Best of TCT 2003

Highlights from the Transcatheter Cardiovascular Therapeutics Meeting, September 15-19, 2003, Washington, DC

[Rev Cardiovasc Med. *2003;4(4):237-249*]

Key words: Chronic kidney disease • COOL-MI • Contrast-induced nephropathy • COURT • Diabetes mellitus • Drug-eluting stents • e-Hepatocyte growth factor • ENDEAVOR-I • Endothelial cells • Everolimus • FUTURE II • Hyperbaric oxygen therapy • Impaired fasting glucose • Iodixanol • ISAR-SMART II • Macrophage immunoreactivity • Neovascularity • ON-TIME • Paclitaxel • Percutaneous coronary intervention • Polytetrafluoroethylene grafts • Power-pulse spray technique • RACTS • REPLACE II • SIRIUS • Sirolimus • TAXUS IV • TIMI

The Transcatheter Cardiovascular Therapeutics (TCT) Annual Meeting 2003 was held once again in Washington, DC, under the direction of Drs. Martin B. Leon and Gregg W. Stone. Presentations included clinical trial results from ENDEAVOR-I, FUTURE II, COOL-MI, ISAR-SMART II, ON-TIME, as well as many other experimental and clinical trials.

Reviewed by David R. Holmes, Jr., MD, Mayo Graduate School of Medicine, Rochester, MN; Alice K. Jacobs, MD, FACC, FAHA, Boston University, Boston, MA; Norman E. Lepor, MD, FACC, FAHA, The David Geffen School of Medicine at UCLA, Los Angeles, CA; Prediman K. Shah, MD, FACC, FACP, FCCP, The David Geffen School of Medicine at UCLA, Los Angeles, CA; Alan C. Yeung, MD, Stanford University School of Medicine, Stanford, CA

Drug-Eluting Stents: New Options to Come

Drug-eluting stents (DES) have proven to be a breakthrough technology for interventional cardiologists. The results of the SIRIUS trial were presented last year at TCT, and another major U.S. trial, TAXUS IV, was presented this year. Beyond these studies, there are many other DES combinations and technologies currently being investigated. The two U. S. trials closest to launching are ENDEAVOR, which utilizes a drug/stent combination developed by Medtronic, Inc. (Minneapolis, MN), and FUTURE, which uses technology licensed from Biosensor (Singapore) by Guidant Corporation (Indianapolis, IN).

ENDEAVOR-I Multicenter Evaluation of ABT-578 Elution from a Phosphorylcholine-Coated Stent

Dr. Ian T. Meredith from Monash Medical Center in Melbourne, Australia presented results of ENDEAVOR-I, which utilized Medtronic's Driver cobalt alloy stent with phosphorylcholine coating, eluting Abbott Laboratories' (Abbott Park, IL) ABT-578. The Driver stent is the company's latest-generation thin strut stent with very low profile and trackability. ABT-578 is a sirolimus analog with similar in vitro activity, the compound on the U.S. Food and Drug Administration (FDA)-approved Cypher™ stent (Cordis Corporation,

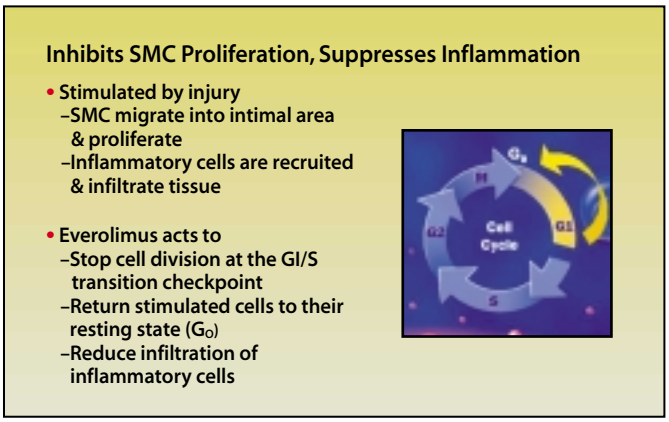


Figure 1. *Mechanism of action of everolimus. SMC, smooth muscle cell.*

Miami, FL). ABT-578, however, is not a U.S. FDA-approved drug, thus the future of this technology is still uncertain.

ENDEAVOR-I was a multicenter, Australasian registry involving 100 patients with *de novo* lesions ranging in diameter from 3.0 mm to 3.5 mm, with a maximum length of 15 mm. Diabetics comprised 16% of the patients. The primary endpoints were late loss at 4 months, with angiographic and intravascular ultrasound follow-up (minimum lumen diameter [MLD] at end-of-procedure minus MLD at follow-up), and major adverse coronary events (MACE).

Results included 1 myocardial infarction at 4 months and 1 target lesion revascularization (TLR). Late loss was 0.33 mm in-stent and 0.20 mm in-segment. Percent angiographic stenosis was 14.4% in-stent and 21.7% in-segment. Neointimal volume was 61 mm^3 representing 4.5% of the stent volume.

The Endeavor DES seems to be effective in the short term (4 months) except for higher than expected late loss in a low-risk group of patients (low diabetes percent and larger vessel size). The late loss in the SIRIUS trial was 0.17 mm at a later time interval and mean tissue volume was lower, as verified by intravascular ultrasound. A larger, randomized ENDEAVOR-II is currently in process to determine whether or not phosphorylcholine is the optimal coating.

FUTURE I and II: Multicenter Evaluation of the Bioabsorbable Polymer-Based Everolimus-Eluting Stent

Everolimus is a second generation agent currently under investigation as a drug-eluting agent. It is a macrolide immunosuppressant originally developed by Novartis Pharmaceuticals (Basel, Switzerland) for the prevention of rejection in kidney, heart, and lung transplants. Everolimus is a novel proliferation-signal inhibitor that possesses both anti-smooth muscle-cell proliferation and immunosuppressant effects by mechanism of the prevention of clonal expansion of activated T-cells (see Figure 1). Guidant is the worldwide exclusive licensee of everolimus from Novartis.

The FUTURE I and FUTURE II trials assessed the safety and performance of an everolimus-eluting stent (EES) in single *de novo* lesions. In FUTURE I, 42 non-diabetic patients were enrolled and in FUTURE II, 64 patients were studied including diabetics. Key endpoints were angiographic and intravascular ultrasound (IVUS) results at 6 months and clinical endpoints at 1, 6 and 12 months. The results of these trials were presented by Eberhard Grube, MD, of the Herzzentrum Siegburg, Germany.

In FUTURE I, the late loss at 6 months was 0.11 mm in the EES group and 0.83 in the bare metal stent (BMS) group (P <.0001) and restenosis rates were 0.0% and 9.1% in the EES and BMS groups, respectively. The MACE were 7.7% in both groups. At 12 months, no new MACE or aneurysms and no in-stent binary restenosis were observed.

In FUTURE I, the late loss at 6 months was 0.11 mm in the EES group and 0.83 in the bare metal stent group and restenosis rates were 0.0% and 9.1% in the EES and BMS groups, respectively.

