation to demonstrate the anti-ischemic effect of ranolazine as monotherapy among patients with chronic severe angina. In MARISA, a 1-week treatment of ranolazine resulted in a dose-related increase in the exercise duration. In the Combination Assessment of Ranolazine In Stable Angina (CARISA) trial, the addition of ranolazine to standard dose of atenolol, diltiazem, or amiodipine significantly (but modestly) increased exercise capacity and time to
electrographic ischemia during stress testing. Of note, ranolazine provided additional anti-ischemic benefits in a setting where some of the traditional anti-ischemic agents have failed to do so. The findings in CARISA were confirmed by the Efficacy of Ranolazine in Chronic Angina trial, which assessed ranolazine in patients with persistent angina despite maximum recommended dosage of amlodipine. Long-term safety information is now available through the Ranolazine Open Label Experience registry that followed on the MARISA and CARISA trials. After 2 years, less than 10% of the patients discontinued ranolazine because of unacceptable adverse events: annualized death rate was of 3%. The recently completed MERLIN trial also established the 1-year safety record of ranolazine in a large placebo-controlled trial of 6560 patients with ACS.

Because ranolazine exerts its antianginal effect differently than the modes of action of nitrates, β-blockers, or calcium antagonists and has minimal effects on heart rate or blood pressure, it is well-suited for add-on therapy in clinically eligible refractory angina patients. This includes patients who do not tolerate additional chronotropic- or inotropic-negative therapy.

Opioids. Opioids are generally reserved for selected cases of refractory angina when other therapeutic options have failed. Under close surveillance, opioids may be administered with reasonable efficacy and with limited side effects. For several years, opioids have been used with success in Denmark for the treatment of chronic refractory angina. Importantly, the use of opioids is limited by frequent side effects such as constipation, nausea, and disorientation.

Mechanical treatments and advances

Although highly effective for the treatment of symptomatic angina, PCI may be challenging with complex coronary anatomy including diffuse disease and chronic total occlusions (CTOs). Significant nonpharmacologic advances are now being proposed to patients with refractory angina (Table IV).

Chronic total occlusion recanalization. By definition, a CTO of a coronary artery is present for more than 3 months. Chronic total occlusions have been identified in up to 30% of diagnostic catheterizations. Advances in coronary interventional techniques have enabled recanalization of CTOs with good procedural success rates in selected cases. Although routine opening of occluded arteries in the days after acute MI does not reduce the occurrence of death, reinfarction, or heart failure, recanalization of chronic occlusions may improve symptoms and possibly even the prognosis of patients with advanced CAD.

Even with the sophisticated interventional tools currently available, CTO recanalization is attempted less frequently than it was 10 years ago. In the 7-year period covered by the National Heart, Lung, and Blood Institute’s (NHLBI) Dynamic Registry, the percentage of attempted CTOs recanalization dropped from 9.6% of all PCI in 1997 to 5.7% in 2004 (P < .0001). The success rate of the procedure remained stable at 71% in spite of a significant increase in the length of lesions attempted (from 17.0 to 22.4 mm, P = .006).

In the largest reported observational study of patients undergoing PCI for a CTO, a successful recanalization was associated with a significant 10-year survival advantage when compared with a failed revascularization. In the stent era, the rate of target vessel revascularization at 1 year after CTO recanalization has declined by approximately 50%. In return, CTO attempts are associated with peri-procedural complication rates exceeding 5%, including MI, emergency cardiac surgery, and death. Progress in CTO recanalization is anticipated with emerging technologies, including new tapered hydrophilic guidewires, laser excimer, and plaque softening formulation.

Enhanced external counterpulsation. By generating precisely timed diastolic pressure augmentation, enhanced external counterpulsation (EECP) produces externally what aortic counterpulsation does internally. Diastolic augmentation is accomplished with inflatable cuffs that sequentially compress the lower limbs during diastole and rapidly deflate before systole. This systemic diastolic pressure augmentation increases coronary perfusion pressure, decreases ventricular afterload, and increases venous return.

