Best of the ACC Scientific Session 2005

Highlights from the American College of Cardiology 54th Annual Scientific Session, March 6-9, 2005, Orlando, FL

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Key words: ABT-578 • ACE inhibitors • ASCOT • Calcium channel blockers • Chronic kidney disease • COMPASS-HF • Contrast-induced nephropathy • Cypher • ENDEAVOR II • EVEREST I • GIK • GIPS-II • Heart failure • Hemodynamic monitoring • ISAR-DIABETES • Natriuretic peptides • PEECH • Prasugrel • REALITY • SIRTAX • TAXUS

In conjunction with the 2005 Scientific Session of the American College of Cardiology (ACC), abstracts were published and trials presented reporting significant findings in every subspecialty of cardiovascular medicine. Our board members have selected findings of particular significance and report them here.

Chronic Kidney Disease as a Cardiovascular Risk Factor

Our group from the William Beaumont Hospital in Royal Oak, MI presented cardiovascular disease (CVD) results of the Kidney Early Evaluation Program (KEEP), a multicenter community screening program of individuals at risk for chronic kidney disease (CKD). Volunteers in US centers were evaluated for estimated glomerular filtration rate (GFR) based on measured serum creatinine, age, gender, race, and other factors. Of the 24,070 (age 52.6 ± 15.8 years, 68.9% female, 39.4% African American) subjects who volunteered for screening, 3,883 (16.1%) had a self-reported history of CVD (myocardial infarction, stroke, peripheral artery disease). Multivariate analysis found the following characteristics independently associated with CVD: age > 75 years (referent: 46-60), OR = 2.17, $P < .0001$; male gender, OR = 1.20, $P = .0004$; urine microalbumin > 30 mg/L (referent: ≤ 10), OR = 1.63, $P < .0001$; GFR 30-59 mL/min (referent: ≥ 90), OR = 1.37, $P < .0001$; GFR < 30 mL/min (referent: ≥ 90), OR = 1.84, $P = .0004$; hemoglobin < 12.8 g/dL (referent: > 14.6), OR = 1.45, $P < .0001$. Overall, subjects with all 3 CKD-related factors had a 35.8% rate of CVD. However, when stratified by stage of CKD, the prevalence of CVD was over 70% in subjects in Stage 4 CKD (GFR < 30 mL/min), when there was concomitant anemia and microalbuminuria (Figure 1).

This study strongly suggests that CKD is an important signal for the presence of CVD. Future studies evaluating the hemodynamic,

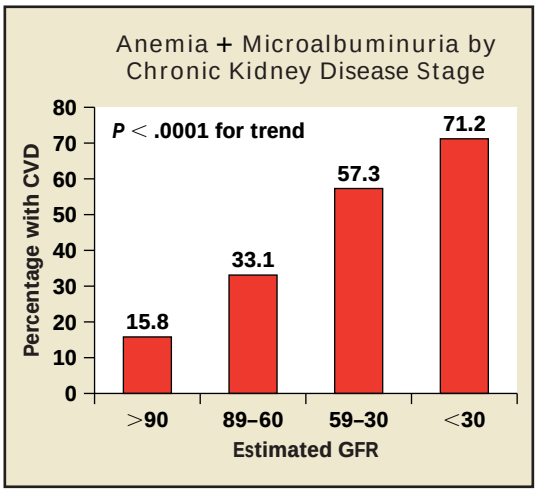


Figure 1. *Prevalence of cardiovascular disease (CVD) in patients with microalbuminuria and anemia (hemoglobin < 12.8 g/dL), who participated in a community screening program. GFR, glomerular filtration rate.*

neurohormonal, metabolic, and hematopoietic aspects of CKD are warranted.

Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI 28)

This recent trial from the Thrombolysis in Myocardial Infarction (TIMI) group tested the use of clopidogrel after fibrinolysis for ST segment myocardial infarction. A total of 3491 patients were randomized after receiving aspirin, heparin, and fibrinolysis to either a 300 mg oral loading dose of clopidogrel followed by 75 mg daily versus placebo. There was a reduction in the rate of occluded coronary vessels at the time of angiography, death, or recurrent myocardial (pre-angiography) infarction with clopidogrel (15.0% versus 21.7% with placebo, $P < .0001$, 36% relative reduction). See Table 1. This finding was internally consistent among all prespecified subgroups and the benefits extended to a reduced rate of death or MI at 30 days (Figure 2). These data support the use of early clopidogrel before angiography in those patients with ST-segment elevated myocardial infarction (STEMI), who receive lytic therapy.

Aspirin for Primary Prevention in Women

The Women's Health Study randomly assigned 39,876 initially healthy women, aged 45 years or older, to receive 100 mg of aspirin on alternate days or placebo and found that aspirin provided a 9% relative risk reduction for a first CVD event (ie, nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes), $P = 0.13$. However, there was a 17% risk reduction in stroke ($P = .04$) driven by a 24% reduction in the risk of ischemic stroke ($P = .009$), without a significant risk of hemorrhagic stroke. As compared with placebo, aspirin had no significant effect on the risk of fatal or nonfatal myocardial infarction or death from cardiovascular causes. Gastrointestinal bleeding requiring transfusion was more frequent in the aspirin group than

Table 1
Short-Term Results of the CLARITY-TIMI 28 Trial

Outcome	Clopidogrel (n = 1752)	Placebo (n = 1739)	Odds Ratio (95% CI)	*P* Value
Primary efficacy endpoint—no. patients (%)	262 (15.0)	377 (21.7)	0.64 (0.53-0.76)	< .001
TIMI flow grade 0 or 1	192 (11.7)	301 (18.4)	0.59 (0.48-0.72)	< .001
Death	45 (2.6)	38 (2.2)	1.17 (0.75-1.82)	0.49
Recurrent myocardial infarction	44 (2.5)	62 (3.6)	0.70 (0.47-1.04)	.08
Other Angiographic Measurement—No. of Patients (%)				
TIMI flow grade 3	1112 (67.8)	993 (60.8)	1.36 (1.18-1.57)	< .001
TIMI myocardial-perfusion grade 3	885 (55.8)	817 (51.2)	1.21 (1.05-1.40)	.008
Intracoronary thrombus	697 (43.0)	822 (50.8)	0.73 (0.64-0.84)	< .001
Mean stenosis , %	68.4	70.8	−2.3 (−3.8-−0.9)	.001
Mean minimal luminal diameter, mm	0.82	0.75	0.07 (0.03-0.11)	.001

Reproduced with permission from Sabatine et al.[3]

