Best of TCT 2004

Highlights from the Transcatheter Cardiovascular Therapeutics Meeting, September 27- October 1, 2004, Washington, DC

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Key words: AIMI • ARTS II • CABERNET • Cellular transplantation • DIABETES • Drug-eluting stents • Fenoldopam • Skeletal myoblast • SPIRIT FIRST

The Transcatheter Cardiovascular Therapeutics (TCT) 2004 meeting was held again this year in Washington, DC, and provided an opportunity to observe and discuss the latest innovations in the field of interventional cardiology. Following are synopses of some of the more important developments, particularly pivotal clinical trial results that will impact cardiology practice in the future.

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SPIRIT FIRST Trial

The SPIRIT FIRST trial[1] enrolled 60 patients at 9 sites in the Netherlands, Germany, and Denmark. Patients were randomly assigned to either a cobalt chromium, everolimus-eluting stent (MultiLink VISION,™ Guidant Corporation, Santa Clara, CA) with a hemocompatible, durable polymer or a non-drug-eluting, cobalt chromium MultiLink VISION stent. All patients had chronic stable angina and de novo lesions less than or equal to 12 mm long, in native coronary arteries. Dr. Patrick Serruys of the Thorax Centrum, Erasmus Medisch Centrum, Rotterdam, The Netherlands, presented the results of SPIRIT FIRST. The primary endpoint of angiographic in-stent late loss as measured by quantitative coronary angiography (QCA) at 6 months was 0.10 mm for the study (everolimus-eluting) arm versus 0.84 mm for the bare metal control ($P < .0001$). This degree of late loss is similar to that seen in the SIRIUS trial of a sirolimus-eluting stent and lower than late loss values from the study arm of the TAXUS clinical trial series.

Percent diameter stenosis was also significantly decreased from 39% to 16% with the everolimus-eluting stent ($P < .0001$). The binary restenosis rate in the study arm was 0%, compared to 26.9% in the control arm ($P = .01$). Six-month intravascular ultrasound data showed a 73% reduction in neointimal volume and a 70% reduction in in-stent volume obstruction in the everolimus-eluting stent compared to the bare metal stent. The rate of major adverse coro-

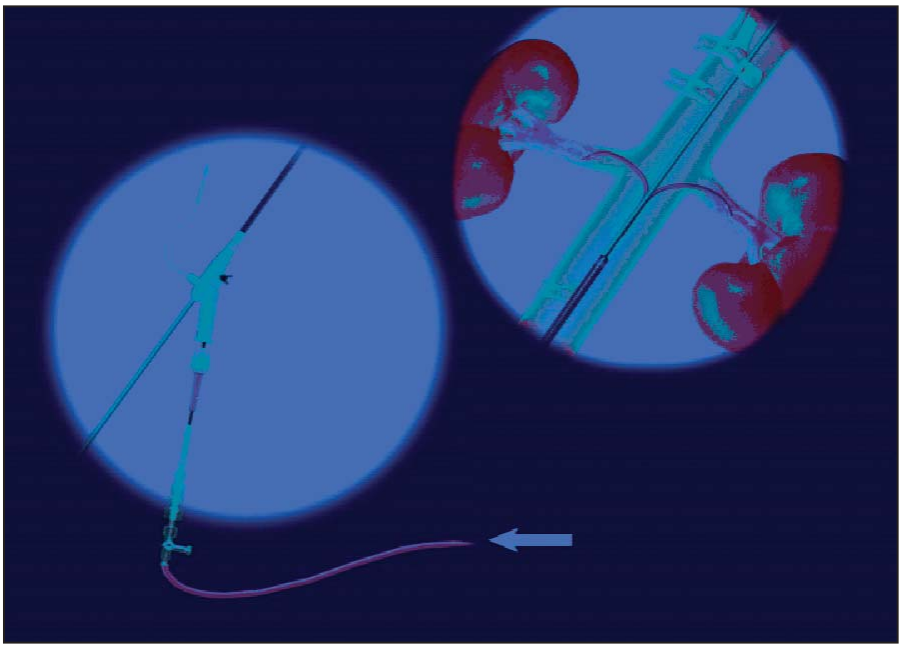


Figure 1. *Illustration of the novel intrarenal infusion catheter (Benephit,™ Flow Medica, Inc., Freemont, CA) utilized for the administration of fenoldopam, post-radiocontrast exposure.*