The efficacy of EECP in patients with angina was assessed by a single randomized sham placebo-controlled Multicenter Study of EECP (MUST-EECP). The trial assessed whether a treatment regimen of 1 hour of active counterpulsation daily for 35 days would improve subjective angina and objective ischemia parameters when compared with sham lower limb compression. When compared with baseline, EECP did not increase ETT duration but did significantly improve the time to ≥1 mm ST-segment depression. Likewise, patients randomized to EECP reported an improvement of their angina symptoms when compared with control patients. Of note, 55% of the patients in active treatment arm reported adverse events (such as lower limb bruise, edema, and leg pain), but only 10% were severe enough to cause withdrawal.

A number of hypotheses have been proposed for the sustained antianginal effect of EECP, including a pressure-driven recruitment of myocardial collaterals, hemodynamic changes, the release of proangiogenic cytokines, and a peripheral training effect. The peripheral training effect seems mediated by a decrease in peripheral vascular resistance and a more appropriate heart rate response to exercise. The vascular shear stress provided by EECP is thought to...
result in a systemic release of growth factors and proangiogenic cytokines.74-76

The use of EECP is limited by the need to commit to 35 days of in-laboratory treatment. Enhanced external counterpulsation is contraindicated in several situations such as decompensated heart failure, severe peripheral arterial disease, and severe aortic insufficiency. These comorbid conditions are frequently encountered in patients with advanced CAD. When applied to the appropriate patient, EECP is well tolerated and associated with low risk of adverse events.77-80

### Table V. Emerging therapies for advanced CAD

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Proposed mechanisms of action</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine87</td>
<td>Sinus node slowing: inhibits pacemaker current (If)</td>
<td>Approved in Europe for patients with chronic stable angina with sinus rhythm and contraindication to beta-blockers. Limited use for patient with refractory angina</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>1. Opening of ATP-sensitive potassium channels ([KATP]: dilatation of coronary resistance arterioles 2. Nitrate-like effect 3. Mimetic of ischemic preconditioning</td>
<td>Approved in Europe. May be use to bridge the nitrate-free periods required to avoid tachyphylaxis</td>
</tr>
<tr>
<td>Trimetazidine</td>
<td>1. Mitochondrial 3-KetoAcyl CoA thiolase inhibitor 2. Shift ischemic myocardium from fatty acid to carbohydrate use</td>
<td>Approved in Europe for patients with chronic stable angina</td>
</tr>
<tr>
<td>Perhexilene</td>
<td>1. Mitochondrial carnitine-palmitoyl-transferase inhibitor 2. Shift ischemic myocardium from fatty acid to carbohydrate utilization</td>
<td>Serum level monitoring required due to risk of hepatic toxicity</td>
</tr>
<tr>
<td>Therapeutic angiogenesis</td>
<td>1. Sustained tissular expression of proangiogenic factors 2. Neovascularization</td>
<td>See Table VI for review of randomized control trials of gene therapy</td>
</tr>
<tr>
<td>Cellular therapy</td>
<td>1. Paracrine secretion of proangiogenic factors 2. Neovascularization 3. Myogenesis (P)</td>
<td>Various type of cell available with additional possibility to combine stem cell therapy and gene therapy</td>
</tr>
<tr>
<td>Thrombolytic agent</td>
<td>1. Depletion in fibrinogen 2. Improved blood rheology and microcirculatory flow</td>
<td>Urokinase administrated through intermittent dose. Treatment never compared to placebo in a trial</td>
</tr>
<tr>
<td>Chelation therapy</td>
<td>1. Reduced LDL oxidation 2. PTH-related vasodilatory effect 3. Enhanced H-FX production</td>
<td>No direct evidence of clinical efficacy.</td>
</tr>
<tr>
<td>Transmyocardial laser revascularization</td>
<td>Direct myocardial revascularization through microchannels formation</td>
<td>No direct evidence of clinical efficacy</td>
</tr>
<tr>
<td>Extracorporeal cardiac shock wave therapy</td>
<td>1. Cavitation effect 2. Upregulation of VEGF expression by the myocardium 3. Enhanced coronary angiogenesis</td>
<td>Efficacy and safety of SW have been reported in a phase 1 trial including 9 patients</td>
</tr>
<tr>
<td>Neovasc reducer coronary sinus stent</td>
<td>Controlled and permanent narrowing of coronary sinus. Pressure-driven redistribution of antegrade blood flow toward region of lesser resistance</td>
<td>First-in-man reported in 10 patients in 2006</td>
</tr>
<tr>
<td>PICVA</td>
<td>Shunting of arterial blood into the coronary veins with subsequent retroperfusion of capillaries</td>
<td>Evolving technology. Associated with several procedural flaws and with high complications rates</td>
</tr>
</tbody>
</table>