FUTURE II utilized the Biosensor

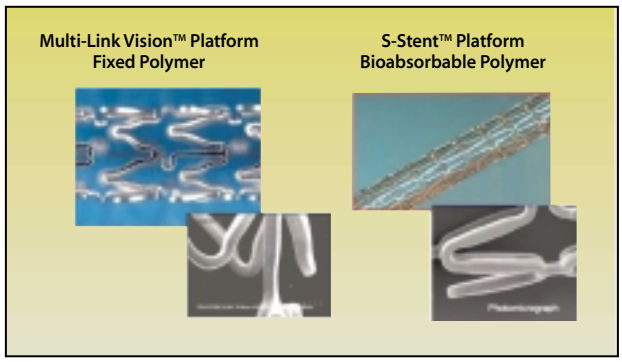


Figure 2. *Stainless steel, strut-based stents currently in development at Guidant Corporation.*

S stent coated with everolimus. The S stent is a proprietary stainless steel stent utilizing a sinusoidal pattern of struts (Figure 2). The coating is unique because it is bio-absorbable. Guidant has licensed the technology from Biosensor and will be using this coating as its drug-elution platform.

FUTURE II was a multicenter, randomized (2:1) German trial involving 64 patients with *de novo* lesions. The lesion diameter ranged from 2.5 mm to 4.0 mm, with length up to 18 mm. Diabetics comprised 25.1% of the patient population. Endpoints were MACE and TLR at 1 month and at 6 months. There was 1 myocardial infarction (MI) at 1 month in the control group. One TLR in the DES group (4.8%) and 6 in the control group (15%) were experienced at 6 months. Rate of angiographic stenosis was 2.9% in the DES group and 30.4% in the control group. Restenosis rates were 4.8% and 31%, respectively.

At 6 months, the in-stent angiographic follow-up revealed late loss of 0.12 mm in the EES group and 0.85 in the BMS group ($P < 0.001$), with a binary restenosis rate of 0.0% and 19.4%, respectively. The differences in both late loss and binary restenosis achieved statistical significance, with an 86% reduction of late loss (P <.001) and a 90% reduction in diameter stenosis (P <.001). IVUS follow-up revealed a 94% reduction of neointimal volume in the EES group. The 6 month in-segment late loss and binary restenosis were, respectively, 0.17 mm and 4.8% in the EES group and 0.54 mm and 30% in the BMS group.

The Biosensor (Guidant) DES seems effective in lowering restenosis rates. The inhibiting magnitude is similar to older sirolimus-eluting stents and the bioabsorbable nature of the coating may allow the stent to be pacified by the vessel wall in the long run.

With the ongoing, successful trials of sirolimus, taxol, ABT-578 and everolimus, interventional cardiologists will soon be provided with a welcome set of stent technology options. [Alan C. Yeung, MD, Norman E. Lepor, MD, FACC, FAHA]

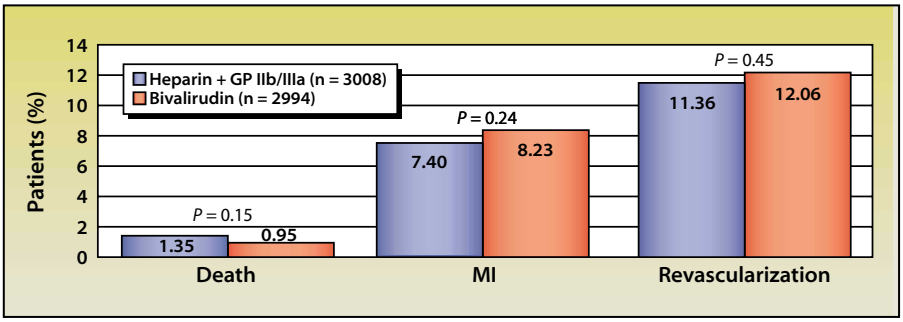


Figure 3. *Six-month results of the REPLACE II trial. Bivalirudin appears to be a viable replacement for unfractionated heparin in patients undergoing percutaneous coronary intervention. MI, myocardial infarction; GP IIb/IIIa, glycoprotein IIb/IIIa.*

New Thrombolytic Techniques

Research comparing the use of urokinase (Abbokinase,® Abbott Laboratories, Abbott Park, IL) versus tenecteplase as therapeutic adjuvants for the treatment of acute limb ischemia was presented by Allie and associates from the Cardiovascular Institute of the South, Lafayette and Houma, LA. The authors studied 49 patients presenting with acute limb ischemia and utilized the power-pulse spray technique in combination with lytic therapy, allowing for high-pressure, concentrated, high-dose, locally pulsed thrombolysis. Of the vessels treated, 15 were iliac arteries, 22 were superficial femoral arteries, and 12 were bypass grafts. The procedural success in the urokinase group was 91.6% with a 30-day and 6-month limb salvage rate of 91% and 84% respectively. Similar results were also achieved with the use of tenecteplase. The authors concluded that the power-pulse spray technique is effective and safe for use in lytic therapy with either urokinase or tenecteplase, and preferable to observed outcomes of therapy using traditional chemical thrombolysis and rheolytic thrombectomy. Advantages included more rapid revascularization, decreased systemic lytic exposure, and fewer bleeding complications.

With the ongoing, successful trials of sirolimus, taxol, ABT-578 and everolimus, interventional cardiologists will soon be provided with a welcome set of stent technology options.

REPLACE II

The REPLACE II trial, as presented by Dr. A. Michael Lincoff of The Cleveland Clinic in Cleveland, OH, assessed whether bivalirudin monotherapy would equal the efficacy of heparin plus GP IIb/IIIa inhibitor therapy in patients undergoing percutaneous coronary intervention (PCI). A total of 6010 patients were randomized to receive 65 U/kg of heparin with abciximab or eptifibatide versus 1.75 mg/kg/h of bivalirudin. The 6-month results show, in this relatively lower-risk patient cohort, that bivalirudin is a reasonable replacement for unfrac-

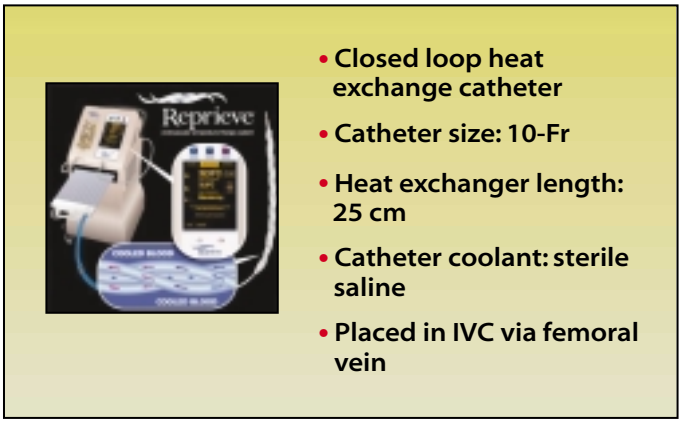


Figure 4. *The Reprieve™ endovascular temperature therapy system. IVC, inferior vena cava.*

tionated heparin in patients undergoing PCI (Figure 3).