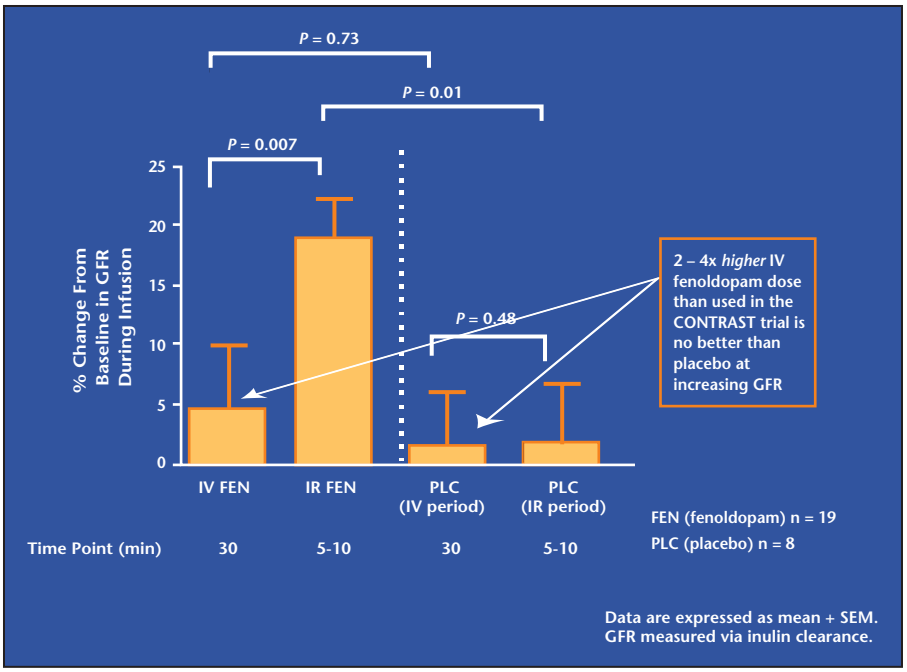
nary events (MACE) was 7.7% for the everolimus group, compared to 21.4% for the control cohort. There was no stent thrombosis reported in either arm. Guidant is also currently researching a stainless steel everolimus-eluting stent (CHAMPION™), which utilizes a bioabsorbable polymer, in the FUTURE series of clinical trials. Combining an effective drug and drug delivery system with a stent that has excellent deliverability could represent a significant improvement on currently available treatment options.

Contrast Nephropathy

Prevention of contrast-induced nephropathy remains an elusive goal, as a whole host of strategies, including the use of N-acetyl cysteine and low-dose intravenous fenoldopam have proven ineffective. One of the most exciting presentations at this year's TCT meeting was made by Dr. Hooman Madyoon of Westside Cardiovascular Medical Group and the UCLA School of Medicine, Los Angeles, CA. Utilizing a novel intrarenal (IR) infusion catheter that allows for simultaneous access both to renal arteries and for a coronary guide catheter, the investigators compared the effect of intravenous (IV) fenoldopam to IR fenoldopam on glomerular filtration rates (GFR). See Figure 1. They then evaluated the ability of IR fenoldopam to blunt the reduction of GFR observed following contrast exposure.

Dr. Madyoon presented results showing that IR delivery of fenoldopam resulted in prevention of slowed GFR, post-contrast exposure, while simultaneously attaining lower serum levels and less hypotension than that observed with IV infusion. Figure 2 illustrates the greater increase in GFR observed with IR infusion compared to IV infusion and to placebo. A lack of significant difference between IV fenoldopam and placebo is notable. This pilot study has formed the basis for the design of the FEN II multicenter randomized trial to be directed by Dr. Madyoon and Dr. Paul Tierstein. We eagerly await the results of this promising trial.

Figure 2. *Changes in glomerular filtration rate (GFR), comparing intravenous (IV) and intrarenal (IR) administration of fenoldopam (FEN) with placebo (PLC).*



DIABETES Trial

The Diabetes and Sirolimus-Eluting Stent (DIABETES) trial[2] is a randomized, prospective, placebo-controlled trial of the sirolimus-eluting stent (SES) in diabetic patients with de novo coronary stenoses. Patients (n = 160, total lesions = 221) were treated at 4 university hospitals in Spain and randomly assigned to either an SES or a bare metal stent (BMS). Eligible patients were either noninsulin-dependent or insulin-dependent with symptoms or objective evidence of coronary ischemia. The primary endpoint was in-segment (in-stent + 5 mm distal and proximal) late lumen loss as assessed by QCA at 9-month follow-up.