LDL, Low-density lipoprotein; SW, shock wave.

Neuromodulation. Neuromodulation includes transcutaneous electric nerve stimulation and spinal cord stimulation. Long-term transcutaneous electric nerve stimulation therapy is limited by electrode-related skin irritation associated with prolonged use. Spinal cord stimulation has been used in the past 30 years to relieve various pain syndromes. It is now recognized as a valid therapeutic option in Europe (class IA) for the treatment of refractory angina.4 Modern spinal cord stimulators are entirely subcutaneously implantable and can be installed under local anesthesia using a minimally invasive...
procedure. The therapy is self-administered by the patient and requires stimulation during 1 hour, 3 times a day, and whenever angina is felt.

The analgesic effect of neuromodulation is not fully understood but likely results from several simultaneous mechanisms. In addition to the analgesic modulation of A-beta neurons abnormal activity and to the restoration of normal gamma (γ)-aminobutyric acid levels in the dorsal horn, relief of angina may also be the consequence of adenosine-mediated coronary vasodilatation and of reduced sympathetic afference.81

An anti-ischemic effect has been demonstrated both with exercise stress testing and ambulatory electrocardiogram monitoring.82

Spinal cord stimulation has been compared with transmyocardial laser revascularization in patients with refractory angina83; no difference in the mean total exercise time, angina-free exercise capacity, and Canadian Cardiovascular Society (CCS) class could be identified between the 2 groups.

Overall, spinal cord stimulation appears safe. The initial concerns regarding a possible deprivation of a