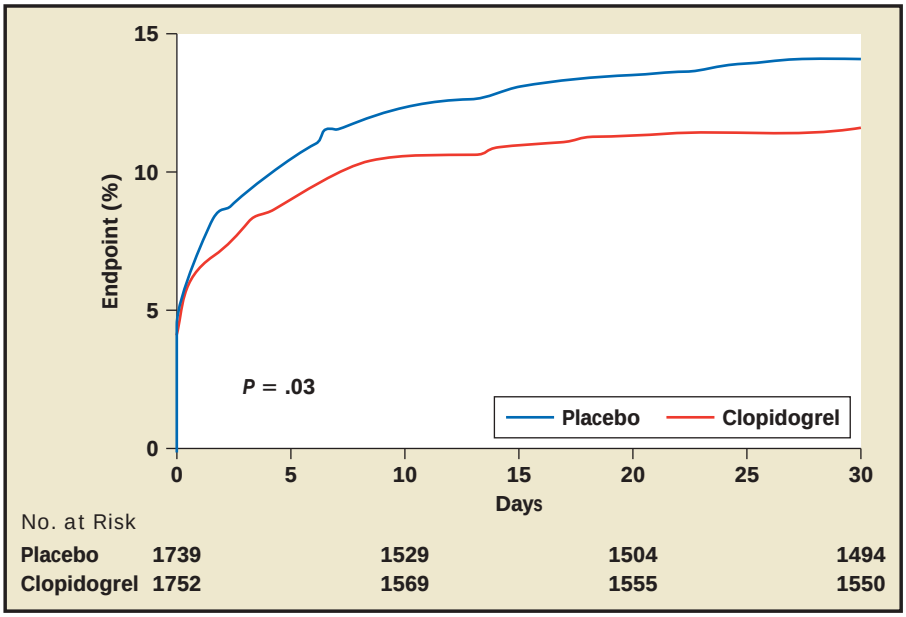


Figure 2. *Thirty-day outcomes from design of the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY): Thrombolysis in Myocardial Infarction (TIMI) 28 Trial. Reproduced with permission from Sabatine et al.*[3]

in the placebo group (RR, 1.40, $P = .02$). Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women aged 65 years or older. This study confirms a benefit for women that had been previously shown in men.

Endothelin Receptor Antagonists for Acute Decompensated Heart Failure

The Value of Endothelin Receptor Inhibition With Tezosentan in Acute Heart Failure Studies (VERITAS), 2 multi-center, double-blind, placebo-controlled, parallel-group trials that assessed the efficacy, safety, and tolerability of tezosentan in acute heart failure, found that the immediate administration of intravenous tezosentan (n = 727) caused no change in dyspnea scores or other measures of intermediate outcomes compared to placebo (n = 708). The rates of death or worsening heart failure were 26.3% and 26.4% at 7 days, and 33.2% and 31.9% at 30 days, for tezosentan and placebo, respectively ($P > .05$). Despite the solid rationale for endothelin receptors as therapeutic targets in patients with heart failure who have elevated endothelin levels and vasoconstriction, the use of agents that block these receptors has proven disappointing. Commentary from the investigators after this trial's presentation suggests that these results may end the commercial development of these compounds in the heart failure population.

[Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA]

Cypher Versus TAXUS Drug-Eluting Stents

Drug-eluting stents (DES) have had a dramatic impact on the practice of interventional cardiology. Over 90% of current coronary interventions utilize DES. Two stents have been approved in the US, the Cypher® sirolimus-eluting stent (Cordis Corp., Miami Lakes, FL) and the TAXUS® paclitaxel-eluting stent (Boston Scientific Corp., Natick, MA). Both stents have been shown to be highly effective in reducing restenosis. Whether one is better than the other continues to be hotly debated. Three clinical trials that addressed this controversy were presented in the late-breaking sessions of the 2005 ACC meeting in Orlando.

REALITY Trial

The Prospective, Randomized, Multicenter Head-to-Head Comparison of Cypher and TAXUS Stent Systems (REALITY) Trial, a multi-center randomized trial conducted in 90 centers in Europe, Asia, and Latin America, enrolled 1386 patients with 1911 lesions and was presented by Marie-Claude Morice, MD, of the Institut Hospitalier Jacques Cartier in Massy, France. Patients with more than 2 lesions, vessels less than 2.25 mm or greater than 3.0 mm in diameter, and longer than 33 mm, were excluded. Patients with acute myocardial infarction, left main disease, an ejection fraction less than 25%, or in-stent restenosis were also excluded. The primary endpoint of the study was in-lesion binary restenosis at 8 months. The secondary endpoint was late loss as determined by quantitative angiography. The patient groups were well matched with an average vessel size of 2.4 mm. The primary endpoint

Subgroup analyses showed that aspirin significantly reduced the risk of major cardiovascular events, ischemic stroke, and myocardial infarction among women aged 65 years or older.