Dr. Manel Sabate of the Hospital Clinico San Carlos in Madrid, Spain, presented the results of the DIABETES Trial. At 1 month, there were no deaths, Q-wave or non-Q-wave myocardial infarctions (MIs), or target lesion or vessel revascularizations in the SES arm, compared to 2 deaths and 3 non-Q-wave MIs in the control arm (MACE = 6.3%; $P = 0.1$ compared to the SES cohort). Results at 9 months show a target vessel revascularization rate of 7.5% in the SES arm and 31.3% in the BMS arm ($P < .0001$). MACE rates were 11.3% in the SES arm and 36.3% in the BMS arm ($P < .0001$). These results confirm the benefit of SES use in diabetic patients versus BMS.

AIMI Trial

The AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AIMI) trial was presented by Dr. Arshad Ali of the St. John Hospital and Medical Center, Detroit, MI. It studied 468 patients in a prospective comparison of AngioJet® (Possis Medical, Inc., Minneapolis, MN) rheolytic thrombectomy followed by definitive percutaneous coronary intervention (PCI) versus primary PCI alone. All patients presented with ST-elevation acute MI.

The primary endpoint of infarct size as determined by Tc-99m sestamibi SPECT imaging, at 14-28 days, was significantly lower in the primary PCI group. No significant differences were noted with regard to the secondary endpoints of ST-segment resolution at 90 minutes and follow-up ejection fraction (by SPECT). TIMI 3 flow was seen more often in the control group (97% vs 92% for the AngioJet group, $P < .02$).

MACE (death, Q-wave MI, stroke, emergent coronary artery bypass graft, or target lesion revascularization/subacute thrombosis) at 30 days was significantly lower in the control group (1.7% vs 6.7% for the AngioJet arm; $P < .01$), mostly due to an excess number of deaths in the thrombectomy group (11 versus 2 in the control group; $P < .02$). See Figure 3.

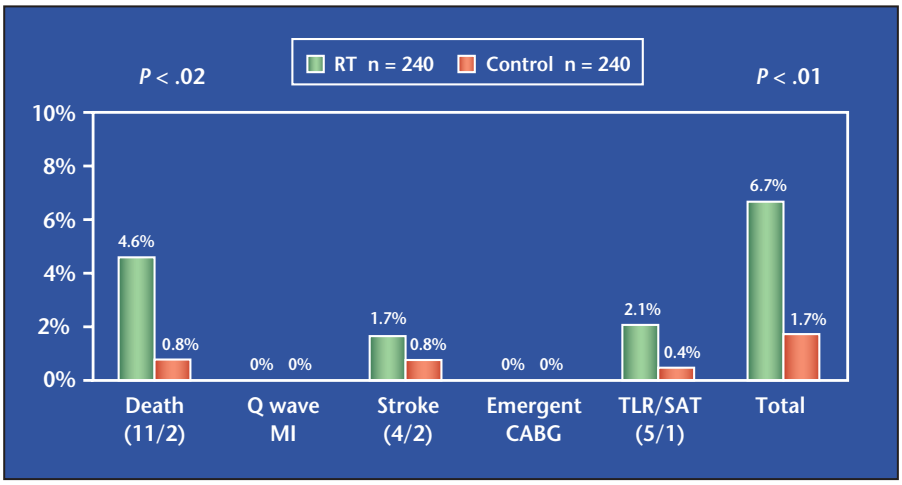


Figure 3. *Rates of major adverse coronary events at 30 days following percutaneous coronary intervention (PCI) in the AIMI Trial. Patients received either rheolytic thrombectomy (RT) therapy prior to PCI or PCI alone (Control). CABG, coronary artery bypass graft; MI, myocardial infarction; SAT, subacute thrombosis; TLR, target lesion revascularization.*

Dr. Ali concluded that the routine use of rheolytic thrombectomy with primary PCI in ST elevation MI is not supported by clinical data and should not replace therapies such as abciximab, which lower risk in this population

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CABERNET Registry

Cardiologists who perform carotid artery stent implantation have battled claims that surgical carotid endarterectomy is superior to stent implantation. Of interest in this debate are the 30-day results of the Carotid Artery Revascularization Using the Boston Scientific Filter Wire EX/EZ™ and the EndoTex™ NexStent™ (CABERNET) Registry[3] presented by Dr. L. Nelson Hopkins of the Department of Neurosurgery at the State University of New York, Buffalo, NY.