### Table VI. Randomized placebo-controlled trials of therapeutic angiogenesis in patients with CAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy/Delivery method</th>
<th>Outcomes</th>
<th>Safety</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laitinen et al,2000 (15 patients)</td>
<td>1000 μg plasmid-liposome + mouse VEGF/IC infusion</td>
<td>Trial intended to assess the effect of local VEGF therapy on post-PCI restenosis; no effect. Ischemia not assessed</td>
<td>No major serious adverse events reported at 6 mo</td>
<td>Murine gene used. Strong suspicion of inefficient gene transfer. Patients with advanced CAD excluded</td>
</tr>
<tr>
<td>FIRST,19 2002 (337 patients)</td>
<td>Ascending doses of rFGF2/IC</td>
<td>No effect on ETT total time at 90 and 180 d</td>
<td>5 deaths (1%) reported in the rFGF-2 treated patients; similar to placebo (1%)</td>
<td>Angina frequency ↓ by rFGF-2 at 90 d: difference no longer present at 180 d</td>
</tr>
<tr>
<td>Losordo et al,2002 (19 patients)</td>
<td>Ascending doses of plasmid DNA VEGF-2/Transendo</td>
<td>Reduction in CCS angina class significantly better in VEGF-2 patients at 12 wk</td>
<td>No major serious adverse events reported</td>
<td>Patients with class II or III angina. Trial interrupted by FDA due to a death in an unrelated adenoviral gene therapy trial</td>
</tr>
<tr>
<td>AGENT,94 2002 (79 patients)</td>
<td>Ascending doses of Ad5-FGF4/IC infusion</td>
<td>Nonsignificant trend toward improvement of ETT total time and time to angina</td>
<td>No major serious adverse event (mean f/u, 311 d); One case of brain tumor</td>
<td>Patients with class II or III angina. No significant dose-response effect</td>
</tr>
<tr>
<td>AGENT II,95 2003 (52 patients)</td>
<td>10⁹ pfu Ad5-FGF4/IC infusion</td>
<td>Nonsignificant change in SPECT reversible perfusion defect size</td>
<td>No major serious adverse event reported</td>
<td>Total perfusion defect size (necrosis + ischemia) significantly improved with Ad5-FGF4 (4.2% vs 0%, P = .001). Clinically significant reduction of angina class by day 120 in the high-dose group</td>
</tr>
<tr>
<td>VIVA,16 2003 (178 patients)</td>
<td>rhVEGF low and high doses/IC infusion day 0 then IV infusion days 3, 6, and 9</td>
<td>No effect on ETT total time, myocardial perfusion (SPECT) or on angina at day 60</td>
<td>Significant improvement in total ETT time and reduction of angina class by day 120 in the high-dose group</td>
<td></td>
</tr>
<tr>
<td>KAT,96 2003 (103 patients)</td>
<td>2 x 10⁹ pfu AdVEGF-165 vs 2 mg plasmid-liposome VEGF/IC infusion</td>
<td>Improvement in SPECT reversible perfusion defect size in AdVEGF group. No effect on ETT parameter</td>
<td>Two new cancers diagnosed in the plasmid arm</td>
<td>Moderate angina patients (CCS 2-3). Study designed to assess effect of VEGF on restenosis post-PCI</td>
</tr>
<tr>
<td>Euroinject,17,97 2005 (80 patients)</td>
<td>0.5 mg of plasmid VEGF-A165/Transendo</td>
<td>No effect on SPECT reversible perfusion defect size. Improved regional wall motion in the active group</td>
<td>NOGA procedure related events in 5 patients</td>
<td>No-option patients with severe angina. First trial to use a gene vector (blind plasmid) as a placebo control</td>
</tr>
<tr>
<td>AGENT III and IV,98 2007 (pooled analysis 532 patients)</td>
<td>10⁹ pfu vs 10¹ pfu Ad5-FGF4 vs placebo/IC infusion</td>
<td>No effect on total ETT time. No major serious adverse event reported</td>
<td>Significant improvement in total ETT time and reduction of angina in women treated with either 10⁹ or 10¹ pfu Ad5-FGF4 vs placebo</td>
<td>Significant improvement in total ETT time and reduction of angina in women treated with either 10⁹ or 10¹ pfu Ad5-FGF4 vs placebo</td>
</tr>
</tbody>
</table>

Ad, Adenovirus; f/u, follow-up; IC, intracoronary; IV, intravenous; pfu, plaque forming units; Transendo, transendocardial injection.
pain warning signal, as would be the case during a threatened MI, do not appear to be warranted. Animal studies even suggest that thoracic spinal cord stimulation reduces the risk of ischemic ventricular arrhythmias in postinfarction heart failure. The only randomized placebo-controlled trial, the Stimulation Therapy for Angina Refractory to Standard Treatments, Interventions, and Medications trial, was prematurely suspended in 2006. Results from this study have not been published.

Other therapeutic options such as thoracic epidural anesthesia, thoracic sympathectomy, and left stellate ganglion blockade have been associated with anecdotal success but are rarely used because of their frequent side effects and invasive nature.

Emerging therapies for chronic refractory angina

Although some of the emerging therapies presented in the Table V are experimental, others are currently accepted for clinical use and are gaining wider acceptance.

Nicorandil

Nicorandil has been assessed among patients with established CAD and recently diagnosed as having angina during the IONA trial. In addition to a nitrate-like effect, nicorandil opens the mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels (K<sub>ATP</sub>), a property presumed to mimic the ischemic preconditioning phenomenon. Compared with placebo, nicorandil reduced the combined end point of cardiovascular death, non-fatal MI, and hospital admission for cardiac chest pain (13.1% vs 15.5%, P = .014). Although nicorandil favorably influenced death and MI in a combined end point, neither component was improved when taken separately. Despite its apparent clinical benefit, nicorandil is currently not approved for use in North America. Trial data on the efficacy of nicorandil as an antianginal drug are inconsistent. The IONA trial highlights issues around the FDA requirements for approval of new antiangina medication (please see Part II: Trial Design, End points, and Regulatory Issues). Like many other therapies discussed in this section, nicorandil has not been specifically investigated in patients with refractory angina; little information is available on the safety of nicorandil in combination with traditional antiangina therapy.