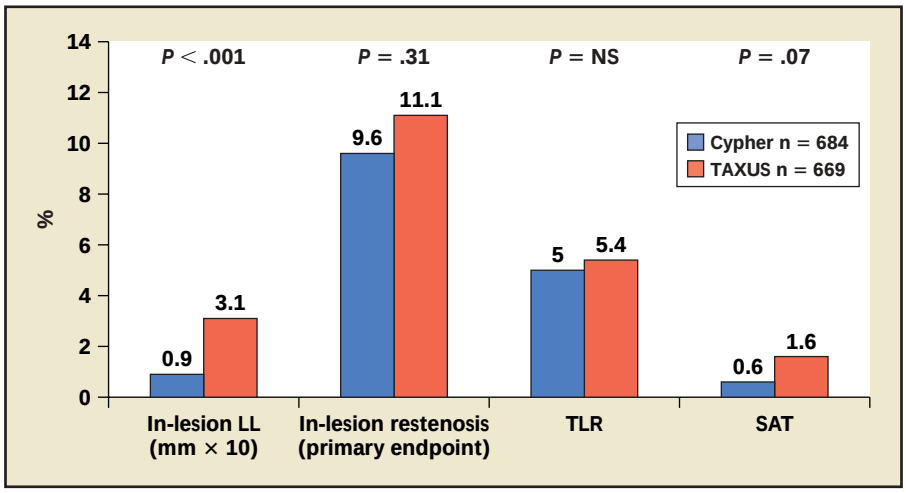


Figure 3. *Cypher versus TAXUS drug-eluting stents: results of the REALITY trial. LL, late loss; SAT, subacute stent thrombosis; TLR, total lesion revascularization. Presented by Morice M. at the 2005 American College of Cardiology Late-Breaking Clinical Trials Session.*

was not significantly different between the groups (9.6% for Cypher and 11.1% for TAXUS, $P = 0.31$). Likewise, in-stent restenosis was not significantly different (7.6% vs. 8.3%, respectively). Mirroring these findings, rates of clinical restenosis or target lesion revascularization were also similar (5.0% vs. 5.4%, respectively). See Figure 3. However, the secondary angiographic endpoint of in-stent late loss was significantly lower in the Cypher group (0.09 mm vs. 0.31 mm, $P < 0.001$). In addition, in-lesion late loss and mean lumen diameter measurements also favored the Cypher stent. One unexpected finding was a slightly higher rate of subacute stent thrombosis in the TAXUS group (1.6% vs 0.6% for Cypher, $P = .07$). The clinical significance of this observation is unclear and it is not consistent with the prior randomized trials of the TAXUS stent or the large WISDOM registry.

ISAR-DIABETES Trial

The second trial addressing this question was the Paclitaxel-Eluting Stent Versus Sirolimus-Eluting Stent for the Prevention of Restenosis in Diabetic Patients With Coronary Artery Disease (ISAR-DIABETES) Trial, comparing the 2 stents in patients with diabetes, presented by Adnan Kastrati, MD, of the Deutches Herzzentrum in Munich, Germany. Building on the prior ISAR-DESIRE Trial that showed a better outcome with the Cypher stent but did not reach statistical significance, the ISAR investigators hypothesized that significant differences in outcome might be seen in a higher-risk group.

In this study, 250 patients with diabetes undergoing PCI were randomized to the Cypher or TAXUS stent. The study was designed as a non-inferiority trial. The primary endpoint was angiographic, in-segment late loss and the secondary endpoint was target lesion revascularization. The groups were well matched and one quarter of both groups was made up of diet-controlled diabetics. The average measure of HgA1C was 7.4%. The average diameter of the affected vessel was 2.75 mm and length 12 mm. The primary endpoint of in-segment late loss was significantly lower in the Cypher group (0.43 mm for Cypher and 0.67 mm for TAXUS, $P = .001$). Measures of in-stent late loss also favored Cypher as did the incidence of binary restenosis (6.9% vs. 16.5% for TAXUS, $P = 0.03$). However, target vessel revascularization was not significantly different (6.4% vs. 12.2%, respectively, $P = 0.13$) although directionally similar to the angiographic findings.