CABERNET enrolled 488 patients who were either symptomatic with a stenosis greater than or equal to 50% by ultrasound and angiography, or

Table 1
CABERNET Enrollment Criteria: Surgical High-Risk Categories

Anatomic Risks	Comorbidity Risks
1 Criterion Required	*1 Criterion Required*
• Restenosis post-carotid endarterectomy	• Unstable angina
• Contralateral carotid occlusion	• LVEF ≤ 30%
• Previous neck radiation or surgery	• CHF (NYHA Class III/IV)
• Surgically inaccessible lesions: above C2 / below clavicle	• Dialysis-dependent renal failure • Severe COPD
• Neck immobility	• Planned CABG or valve replacement
• Tracheostomy	
• Contralateral laryngeal palsy	
• Bilateral stenosis requiring treatment	
	2 Criteria Required
	• Age ≥ 75 years
	• MI within last 6 weeks
	• Planned peripheral vascular surgery
	• ≥ 2 major diseased coronary arteries with ≥ 70% stenosis

CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association.

asymptomatic with a stenosis 80% or greater by ultrasound and 60% or greater by angiogram. The target segment reference diameter was 4.00 mm or greater and 9.00 mm or less, with a lesion length of less than 30 mm. The vessel diameter distal to the target lesion was 3.5 mm or greater and 5.5 mm or less, as an optimal FilterWire landing zone. Patients were classified as "surgical high-risk" due to an anatomic risk and/or comorbid risk (Table 1).

At 30 days, the composite rate of endpoint was 3.8% (n = 17). This cohort was comprised of all deaths (0.5%, n=2), all stroke (3.4%, n=15) and all MI (0.2%, n=1). The 30-day stroke rates were 1.4% (n=6) for major strokes and 2.0% (n=9) for minor strokes, totalling 3.4% (n=15). These preliminary outcomes compare very favorably with other carotid stent registries conducted in the United States as illustrated in Table 2, as well as the published results of surgical endarterectomy studies.

The CABERNET registry showed the lowest to date composite endpoint of death, MI, and stroke in a surgical high-risk population. This reconfirms the safety of carotid stenting for high-risk patients with obstructive carotid artery disease compared to carotid endarterectomy, when performed by operators with high levels of experience. With the US Food and Drug Administration's approval of the Guidant distal protection device and carotid stent system, as well as other, soon-to-be-approved systems from Cordis and other device manufacturers, we can expect an acceleration of the adaptation of this technology.

[Norman E. Lepor, MD, FACC, FAHA]

Cell Therapy: Current Status

The concept of cellular transplantation to regenerate damaged myocardium is one of the most exciting and promising therapies currently under investigation. It is hoped that one day, cardiologists and cardiac surgeons will be able to offer this option to patients with severe heart failure or end-stage coronary disease. How close is this theoretical application to becoming a clinical reality? A full afternoon session at TCT addressed this issue.

The major controversy in this field is whether or not adult stem cells can transform themselves into contracting cardiac myocytes. In a debate format, Dr. Bernardo Nadal-Ginard of New York Medical College in Valhalla, NY, provided evidence that bone marrow-derived stem cells

Table 2
30-Day Composite Endpoint Results in US Carotid Stenting Registries

CABERNET	3.8%
BEACH	5.4%
SAPPHIRE (AHA 2002)	7.8% (stent) vs 12.6% (CEA)
ARCHeR 2 (ACC 2003)	7.8%
SECuRITY (TCT 2003)	7.2%

CEA, carotid endarterectomy.

can differentiate into cells that contain myosin, divide themselves into large numbers, and improve the function of infarcted rat myocardium. Dr. Michael Parmacek of the University of Pennsylvania, Philadelphia, PA, countered these arguments by providing evidence that many of these cells are small, are not contractile, and that a large proportion die soon after implantation. A fair conclusion can be made that much more work needs to be done to show that myocardium can indeed be regenerated from adult stem cells.