Metabolic modulation of ischemic myocardium

In contrast to the traditional antianginal agents that operate through negative-chronotropic or negative-inotropic means, newer agents that favorably modulate energy metabolism of the myocardium are being developed. In normal conditions, free fatty acids are the main source of energy for cardiomyocytes. Agents like trimetazidine and perhexiline inhibit fatty acids β-oxidation pathways at the mitochondrial level. As a result, in cardiomyocytes glucose metabolism is favored over the fatty acids metabolism. When compared with free fatty acids, glucose metabolism results in a higher ATP production for the same level of oxygen requirements; accordingly the imbalance between oxygen level and supply takes place at higher work loads. Metabolic modulators minimally affect blood pressure and pulse rate so that they may be useful in hypotensive and brady-cardiac patients already on maximal traditional therapy.

Therapeutic angiogenesis

Therapeutic angiogenesis could be defined as the use of angiogenic growth factors, genes that encode for growth factors, or cell-based therapies to enhance the natural process of collateral vessel development in ischemic tissue. Enthusiasm for gene therapy expanded in response to the lack of definitive efficacy of short-lived recombinant protein therapy (Table VI). Unlike protein therapy, gene therapy has the potential to induce a sustained tissue-based expression of proangiogenic factors. Several phase I trials established the safety of gene therapy for patients with CAD. Although phase II trials have generally been disappointing given their negative primary end point (total exercise time or reduction of ischemia using single-photon emission computed tomography [SPECT] imaging), some have however demonstrated a reduction in angina and an improvement in quality of life (Table VI).

Losordo et al have shown a positive effect of vascular endothelial growth factor-2 (VEGF-2) gene therapy in a randomized placebo-controlled trial. Using plasmid DNA delivered by a NOGA transendocardial delivery system (Biosense Webster, Diamond Bar, CA), not only could they objectively reduce angina in the active treatment group, but they also were able to document a clinically encouraging trend in exercise stress test time improvement (1.5 minutes prolongation on a Bruce protocol in the active treatment group; P = .26). The trial was interrupted prematurely at FDA request after a patient died from gene therapy in an unrelated adenosiviral trial. In 2003, the Kuopio Angiogenesis Trial suggested that intracoronary adenosiviral VEGF infusion was superior to plasmid VEGF or placebo at reducing the size of SPECT reversible perfusion defect. However, exercise stress test parameters did not improve. Although encouraging, the Kuopio trial needs to be interpreted with caution because it was primarily intended to assess the effect of VEGF gene therapy on post-PCI restenosis. Likewise, the variability brought by the concomitant PCI complicates the interpretation of the anti-ischemic effect observed in the trial.
More recently, Henry et al reported the analysis of the pooled results of the Angiogenic GENe Therapy (AGENT) III and IV trials that assessed Ad5FGF-4 in patients with advance CAD. In the overall study population, total exercise time was not significantly modified by the different doses of Ad5FGF-4 when compared with placebo. However, a prespecified analysis suggested that women significantly benefited from the gene therapy. The beneficial effect was consistently observed in several angina or ischemia measures: total ETT time, time to 1 mm ST-segment depression, and CCS angina class. As reported by the investigators, a negligible placebo effect in women and a large placebo effect in men might explain the difference observed in sexes.