COOL-MI TRIAL

Dr. William O'Neil from the William Beaumont Hospital, Royal Oak, MI, presented the results of the COOL-MI trial, an important study assessing the safety and efficacy of systemic cooling in patients undergoing PCI for acute MI. The Reprieve™ endovascular temperature therapy system (Radiant Medical, Inc., Redwood City, CA) is a closed-loop heat-exchange catheter that is placed into the inferior vena cava through a 10-Fr sheath inserted into the femoral vein (Figure 4). Patients in the trial presented within 6 hours of symptom onset with an electrocardiogram consistent with acute anterior or inferior MI. The trial included 392 patients, of whom 193 were randomized to treatment with the cooling catheter and targeted to achieve a body temperature of 33°C for 3 hours (Figure 5). The remainder received standard PCI without cooling therapy. The target temperature was achieved in 72% of the cooling catheter patients and there was no significant difference in mean infarct size between the two groups. However, in the group of patients presenting with an anterior MI who were cooled to less than 35°C, the infarct size was 9.3% versus 21.9% for those who were not cooled. Severe adverse cardiovascular events occurred in 3.9% of the control patients and 6.2% of the cooled patients. The investigators concluded, despite their incomplete understanding of optimal cooling, that patients require cooling to < 35°C before reperfusion.

RACTS Trial

Results from the Prospective Randomized Multicenter Study of Antiplatelet using Cilostazol versus Ticlopidine Undergoing Coronary Artery Stenting (RACTS) trial were presented by Dr. Junbo Ge from the Shanghai Institute of Cardiovascular Disease, Shanghai, China. RACTS was designed to compare the safety and efficacy of the phosphodiesterase III inhibitor cilostazol versus ticlopidine in patients undergoing coronary stenting. Patients were randomized to either cilostazol 100 mg twice daily for 6 months or ticlopidine 250 mg twice daily for 1 month following procedure, with all patients receiving aspirin 100 mg daily. Six month angiographic follow-up and 9 month clinical results were similar with a slight benefit from cilostazol therapy in rates of target vessel revascularization. The results of this trial imply that cilostazol may be an alternative to clopidogrel or ticlopidine in patients who develop allergies to the ADP blockers.

Diabetic Patients and Cardiovascular Risk

Dr. Diane Turcot and associates from Hartford Hospital in Hartford, CT, reported on the detrimental impact of chronic renal failure and diabetes mellitus after PCI. The impact of diabetes and chronic kidney disease (CKD) on the prognosis of patients following PCI is profound and has only recently been appreciated. For the purposes of this study, CKD was defined as a creatinine clearance less than 90 mL/min for men and 70 mL/min for women. In 1660 diabetic patients undergoing PCI, the most important predictors of 1-year mortality were dialysis and the presence of CKD. In-hospital and 1-year mortality following PCI were 11.6% and 53%, respectively, in patients with

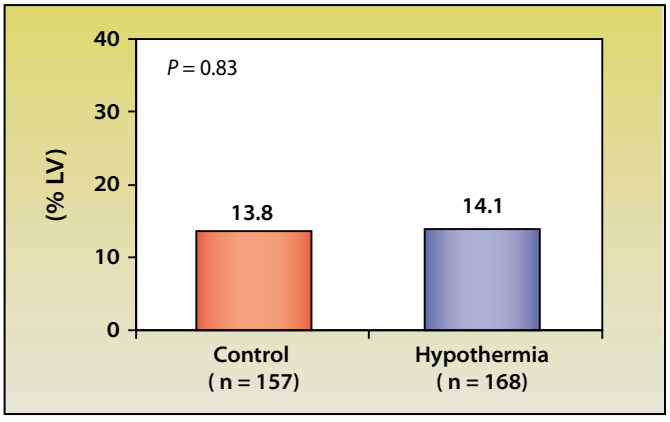


Figure 5. *Results of the COOL-MI trial. The hypothermia group was treated with the Reprieve™ endovascular temperature therapy system.*

end-stage renal disease (ESRD), 2.3% and 24% in patients with CKD but not ESRD, and 0.3% and 14% in non-CKD patients.

These results are consistent with previous analyses showing a gradient of risk for patients undergoing PCI based on the presence and severity of CKD. This should lead to the utilization of treatments including abciximab, a glycoprotein (GP) IIb/IIIa inhibitor, that is not dependent on a renal mechanism for metabolism. The aggressive use of ß-blockers, lipid-lowering strategies, and antiplatelet therapy in this very high-risk patient population may also be recommended.

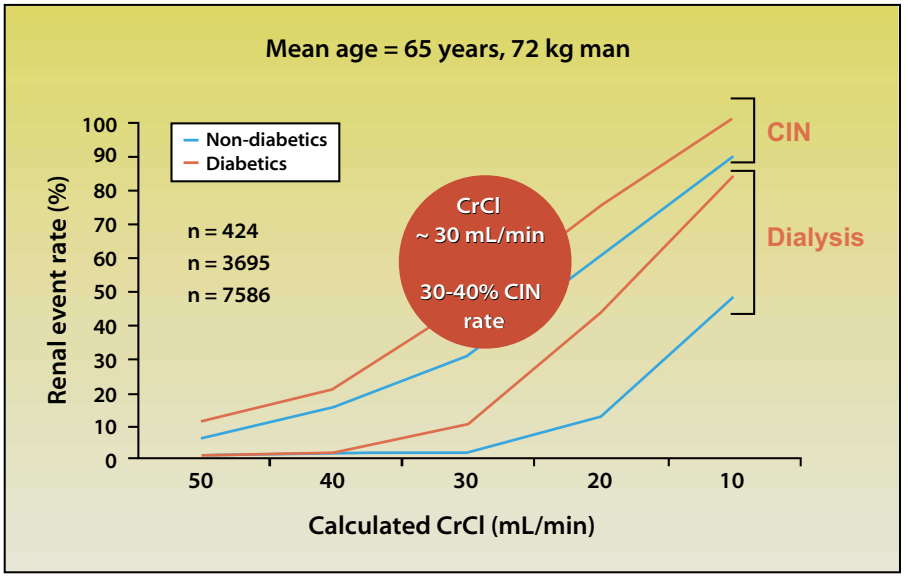
Additional focus was placed this year on the treatment of the diabetic patient, with an emphasis on the cardiovascular manifestations of diabetes mellitus, at a session chaired by Dr. Michael Farkouh of Mount Sinai Hospital in New York and Dr. Richard Nesto of the Lahey Clinic Medical Center in Burlington, MA. Of particular interest were discussions differentiating varying medical treatment courses for diabetes and concomitant cardiovascular disease.