European and US experiences in skeletal myoblast transplantation for chronic myocardial disease were then presented. The European study looked at data from a trial utilizing skeletal myoblasts (Bioheart Inc., Weston, FL) in an endocardial injection technique. In 12 patients undergoing follow-up for 3 years, no change was seen in ejection fraction, low dose-dobutamine stress, or pooled multiple gated acquisition scan. Interestingly, functional class improved and the improvement was sustained. The US experience implanting skeletal myoblasts at the time of coronary bypass surgery was undertaken in 22 patients. Following procedure, PET scan showed a significant overall improvement in uptake. Ejection fraction also improved over a 3-year period. The implantation appeared safe but the role played by transplantation versus revascularization by bypass in patient improvement remains unclear.

Dr. Emerson Perin of the Texas Heart Institute, Houston, TX, injected bone marrow cells into viable but ischemic myocardium using NOGA mapping guidance. The procedure was safe and perfusion seems to improve at early, 6-month review of the data.

In an acute MI patient population, several clinical trials were reported. A group from Dusseldorf, Germany reported a 3-year result after infusing whole bone marrow cells into the infarct-related artery, 8 days after primary angioplasty. The infarct area as a percent of area at risk was smaller in the treatment group when compared to the control group. Ejection fracture was higher (66%) compared to the control (55%), though the result was not significant (P = ns).

Several randomized studies are currently ongoing to test whether intracoronary infusion of bone marrow cells is efficacious. The BOOST trial[4] randomized 60 post-PCI patients to 2 groups, 1 that received optimal medical treatment (n = 30) and 1 receiving the same treatment plus bone marrow-cell infusions (n = 30). Early data again suggest an improvement in ejection fraction, though this is unconfirmed by infarct size measurements.

Given all of this information, has the time come to routinely infuse cells to regenerate myocardium? There are several questions still to be answered 1) Which patients are appropriate for this therapy? The myocardial milieu in patients with chronic cardiomyopathy is very different from that of patients "fresh" after suffering a myocardial infarction. 2) What types of cells provide the most benefit? Certainly no one knows which type of cell is better or which stem cells can transform into functioning myocardium in a human and there is not yet any evidence showing whether engraftments are transient or permanent. 3) What is the best method of administration? Intracoronary administration is easiest but it is unclear how many cells actually make it into the myocardium and sustain clinical benefit. Intramyocardial and transvenous methods are both possible but their efficiency is yet to be quantified. 4) What is the clinical efficacy? This is the ultimate question, as it is clear that many treatments can be efficacious in the experimental world but not necessarily in the clinical arena. Thus, randomized, blinded trials will be needed to prove that this promising but unproven therapy is genuinely helpful to patients.
[Alan C. Yeung, MD]

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ARTS II Trial

Following the maturation of percutaneous revascularization as a therapeutic modality, and its extension to patients with complex coronary anatomy and comorbid disease, several randomized clinical trials[5-11] were undertaken to determine whether coronary angioplasty would be as effective as coronary artery bypass grafting (CABG) as an initial strategy in the treatment of patients with coronary artery disease. For patients with multivessel disease, these trials demonstrated that the 2 strategies had similar efficacy results in terms of freedom from death, MI, and anginal symptoms. However, to achieve a similar clinical status, patients treated with coronary balloon angioplasty as the initial strategy were more likely to require repeat revascularization and anti-anginal medications. Subsequent trials comparing CABG with percutaneous coronary intervention (PCI),[12-14] in which the majority of patients received stents, reported similar findings although, as anticipated,

Table 3
Rates of Periprocedural CK-MB Elevation in ARTS I and II Subgroups

Level	ARTS II DES (%)	ARTS I CABG (%)	ARTS I PCI (%)
1 – 3 fold increase	1.5	40.2	21.2
3 – 5 fold increase	0.3	7.0	4.3
> 5 fold increase	1.5	12.7	6.2

ARTS, Arterial Revascularization Therapies.

the incidence of repeat revascularization in the PCI group was lower than in the balloon angioplasty group in the earlier studies.

One such trial, the Arterial Revascularization Therapies (ARTS) I,[13] enrolled 1205 patients with multivessel coronary disease and compared multivessel stenting with CABG. At 1 year, there was no difference in freedom from death, stroke, or MI between the 2 groups, although there was a 17% reduction in repeat revascularization in favor of surgery. With the introduction of drug-eluting stents that decrease restenosis and repeat revascularization following PCI to astonishingly low levels, repeat comparison of CABG and PCI was anticipated.