Interpretation of gene therapy should take into account the gene, its carrying vector, and the delivery method used. To date, most clinical data have been obtained with genes encoding for different isoforms of VEGF and fibroblast growth factor (FGF). These genes have been selected for their potent proangiogenic capacity. The choice of vectors depends on the goal of the therapy and the admissible side effects. DNA plasmids are regarded as safe, low-immunogenic agents; however, they have poor transduction efficiency and result in a transitory gene expression. Adenovirus results in more efficient transduction rates. However, adenoviruses show transient cellular expression and provoke immunogenic reaction. Alternative vectors such as adeno-associated virus and retrovirus, although endowed with attracting properties, have not yet been studied in the cardiovascular clinical arena.

The delivery methods currently used in clinical trials are direct intramyocardial injection (either epicardial or endocardial) and catheter-based intracoronary perfusion. Direct injection assures an efficient albeit focal myocardial gene delivery but is invasive and may result in major complications. Innovative delivery methods such as ultrasound-targeted microbubble destruction and coronary sinus retroinfusion may well be used soon in clinical trials.

Cellular therapy

Aside from their theoretical regenerative capacity, certain cells, including endothelial progenitor cells, have the potential to promote angiogenesis in patients with advanced CAD. Stem cells of various types are capable of secreting cardioprotective and proangiogenic factors to support the development of new blood vessels when transplanted in severely ischemic myocardium. It is hoped that the neovascularization resulting from stem cell transplantation will reduce the ischemic burden and relieve symptoms like angina or heart failure. Although the clinical experience with cellular therapy in acute MI and CHF is growing, the number of trials directed at patients with advanced CAD remains limited. The analysis of clinical trials using stem cell therapy in patients with refractory angina should take into account the type of cell and the mode of delivery. In patients with refractory angina, 3 distinct types of cell preparations have been studied so far: skeletal myoblasts, bone marrow mononuclear cells (BMMCs), and circulating CD34+ progenitor cells.

With the exception of the POZNAN trial, all of the clinical experiments using skeletal myoblasts were performed concomitantly with CABG surgery. Although early phase 1 trials consistently demonstrated the feasibility and safety of myoblast transplantation for ischemic heart failure, proof of efficacy is still awaited. In the first randomized placebo control Myoblast Autologous Grafting in Ischemic Cardiomyopathy trial, patients undergoing CABG surgery were concomitantly transplanted with either autologous skeletal myoblasts or placebo within their nonrevascularizable myocardial segments. The trial was terminated prematurely after the independent data monitoring board advised that a therapeutic effect of skeletal myoblasts was unlikely to be shown. It is generally felt that the variability brought by a concomitant CABG surgery significantly hampered the detection of any potential beneficial effect of skeletal myoblasts. Skeletal muscle cells have not been assessed properly in patients with refractory ischemia.

Bone marrow mononuclear cells are obtained from the centrifugation of a filtered bone marrow harvest. The BMMCs contain several subpopulations of cells, among which hematopoietic and mesenchymal stem cells have been shown to possess stem cell properties: They are estimated to represent 2% to 4% of BMMCs’ cellular composition. In an open label clinical trial, Perin et al reported a significant reduction of the reversible ischemic defect (assessed by SPECT) among patients with nonrevascularizable ischemia who were treated with BMMCs using a NOGA Myostar catheter (Biosense Webster). Four months after transplantation, BMMCs have shown a significant improvement in LVEF (from 20% to 29%, \( P = .003 \)). At least one other phase I to II trial reported similar conclusions.

Circulating progenitor cells represent a heterogeneous group of cells expressing the hematopoietic marker proteins CD133, CD34, and the endothelial marker VEGFR2. Despite the debate around the definition of circulating progenitors cells, the clinical experience with circulating CD34+ cells in chronic or refractory angina is probably the most advanced. CD34+ circulating progenitor cells are usually collected from the blood after being mobilized from the bone marrow with granulocyte colony-stimulating factor for several days. One potential problem with granulocyte colony-stimulating factor in patients with advanced CAD is that it may transiently increase angina as a result of increases in blood viscosity, metabolic demand, and thrombocytosis. Erbs et al compared the efficacy of an intracoronary infusion of CD34+ circulating cells to a sham placebo in
Over the years, several putative mechanisms have been proposed to explain how EDTA may reduce atherosclerosis progression. Current hypotheses state that EDTA reduces low-density lipoprotein oxidation by binding copper and iron. The resultant antioxidant effect is believed to reduce the risk of developing atherosclerosis. Indirect mechanisms involving parathyroid hormone (PTH) may also be involved. By inducing hypocalcemia, EDTA stimulates the secretion of PTH, which is known to relax smooth muscle cells (inhibition of L-calcium channel), induce vasodilation, and decrease systemic blood pressure. Other mechanisms of action, linking PTH and t-PA production, have also been proposed.