SIRTAX Trial

The Randomized Comparison of a Sirolimus- vs a Paclitaxel-Eluting Stent for Coronary Revascularization (SIRTAX), presented by Stephan Windecker, MD, of the University Hospital Bern in Bern, Switzerland, also compared the 2 drug-eluting stents in patients with diabetes. SIRTAX was a single-center, randomized trial of 1005 patients. The primary endpoint was the composite clinical endpoint of death, myocardial infarction, or target lesion revascularization at 9 months. The study found a significant difference between the groups with 6.5% of the Cypher group versus 10.8% of the TAXUS group reaching the primary endpoint ($P = .009$). This difference was driven largely by the rate of target lesion revascularization (4.8% vs. 8.3%, respectively, $P = .025$). In addition, rates of target vessel failure were better with the Cypher stent, as were in-stent and in-segment late loss measurements.

Figure 4 shows results from both ISAR-DIABETES and SIRTAX trials.

Comment

These 3 trials were consistent in the finding of lower late loss with the Cypher stent but were not consistent as far as clinical outcomes were concerned, with only 1 trial showing a reduction in clinical restenosis. This is surprising and raises the concern that late loss may not directly parallel clinical restenosis. On the other hand, the differences in late loss were small and may not be

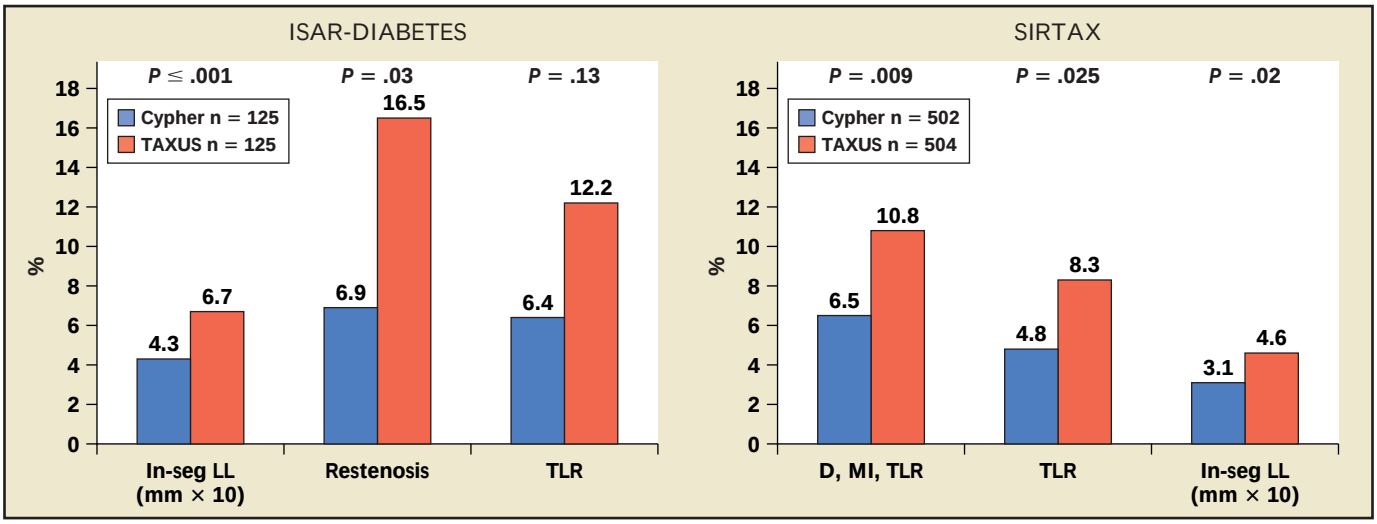


Figure 4. *Cypher versus TAXUS drug-eluting stents in diabetic patients: ISAR-DIABETES and SIRTAX trials. LL, late loss; TLR, total lesion revascularization; D, death, MI, myocardial infarction. Presented by Kastrati A and Windecker S at the 2005 American College of Cardiology Late-Breaking Clinical Trials Session.*

of clinical significance when dealing with normally sized vessels or patients who start out with a low risk of restenosis. The rate of clinical restenosis in each of these studies ranged from 4% to 12%, not very high. Whether the result will change practice remains to be determined but the findings do suggest that the Cypher stent may offer advantages in the highest risk groups such as those with diabetes and small vessels. Unfortunately other high-risk groups were not studied and discussion will need to await further trials.