According to the Intermountain Health Collaborative, among patients undergoing PCI with known coronary artery disease, only 39% had fasting glucose measurements in the normal range. Twenty-four percent fell into the range of impaired fasting glucose (IFG). Eighteen percent not presenting with previously diagnosed diabetes measured fasting glucose consistent with diabetes mellitus and another 19% presented with known diabetes. It is clear that if the status of this cohort can be generalized to the population at large, the majority of patients undergoing PCI have abnormalities of glucose metabolism. Implications of this idea are quite profound as patients with known diabetes have a Cox hazard ratio of survival of 5.0 compared to 4.1 in patients who meet the American Diabetes Association criteria for diabetes and 3.2 for patients with IFG. Regarding predictors of angiographic restenosis after coronary intervention in diabetic patients, a glycosylated hemoglobin >8%, a reference vessel diameter of <2.87 mm and percutaneous transluminal coronary angiography (PTCA) versus stent had the highest predictive value. Hyperinsulinemia seemed to also be predictive of restenosis following PTCA.

Looking at the variety of agents used to treat diabetes mellitus, there did seem to be significant differences in cardioprotective effects. The insulin sensitizing glitazones have many positive effects, including improvement of glycemic control and reduction of blood pressure and central obesity, as well as decrease in triglyceride levels, increase in high-density lipoprotein cholesterol (HDL-C) levels and improved low-density lipoprotein cholesterol particle size. In addition, they decrease C-reactive protein and metalloproteinase levels, improve endothelial function, and reverse the fibrinolytic and coagulation defects that are considered part of the metabolic syndrome.

In a substudy of the United Kingdom Prospective Diabetes Study (UKPDS) of overweight diabetics, those who were assigned to the aggressive treatment group fared better if treated with metformin than with either insulin or sulfonylurea agents. Glitazones were not evaluated in the UKPDS, perhaps explaining the lack of a significant reduction in macrovascular events in the aggressive treatment group versus the conventional treatment arm. Acarbose also seems to have a protective cardiovascular effect as it reduced the cardiovascular event rate compared to placebo in patients with impaired glucose tolerance (IGT). Data also shows that not all insulin secretagogues are alike in regard to cardiovascular risk, with the highest risk attributed to glyburide. Some would

Figure 6. *Prediction of contrast-induced nephropathy (CIN) and dialysis following percutaneous coronary intervention. Likelihood of adverse renal events rises in direct proportion to falling rates of creatinine clearance (CrCl). Data from Berns et al.* Kidney Int. *1989;36(4):730-740, Rihal et al.* Circulation. *2002;105(19):2259-2264. McCullough et al.* Am J Med. *1997;103(5):368-375.*



recommend avoiding the use of glyburide in diabetic patients altogether, because of this attributed risk.

The metabolic syndrome is characterized by the following components: abdominal obesity, hypertriglyceridemia, low HDL-C levels, hypertension, and high fasting glucose or required medication for hyperglycemia. Over 71% of Americans have 1 or more of these metabolic abnormalities, 44% have 2 or more and 24% have 3 or more.

Contrast-Induced Nephropathy

A satellite symposium entitled "A Contrast in Risk: Radiographic Imaging in the Renally Compromised Patient" reviewed the implications of development of contrast-induced nephropathy (CIN), identified patients at risk for developing CIN, the characteristics of contrast agents associated with high CIN risk, and measures that can be taken to prevent the occurrence of CIN. Evidence continues to accrue showing that the risk of developing CIN increases dramatically when patients exposed to contrast have creatinine clearances of less than 30 mL/min. This level of creatinine clearance represents the status of about 30% of patients undergoing PCI. At this level of renal function, 30% to 40% of patients can be expected to develop CIN as defined by an increase in serum creatinine of at least 0.5 mg/dL from baseline.

Table 1
Risk Factors for Contrast-Induced Nephropathy

Patient-related Risk Factors	Procedure-related Risk Factors
• Renal insufficiency	• Multiple contrast media injections within 72-hour period
• Diabetes mellitus with renal insufficiency	• Intra-arterial injection site
• Age	• High volume of contrast media
• Volume depletion	• High osmolality of contrast media
• Hypotension	
• Low cardiac output	
• Class IV congestive heart failure	
• Other nephrotoxins	
• Renal transplant	
• Hypoalbuminemia (<35 g/L)	

Dr. Roxana Mehran of the Lenox Hill Heart and Vascular Institute in New York described both the risk factors for and the consequences of developing this complication of contrast exposure (Figure 6, Table 1). The major risk factor for the development of CIN is diabetes mellitus associated with renal insufficiency. The development of CIN is associat-

Table 2
Representative Contrast Media

Brand Name	Compound	mOsm/kg H_2O	Viscosity	Iodine (mg/mL)	Sodium (mEq/L)	gI/kg	LD50 (mouse)
Hypaque®-76*	Sodium-meglumine	2,160	13.3	9.0	370	160	7.5
Renografin®-76†	Diatrizoate meglumine/sodium	1,940	10.0	8.4	370	190	7.5
Hexabrix®	Ioxaglate meglumine/ioxaglate	600	15.7	7.5	320	150	11.2
Isovue®	Iopamidol	796	20.7	9.4	370	2	21.8
Omnipaque®	Iohexol	844	20.4	10.4	350	5	24.2
Opitray®	Ioversol	702	9.9	5.8	320	2	17
Visipaque®‡	Iodixanol	290	26	11.8	320	19	>21

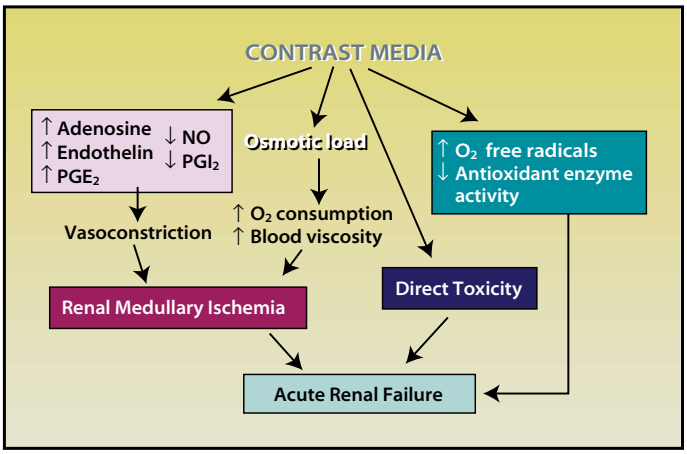
*Formulated with the additives of calcium disodium EDTA.
†Originally formulated with the additives of sodium citrate, sodium EDTA.
‡Formulated with the addition of a "balanced" sodium and calcium salts to bring to isotonicity.
All nonionic contrasts have additives of tromethamine and calcium disodium EDTA.
Hypaque-76: Sanofi Winthrop; Renografin-76: Squibb Pharmaceuticals; Hexabrix: Mallinckrodt Inc., Hazelwood, MO; Isovue: Squibb Pharmaceuticals; Omnipaque: Amersham Health, Princeton, NJ; Opitray: Mallinckrodt Inc., Hazelwood, MO; Visipaque: Amersham Health, Princeton, NJ.

ed with in-hospital mortality rates as high as 35%.