ARTS II was designed as a single-arm trial to evaluate major adverse cardiac events (MACE) at 1 year following PCI using a drug-eluting stent. Accordingly, 607 patients undergoing multivessel stenting using the sirolimus-eluting stent were compared with the CABG (n = 605) and PCI (n = 600) groups from ARTS I. Despite the higher risk profile (increased prevalence of hypertension, diabetes, and hypercholesterolemia) and more complex coronary anatomy requiring a greater number of stents and longer stent length in the ARTS II patient population, subacute stent thrombosis at 30 days (0.8% vs 2.8%) and peri-procedural CK-MB levels (Table 3) were lower in ARTS II when compared to ARTS I patients.

As anticipated, repeat revascularization following PCI using the sirolimus-eluting stent in ARTS II was lower than that following PCI using a bare-metal stent in ARTS I.

Table 4
Clinical Outcomes in ARTS I and II Subgroups

Endpoint	ARTS II DES (%)	ARTS I CABG (%)	ARTS I PCI (%)
Death	0.5	1.8	2.3
Cerebrovascular accident	0.5	1.2	1.5
MI	0.7	3.8	4.5
Re-CABG	1.6	0.5	3.8
Re-PCI	3.1	2.0	7.8
Any MACE	6.4	9.0	20

ARTS, Arterial Revascularization Therapies; CABG, coronary artery bypass grafting; DES, drug-eluting stent; MACE, major adverse cardiac event; MI, myocardial infarction; PCI, percutaneous coronary intervention.

The outcomes at 6 months were presented by Dr. Patrick Serruys of the Thorax Centrum, Erasmus Medisch Centrum, Rotterdam, The Netherlands. Overall MACE was lower in ARTS II (6.4%) when compared to ARTS I CABG (9.0%) and PCI (20%) patients (Table 4). In fact, rates of event-free survival were similar in the ARTS II and ARTS I CABG groups.

Comment

As anticipated, repeat revascularization following PCI using the sirolimus-eluting stent in ARTS II was lower than that following PCI using a bare-metal stent in ARTS I. However, the reason for the reduced rates of subacute stent thrombosis and periprocedural CK-MB levels in ARTS II is unclear, but may be related to IIb/IIIa glycoprotein platelet receptor antagonists administered to 32.5% of patients in ARTS II. Although promising and provocative, the results of ARTS II must be interpreted with caution in the absence of a randomized trial design, and a comparison of outcomes at 1 year following the procedure is eagerly awaited. ■

[Alice K. Jacobs, MD, FACC, FAHA]

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Main Points

- The SPIRIT FIRST trial enrolled chronic stable angina patients and randomly assigned them to either a cobalt chromium, everolimus-eluting stent with a hemocompatible, durable polymer or a non-drug-eluting, cobalt chromium stent. Late loss at 6 months was 0.10 mm for the study (everolimus-eluting) arm versus 0.84 mm for the bare metal control ($P < .0001$). This degree of late loss is similar to that seen in the SIRIUS trial of a sirolimus-eluting stent and lower than late loss values from the study arm of the TAXUS clinical trial series.
- A pilot study of intrarenal delivery of fenoldopam resulted in the prevention of slowed glomerular filtration rate, post-contrast exposure, while simultaneously attaining lower serum levels and less hypotension than that observed with intravenous infusion.
- The DIABETES trial is a randomized, prospective, placebo-controlled trial of the sirolimus-eluting stent (SES) in diabetic patients with de novo coronary stenoses. Major adverse coronary event (MACE) rates at 9 months were 11.3% in the SES arm and 36.3% in the bare metal stent arm. These results confirm the benefit of SES use in diabetic patients versus bare metal stents.
- The CABERNET registry reconfirms the safety of carotid stenting for high-risk patients with obstructive carotid artery disease compared to carotid endarterectomy, when performed by operators with high levels of experience.
- Cellular transplantation to regenerate damaged myocardium continues to hold promise as a groundbreaking therapeutic option but questions regarding the appropriate patient populations, the types of cells used in therapy, methods of administration, and, most importantly, trials that will show clinical, as opposed to experimental, efficacy still require answers.
- ARTS II was designed as a single-arm trial to evaluate MACE at 1 year following PCI using a drug-eluting stent and, despite the higher risk profile and more complex coronary anatomy requiring a greater number of stents and longer stent length in its patient population, subacute stent thrombosis at 30 days and peri-procedural CK-MB levels were lower in ARTS II when compared to ARTS I patients who were treated with bare metal stents.