The Program to Assess Alternative Treatment Strategies to Achieve Cardiac Health trial was a double-blind, randomized controlled trial comparing EDTA with placebo in 81 patients with stable angina. Seven months of EDTA administration resulted in a trivial 9-second improvement in the exercise treadmill ischemic time (as assessed by the time to 1 mm ST-segment deviation) when compared with placebo. Likewise, total exercise capacity and quality of life scores improved by similar degrees in both groups, again suggesting an important placebo effect.

The Trial to Assess Chelation Therapy (TACT), sponsored by the NHLBI and the National Center for Complementary and Alternative Medicine, is a phase III trial currently recruiting patients in the United States. TACT aims to randomly assign 1950 patients with recent MI to receive 40 infusions of either the standard chelation solution or placebo. The primary end point will be a composite of all-cause mortality, MI, stroke, and hospitalization for angina or for CHF over a mean follow-up of 2.5 years. TACT is expected to bring a significant positive result or an informative null result upon which rational clinical decision making and health policy can be based. Results are expected to be available by 2010. Although not directly related to angina and refractory ischemia, the TACT trial should provide important safety information for an agent frequently used to treat refractory angina. The risks associated with chelation therapy have been reported to be substantial (renal failure, arrhythmia, bone marrow depression, and even death), but the clinical proofs of efficacy are still awaited.

More recently, the Aggressive Reduction of Inflammation Stops Events (ARISE) study assessed the antioxidant succinobucol (AGI-1067) in the prevention of recurrent ischemic events on patients with recent ACS. Before ARISE, atherosclerosis regression was demonstrated by intravascular ultrasound using this agent. In ARISE, however, succinobucol did not significantly influence the combined end point of death, resuscitated cardiac arrest, MI, stroke, coronary revascularization, and hospitalization for unstable angina.

Percutaneous bypasses and retroperfusion technologies

Retroperfusion technologies exploit the coronary sinus to redistribute either flow or pressure from the venules to the capillaries. To date, both flow-driven retroperfusion and pressure-driven retroperfusion have been explored in clinical studies. Both of these techniques are the earliest stage of development but represent important new possibilities in the treatment of advanced CAD.

With flow-driven retroperfusion, blood from an artery is shunted to the coronary vein that drains the ischemic myocardial region. Using this principle, oxygenated blood shunts through the venules and subsequently reaches the capillaries, assuring a backward irrigation of the ischemic myocardium. Recent advances in situ coronary venous arterIALIZATION (PICVA) has been attempted in patients with severe angina and no revascularization options. This technology links
the coronary artery proximal to its site of occlusion to its correspondent coronary vein. The coronary sinus is selectively occluded to permit an appropriate retrograde redistribution of the oxygenated blood to the venules. The PICVA requires either intravascular ultrasound positioning or advanced NOGA navigation system to be performed.

Pressure-driven retroperfusion exploits the principle that coronary flow distribution varies according to coronary perfusion pressure. The anti-anginal effect of a partial occlusion of the coronary sinus has been known for several decades. By selectively occluding venous drainage of a given region of the heart, the resulting imbalance in regional capillary pressure will lead to a redistribution of antegrade blood toward other regions of lesser resistance. As such, it is possible to favor blood flow in diseased coronary segments by selectively occluding venous drainage of other flow-competing, non diseased coronary segments. The Reducer (Neovasc Medical, Israel) is a stainless steel, balloon-expandable, hourglass-shaped stent that creates a selective, permanent, and controlled narrowing of the coronary sinus. First-in-man series reported in 2007 has shown the safety and the feasibility of this technique.