Dr. Jeffrey Brinker of the Johns Hopkins Medical Institutions, Baltimore, MD, compared the characteristics of varying contrast media currently available (Table 2), including ionic properties and osmolality. The COURT trial compared the risk of developing major adverse coronary events (MACE) in patients undergoing PCI, who were randomized to two contrast agents, iohexol or iodixanol. In-hospital MACE was lower in the group exposed to iodixanol (5.4% versus 9.5% [*P* = .027]).

Dr. Michael Rudnick of the University of Pennsylvania School of Medicine in Philadelphia, PA, described in detail the physiological effects of contrast agents on the kidney. These effects include vasoconstriction-induced renal medullary ischemia; contrast-induced increase in tubular oxygen consumption; and increased blood viscosity, direct toxic effects, and tubular toxicity due to an accumulation of oxygen free radicals (Figure 7).

Figure 7. *Potential effects of contrast procedures on the renal system.*



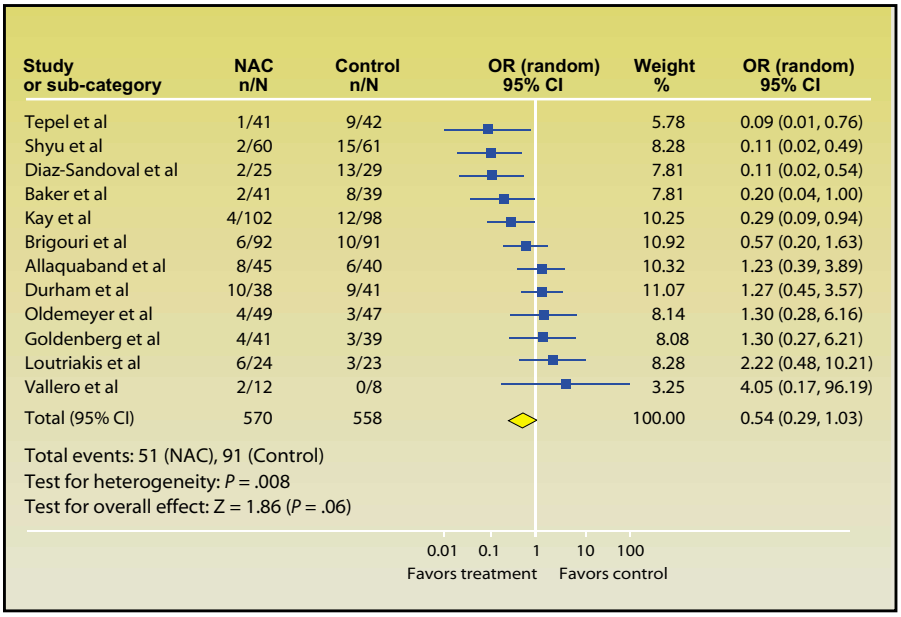
A variety of therapies have been investigated for the prevention of CIN, with intravenous hydration yielding the only consistently positive results. A review of data evaluating the efficacy of N-acetylcysteine showed a lack of consistent benefit, calling into question recommendations for its use in CIN prevention (Figure 8).

Dr. Charles Davidson from the Northwestern University Feinberg School of Medicine in Chicago, IL, reviewed the clinical data comparing the ability of iodixanol, an iso-osmolar agent, to iohexol, a low-osmolar agent, in preventing CIN. In the recently published Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Nonionic Contrast Media (NEPHRIC) trial, the use of iodixanol was associated with a significantly lower incidence of CIN than was treatment with iohexol (Figure 9). Dr. Davidson also described the design of the Visipaque Angiography/Interventions with Laboratory Outcomes for Renal Insufficiency (VALOR) trial, which will compare iodixanol (Visipaque®, Amersham Health, Princeton, NJ) to another low-osmolar contrast agent.

Among the experts assembled at this symposium, the consensus, based on current clinical data, agreed that the use of aggressive pre-procedure hydration, minimal amounts of contrast medium, and use of the iso-osmolar agent iodixanol, represents the optimal approach for the patient at risk for CIN.

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

Figure 8. *Meta-analysis of trials utilizing N-acetylcysteine (NAC) to control contrast-induced nephropathy. Results are mixed and overall analysis proves inconclusive.*



Drug-Eluting Stents: Accumulating Evidence

Drug-eluting stents took center stage for a good portion of this year's meeting. Data continue to accrue on

implantation of the sirolimus-eluting stents, in both wider groups of patients and in angiographic lesions. In addition, new data became available on the TAXUS IV study of paclitaxel-eluting stents.

Sirolimus-Eluting Stents

One- and 2-year clinical follow-up of the SIRIUS trial of the CYPHER™ sirolimus-eluting stent (Cordis Corporation, Miami, FL) was presented. Clinical restenosis defined as target lesion revascularization (TLR) was adjudicated in all patients. At nine months, TLR was required or performed in 16.6% of bare metal stent patients versus only 4.1% of sirolimus-eluting stent patients (P <.001), an absolute reduction in events of 12.5%. At 12 months, the absolute difference in incidence of TLR between the 2 groups had widened to 15.1% (20.0% for bare metal stents versus 4.9% for sirolimus-eluting stents) (P <.001).

Two-year follow-up data on an interim group of patients was also presented. In these patients, the difference in incidence of TLR (clinical restenosis) between the groups was maintained at 19.2% for bare metal control stents and 6.1% for the sirolimus-eluting stent (P <.001). In addition, there were no new stent thromboses at 24 months. A new group of randomized patients (new SIRIUS) was also presented and included 452 patients; 352 from European sites and 100 from Canadian sites. These patients had more complex lesions with more overlapping stents. The minimal lumen diameter post-procedure was smaller (2.45 mm) than that seen in the initial SIRIUS trial.

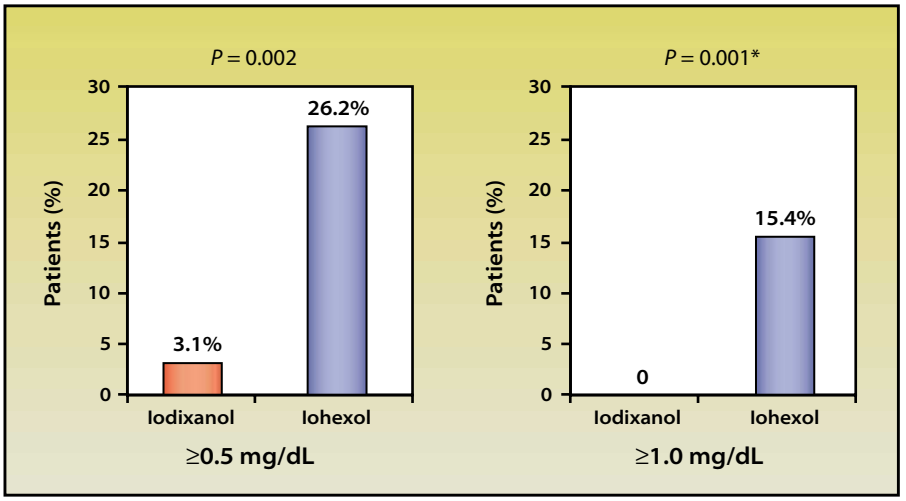


Figure 9. *Results of the NEPHRIC trial, showing a much higher incidence of significantly raised creatinine levels in patients undergoing contrast procedures with iohexol than with iodixanol.*

One of the most striking findings of these additional SIRIUS results was that the proximal edge effect of increased restenosis in the proximal peri-stent area, which had been seen in 5.5% of patients in the initial SIRIUS trial, was reduced to 2.1% in the new SIRIUS experience.

In this group, at the time of follow-up angiography, late loss within stent in the sirolimus-eluting stent patients was decreased by 83% to 0.18 mm versus 1.04 mm in the control group (P <.001) and within the segment treated was decreased by 79% to 0.17 mm versus 0.80 mm (P <.001). As shown in Table 3, binary restenosis rates were dramatically lower with utilization of the sirolimus-eluting stent, as was TLR. In addition, regardless of the subgroup analyzed, the rate of TLR was improved in patients treated with the sirolimus-eluting stent.

One of the most striking findings of these additional SIRIUS results was that the proximal edge effect of increased restenosis in the proximal peri-stent area, which had been seen in 5.5% of patients in the initial SIRIUS trial, was reduced to 2.1% in the new SIRIUS experience (P <.05). This reduction was attributed by the investigators to improved, direct stenting technique that avoids damage to the vessel outside the limits of the stent, shorter balloons for post-stent inflation, and no pullback technique. These results were further confirmed

Table 3
Angiographic and Clinical Outcomes from the New SIRIUS Results

	Sirolimus-eluting Stent	Bare Metal Stent	*P*-Value
Restenosis			
In stent	3.1%	42.7%	<.001
In segment	5.1%	44.2%	<.001
Target lesion revascularization	4.0%	20.3%	<.001

in larger, real-world registries of consecutive patients undergoing treatment with the sirolimus-eluting stent, which were reported from Rotterdam.

Paclitaxel-Eluting Stents

The TAXUS IV study documents striking new findings on the efficacy of the slow-release paclitaxel-eluting stent from Boston Scientific/Scimed (Natick, MA). The early results of a feasibility trial (TAXUS I) and then an international efficacy trial (TAXUS II) had been very positive and laid the groundwork for TAXUS IV, the pivotal U.S. trial of 1326 patients undergoing treatment of *de novo* native coronary arterial lesions in vessels ranging from >2.5 to <3.75 mm in diameter. The primary endpoint for TAXUS IV was 9-month target vessel revascularization (TVR). Patients were well matched in terms of baseline demographic and lesion characteristics with a lesion length of approximately 13.4 mm in a reference vessel diameter of 2.75 mm.

The 9-month quantitative coronary angiography and clinical endpoints data documented significant improvements (Table 4). The binary restenosis rate within the stent was 5.5% in the paclitaxel-eluting stent group versus 24.4% in the control group and 7.9% versus 26.6%, respectively, within the analyzed segment (both P <.001). The primary endpoint of TVR was seen in 4.7% in the paclitaxel-eluting stent group versus 12.0% in the control group (P <.001). Stent thromboses were infrequent; occurring in 0.6% and 0.8% of the two groups, respectively, and were not statistically different. Subgroup analysis showed that higher risk patients and lesions continued to show marked improvement when treated with the paclitaxel-eluting stent.

These data, as well as others presented at the meeting, document that drug-eluting stents have become predicate devices in interventional cardiology and increasingly form the backbone of therapy for patients with coronary artery disease who are undergoing percutaneous revascularization. [David R. Holmes, Jr, MD]

Table 4
TAXUS IV Clinical Outcomes

	Paclitaxel-eluting Stent	Bare Metal Stent	*P*-Value
N	662	652	
Procedural success	97.3%	97.4%	
Restenosis			
In stent	5.5%	24.4%	<.001
Analysis segment	7.9%	26.6%	<.001
Target vessel revascularization	4.7%	12.0%	<.001
Target lesion revascularization	3.0%	11.3%	<.001

ISAR SMART-II

The increased incidence of restenosis following percutaneous coronary intervention (PCI) in small arteries, along with the question of the efficacy of bare metal stents versus balloon angioplasty in lowering restenosis rates, have resulted in an ongoing evaluation of new modalities to improve outcomes in small vessels. Stent coating with phosphorylcholine (PC) has been shown to reduce protein absorption and platelet activation and, in non-randomized studies, these stents have been associated with favorable outcomes when used for lesions in small coronary arteries.

ISAR SMART-II, as presented by Dr. Adnan Kastrati of the Deutches Herzzentrum, Munich, Germany, was designed to test the hypothesis that use of PC-coated stents is associated with a reduction in restenosis in small coronary arteries when compared to balloon angioplasty, and also to test whether abciximab reduces restenosis following PCI in small arteries. Abciximab has been associated with improved outcomes following PCI in general. The study protocol consisted of a 2 × 2 factorial design and the sample size was based on the assumption of a 40% reduction in restenosis through the use of PC-coated stents and a 30% reduction in restenosis through the use of abciximab. Accordingly, 502 patients with symptomatic coronary artery disease, without acute MI, undergoing PCI of a lesion in a native vessel ≤ 2.5 mm in diameter were randomly assigned to treatment with a PC-coated stent (BiodivYsio™ SV, Biocompatibles Ltd., Surrey, UK) versus balloon angioplasty and abciximab (using standard infusion) versus placebo. All patients received aspirin and clopidogrel (the latter for a minimum of 30 days). Clinical follow-up was performed at 30 days and at 12 months, with angiographic follow-up at 6 months. The primary endpoint of the trial was the rate of angiographic restenosis at 6 months. TVR and death or MI served as secondary endpoints.

As expected, baseline clinical, angiographic, and procedural characteristics were similar between groups with the exception of a higher balloon inflation pressure and a larger post-procedure minimal lumen diameter in the PC-coated-stent group. At 30 days and at 12 months, there were no significant differences in the rates of death, MI, or TVR between the PC-coated-stent and balloon-angioplasty groups or between the

abciximab and placebo groups. In addition, at 6 months, there was no difference in angiographic restenosis or TVR between the PC-coated-stent and balloon-angioplasty groups (Figure 10A), between the abciximab versus placebo groups (Figure 10B) or between the PC-coated stent plus abciximab versus balloon-angioplasty groups. The authors concluded that despite the advantages of PC in experimental studies, PC-coated stents failed to reduce the rate of restenosis compared to balloon angioplasty in small arteries. In addition, abciximab in the presence of now standard use of clopidogrel does not reduce the incidence of restenosis in small arteries.