Conclusions
Aside for the traditional nitrates, calcium blockers, and \( \beta \)-blockers, few therapies have been deemed effective to control refractory angina. Ranolazine is the first medical therapy approved in more than a decade for chronic angina and should be considered in the treatment of patients with advanced CAD. Among mechanical therapies, EECP and transmyocardial laser revascularization are approved for the treatment of refractory angina. Finally, CTO recanalization and metabolic modulators have been shown to consistently relieve angina on top of standard treatment but formal evidence of efficacy are still lacking.

Despite these advances, many patients remain symptomatic. It is time to evaluate whether clinical programs dedicated to these no-option patients may provide improved care. Those clinical programs, as was the case for heart failure clinics in the 1990s, would permit a better characterization of the disease and improve accessibility to sophisticated treatments. More importantly, development of these clinical programs would accelerate our ability to provide new and innovative ways to treat CAD in the future.

Developing new therapies for patients with advanced coronary disease is difficult for several reasons. The prevalence of advanced CAD is poorly defined, and the incidence of mortality and coronary events is not known. Because of that, selecting the appropriate trial design, sample size, and outcomes are difficult. Additional challenges stem from the substantial placebo effect encountered with a subjective outcome like angina. This has been illustrated by several trials presented in this review, especially when therapies involving invasive procedures were being investigated. Indeed, such a placebo effect calls for properly blinded, sham controlled trials. In the second part of this article, we will discuss the difficulties encountered by investigators when designing trials for refractory angina in terms of trial design, end point selection, and compliance with regulatory agencies.

The authors thank Jonathan McCall for his excellent editorial assistance.

References


105. Kinnaer T, Stabile E, Burnett MS, et al. Marrow-derived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vitro and in vivo arteriogenesis through paracrine mechanisms. Circ Res 2004;94:678-85.

Appendix A

Members of the Working Group (in addition to coauthors): Karen Alexander, MD, Duke University Medical Center, Durham, NC; Steve C. Mockrin, PhD, NHLBI, NIH, Bethesda, MD.

Presenters to the Working Group: Jonathan Abrams, MD, University of New Mexico Hospital, Albuquerque, NM; Brian Annex, MD, Duke VA Medical Center, Durham, NC; Gregory Barsness, MD, Mayo Clinic Rochester, Rochester, MN; Deepak Bhatt, MD, Cleveland Clinic, Cleveland, OH; Robert Califf, MD, Duke Clinical Research Institute, Durham, NC; Bernard R. Chaitman, MD, Saint Louis University School of Medicine, St. Louis, MO; Bernard J. Gersh, MD, Mayo Clinic, Rochester, MN; David Holmes, MD, Mayo Clinic, Rochester, MN; Timothy D. Henry, MD, Minneapolis Heart Institute, Minneapolis, MN; Andrew Koren, MD, CV Therapeutics Palo Alto, CA; Daniel Mark, MD, Duke Clinical Research Institute, Durham, NC; Alice M. Mascette, MD, NIH, NHLBI, Bethesda, MD; Magnus Ohman, MD, Duke University Medical Center, Durham, NC; Carl Pepine, MD, University of Florida, Gainesville, FL; Beana Pina, MD, Case Western Reserve University, Cleveland Heights, OH; Jyme Schafer, MPH, CMS, Baltimore, MD; Sidney Smith, MD, University of North Carolina, Chapel Hill, NC; Norman Stockbridge MD, PhD, FDA, Silver Spring, MD; Anders Svensson, MD, PhD, AstraZeneca, Molndal, Sweden; Julie Swain, FDA, CDRH, Fallbrook, CA; Robert Temple, MD, FDA, Silver Spring, MD; Lars Wallentin, MD, PhD, Uppsala Clinical Center University Hospital, Uppsala, Sweden; Doug Weaver, MD, Henry Ford Health System, Detroit, MI; Cecelia Witten, MD, PhD, FDA/CBER, Rockville, MD; Bram Zuckerman, MD, FDA, Rockville, MD.