Comment

These data suggest, yet again, that bare metal stents, and now a PC-coated stent, do not reduce the incidence of restenosis in small arteries. Although not surprising, abciximab is likewise ineffective in inhibiting the pathophysiologic stimuli that lead to restenosis. It is likely that future studies in small vessels will involve the use of drug-eluting stents.

Ongoing-Tirofiban In Myocardial Infarction Evaluation (ON-TIME)

It has become increasingly clear that for patients with acute ST segment elevation MI, primary PCI is associated with reduced rates of death, reinfarction, and intracranial bleeding in comparison to fibrinolytic therapy. Given that the majority of hospitals do not have PCI-performing capability, physicians have been faced with the challenge of providing primary PCI to selected patients in a timely fashion. Recent data suggests that patients presenting with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow prior to PCI have improved survival at 1 year. As a result, several strategies that have the potential to restore flow en route to a facility capable of performing PCI are under active investigation.

Suryapranata and associates from the Hospital De Weezenlanden, Zwolle, Netherlands, presented results from the ON-TIME trial, which tested the hypothesis that pre-hospital administration of the GP IIb/IIIa platelet receptor antagonist tirofiban would increase infarct artery patency when compared to administration just prior to initial angiography in patients undergoing primary PCI. Accordingly, 507 patients with acute ST-segment elevation MI who were transported to a PCI center were randomly assigned to early (in the referral hospital or in the ambulance) or late (after coronary angiography but prior to PCI) initiation of tirofiban or placebo. Following the procedure, tirofiban infusion was continued for 24 hours and all patients received standard therapy with aspirin, clopidogrel, and low molecular weight heparin. The primary endpoint of the study was TIMI grade 3 flow in the infarct artery at initial angiography. Secondary endpoints included the effect of tirofiban on each TIMI flow component and the presence of intra-coronary thrombus.

As expected, baseline characteristics and treatment time delays were similar between groups. Of note, 51% of patients were randomized at referral hospitals and transported to PCI centers, 41% of patients were diagnosed and randomized in the ambulance, and 8% of patients were randomized in the emergency department at 1 of the PCI centers. In the early group, tirofiban was administered a median of 59 (range 11–178) minutes earlier than in the late group.

During initial angiography, there was a similar incidence of TIMI 3 flow in the early group (19%) and in the late group (15%) although there was a higher incidence of TIMI grade 2 plus 3 flow in the early group. In addition, the presence of intra-coronary thrombus or total occlusion of the infarct artery was significantly lower in the early group (60%) in comparison to the late group (73%), $P = .002$. At 30 days, the combined incidence of death, reinfarction and stroke was 3.1% in the entire study cohort. The authors concluded that although increased TIMI 3 flow rates in the infarct artery were not achieved, higher patency rates and a decreased prevalence of infarct artery thrombus or total occlusion were found prior to PCI in patients who received early tirofiban treatment during transport to a PCI facility.

Comment

This trial is timely and of interest as enthusiasm for primary PCI in the treatment of acute myocardial infarction continues to increase, and the transfer of patients to PCI centers, despite the inherent time delay, is being performed more frequently. The answer to whether the results of this negative trial will impact clinical practice must await larger studies sized to measure clinical outcomes. [Alice K. Jacobs, MD, FACC, FAHA]

New Research and Experimental Procedures

Neovascularity and Macrophage Immunoreactivity in Human Carotid Plaques

There is growing recognition that atherosclerosis is associated with increased neovascularization, which has been implicated in plaque growth and progression and, possibly, plaque instability. Payar and associates from the Texas Heart Institute in Houston, TX, examined 10 archived human carotid plaques for neovascularity and macrophage immunoreactivity. The authors describe neovascularity in all 10 plaques, making the point

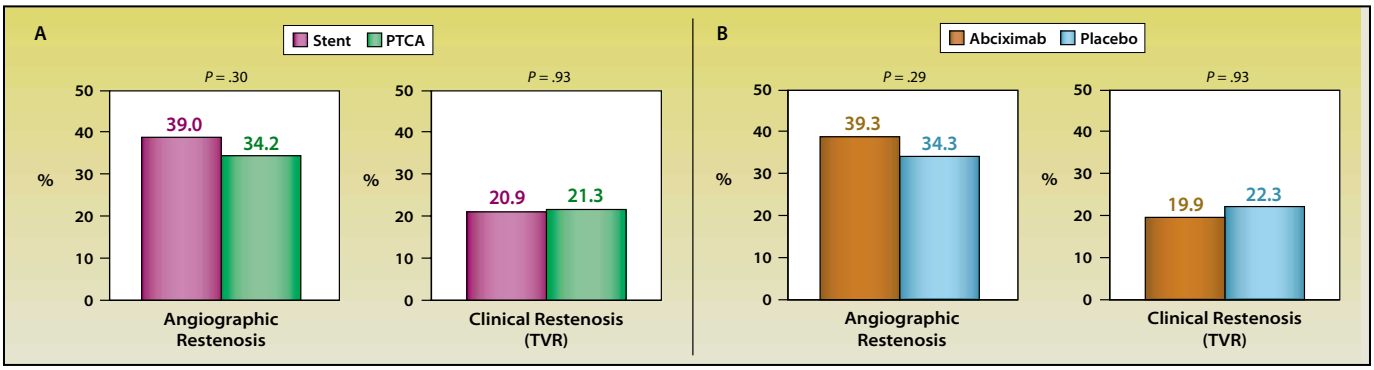


Figure 10. *Six-month results of the ISAR-SMART II trial. Angiographic and clinical restenosis rates were not significantly different when comparing the phosphorylcholine-coated stent and balloon-angioplasty groups* **(A)** *or the abciximab and placebo groups* **(B)**. *PTCA, percutaneous transluminal coronary angioplasty; TVR, target vessel revascularization.*

that 2 patterns of neovascularity can be discerned: neovascularity deep in the plaque at the base of the lipid core, about 817 micronmeters from the lumen, and neovascularity on the intimal side of the plaque, approximately 64 micronmeters from the lumen. In all cases, neovascularity was noted to co-localize with macrophage immunoreactivity. The authors contend that deep neovascular channels may be involved in recruiting inflammatory cells into the plaque, a hypothesis that has been considered by other investigators.

Co-localization of inflammation and neovascularity is not surprising because it is well known that macrophages and their products are capable of stimulating angiogenesis. Although the authors speculate that new vessels at the base of the plaque may recruit macrophages, it is difficult to ascribe a cause and effect since it is equally likely that inflammatory cells are the signal for neovascularization. It is fair to state that at this time the precise cause and effect relationship is unclear. However, angiogenesis inhibitors have reduced atherosclerotic progression and angiogenesis promoters have accelerated atherosclerotic progression in n murine models. These earlier experimental observations have suggested a potential role for neovascularization in atherosclerosis progression.

In Vivo Endothelial Progenitor Cell Seeding

It has been postulated that functional endothelial cell coverage of stents and grafts could prevent thrombosis and reduce neointimal hyperplasia. Kutryk and coworkers employed a novel approach to accelerated endothelial coverage of stents and polytetrafluoroethylene (ePTFE) grafts. After coating stents and ePTFE grafts with a murine-CD34 antibody (antibody to circulating endothelial progenitor cells) through a polymeric dextran intermediate, they deployed the stents in coronary arteries and the ePTFE grafts into carotid arteries

Table 5
Numbers of Adverse Events in Patients Treated with Percutaneous Coronary Intervention (PCI) With and Without Hyperbaric Oxygen Therapy (HOT)

MACE	PCI	PCI+HOT	*P*-Value
Death/MI/CABG/TLR	13	1	<.001
Death	3	0	ns
MI	7	1	0.06
CABG	0	0	
TLR	8	0	<.003

CABG, coronary artery bypass grafting; MACE, major adverse coronary event; MI, myocardial infarction; TLR, target lesion revascularization.

Table 6
Effect of Intravenous eHGF Therapy on Myocardial Infarction in an Animal Model

	Control	eHGF Treated	*P*-Value
Infarct size	31.7 + 6.6	14 + 4.6	.002
Apoptotic index	57.7 + 7.5	33.2 + 5.3	.02

eHGF, e-hepatocyte growth factor.

of Yorkshire swine. Stents were explanted 1 hour, 48 hours, or 28 days after implantation and grafts were explanted 4 hours or 72 hours after implantation. Antibody-coated stents showed >90% coverage with endothelial cells at 1 hour post-deployment and confluent monolayer-type coverage at 48 hours after deployment. At 28 days there was a modest but significant reduction in in-stent neointima with the antibody coated stents compared to bare metal stents (1.18 + 0.38 vs 1.58 + 0.24; $P = .05$). Antibody-coated grafts showed a rich population of endothelial cell-marker-positive cells, 4 hours after explant.

The authors showed the feasibility of their novel technique for auto-seeding of endothelial cells. However, surprisingly, the degree of neointimal thickening was only marginally affected, despite full endothelial coverage. Further validation of this interesting approach is needed.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HOT) is used to accelerate wound healing and has been shown to induce a number of biochemical changes that could favorably influence the healing of injured vessel walls, preventing excessive healing and restenosis. In this prospective study, Sharafi and colleagues of Texas Tech University in Odessa, TX, assigned 24 patients to PCI plus HOT versus 37 assigned to routine PCI. All patients underwent procedures for unstable angina or acute MI. HOT was used immediately before or after PCI and again within 18 hours of the procedure. Each HOT treatment consisted of 100% oxygen at 2 bars for 90 min-

Main Points

- Based on results of the ENDEAVOR-I trial, the Endeavor drug-eluting stent seems to be effective in the short term (4 months); results from the larger, randomized ENDEAVOR-II will determine whether phosphorylcholine is the optimal coating.
- The results of FUTURE I and II showed the Biosensor, everolimus-coated stent to be effective in lowering restenosis and late loss rates and held future promise for bioabsorbable coating technology.
- The power-pulse spray technique is effective and safe for use in lytic therapy with either urokinase or tenecteplase, and preferable to observed outcomes of therapy using traditional chemical thrombolysis and rheolytic thrombectomy.
- Six-month results of the REPLACE II trial show, in a relatively lower-risk patient cohort, that bivalirudin is a reasonable replacement for unfractionated heparin in patients undergoing percutaneous coronary intervention (PCI).
- The insulin-sensitizing glitazones have many positive cardiovascular effects, including improvement of glycemic control and reduction of blood pressure and central obesity, as well as decrease in triglyceride levels, increase in high-density lipoprotein cholesterol levels and improved low-density lipoprotein cholesterol particle size.
- The roundtable consensus, based on current clinical data, agreed that the use of aggressive pre-procedure hydration, minimal amounts of contrast medium, and the iso-osmolar agent iodixanol, represent the optimal approach for the patient at risk for contrast-induced nephropathy.
- In the 1- and 2-year clinical follow-up data for the SIRIUS trial, the sirolimus-eluting stent provided dramatically lower binary restenosis rates versus a bare metal stent.
- TAXUS IV showed marked improvement in restenosis rates with use of a paclitaxel-eluting stent versus the bare metal stent, even in higher risk patients.
- In the ISAR-SMART II trial, the phosphorylcholine-coated stent failed to lower rates of restenosis in the treatment of small vessels compared to balloon angioplasty. Abciximab also had no measurable effect versus placebo when both were coupled with standard clopidogrel therapy.
- The authors of the ON-TIME study explored the option, in hospitals without primary PCI facilities, of immediate administration of tirofiban as an adjunctive therapy while transporting patients to a PCI center. They concluded that although increased Thrombolysis in Myocardial Infarction 3 flow rates in the infarct artery were not achieved, higher patency rates and a decreased prevalence of infarct artery thrombus or total occlusion were found prior to PCI in patients who received early tirofiban treatment.
- Animal studies have shown possible positive results in the use of murine CD34 antibody-coated stents and grafts to seed the growth of endothelial cells, as well as e-hepatocyte growth factor therapy to minimize damage from myocardial infarction.

utes with a total chamber dwell time of 120 minutes. All patients had at least 1 stent placed in a native artery or bypass graft. Incidence of major adverse coronary events in both groups can be seen in Table 5.

This provocative study suggests a novel approach for improving outcomes after PCI. Additional large, controlled trials with well matched subjects will be needed to prove whether the striking results observed here will stand the test of time.

e-Hepatocyte Growth Factor and Left Ventricular Dysfunction in a Rabbit Model of Acute Myocardial Infarction

Huang and associates of the Xinqiao Hospital at the Third Military University in Chongqing, China, created a model of MI in rabbits using left anterior descending coronary artery ligation. In view of known biological actions of e-hepatocyte growth factor (mitogen with growth regulating and cardiotrophic effects, eHGF), they compared the effect of intravenous eHGF administration (2 mg/kg/12 h) to that of saline, measuring in vivo hemodynamic performance and examining the explanted hearts 2 days or 4 weeks after treatment. Rabbits receiving eHGF treatment had a substantially smaller infarct size, smaller myocardial apoptotic index (Table 6), lower end-systolic and end-diastolic volumes, higher ejection fraction, and higher capillary density in the myocardium. eHGF therapy was associated with increased phosphorylation of ERK1.

The authors conclude that eHGF therapy may reduce infarct size, most likely by promoting the expression of *bcl-2*, an anti-apoptotic gene, and through angiogenic effects via phosphorylation of ERK1.

A number of experimental studies have examined the effects of varying adjunctive interventions in acute MI models, in the hope of reducing infarct size over and above the effects of reperfusion by targeting pathways other than restoration of flow. Despite many positive studies, nearly every clinical trial that has tested an intervention other than reperfusion has been disappointing in this regard. While the authors make a convincing case from their study, the history of such interventions has been uniformly discouraging in the human model. ■

[Prediman K. Shah, MD, FACC, FACP, FCCP]