[David P. Faxon, MD, FACC, FAHA]

The ENDEAVOR II Trial

Worth the Wait?

Following the large-scale trials and marketing of the TAXUS paclitaxel-eluting and Cypher sirolimus-eluting stent systems, a third major DES system has been tested in the international Randomized Comparison of the Endeavor ABT-578 Drug-Eluting Stent With a Bare Metal Stent for Coronary Revascularization (ENDEAVOR) II trial. ENDEAVOR II was presented at a late-breaking trial session by Dr. William Wijns of the OLV Ziekenhuis in Aalst, Belgium.

The Endeavor™ DES [Medtronic AVE, Santa Rosa, CA] is composed of Medtronic's DRIVER stent system coated with phosphorylcholine (PC), eluting ABT-578. The PC coating is a bio-mimetic polymer that emulates the surface of a cell, theoretically providing enhanced biocompatibility and less potential for thrombosis. ABT-578 is part of the same class of drugs as sirolimus and everolimus and is slightly less potent, on an mmol per mmol basis, but more lipophilic, than sirolimus.

The trial was designed to enroll 1200 patients with de novo lesions, randomizing 1:1 between the Endeavor DES and the bare-metal DRIVER stent. The primary endpoint was target vessel failure (TVF) (death, MI, or target vessel revascularization) at 9 months. Fifty percent of the patients received angiographic follow-up and 25% were followed up via intravascular ultrasound. Twenty percent of the patients were diabetic, the average reference vessel diameter was 2.75 mm, and average lesion length was 14.25 mm. This profile made the trial slightly less risky than the TAXUS IV trial of the TAXUS stent system and the SIRIUS (Cypher DES) trial.

The primary endpoint of TVF was significantly reduced from 15.4% in the bare metal stent group to 8.1% in the DES group. Target lesion revascularization (TLR) went from 12.1% to 4.6%, respectively. See Figure 5. The Endeavor stent was shown to be very safe, with thrombosis rate of 0.5% during the first 30 days and no late thrombosis. Diabetic patients had a similar reduction of TVF (15.4% to 7.6% in the DES and bare-metal groups, respectively). However, insulin-dependent diabetics did not benefit (n = 70). The angiographic follow-up subset revealed an in-stent late loss reduction from 1.03 mm for bare-metal to 0.62 mm for drug-eluting, and a reduction in binary restenosis from 32.7% to 9.5%, in the respective groups.

ENDEAVOR II confirms that the sirolimus family of drugs is effective in preventing restenosis in the setting of DES. However, the overall biological effect as reflected in the reduction of late loss is moderate. What causes the difference? The drug could be less effective, but this is unlikely, given the in vitro data.

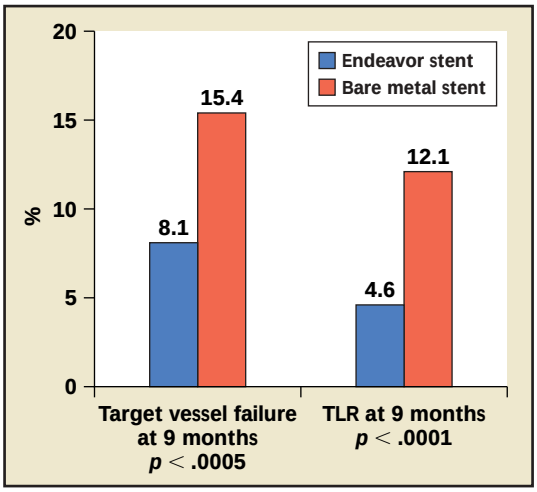


Figure 5. *Results of the ENDEAVOR II trial of the Endeavor drug-eluting stent compared to the bare-metal DRIVER stent, in patients with de novo lesions. Reproduced with permission from www.cardiosource.com.*

The more probable culprit is the elution profile of the polymer. The Endeavor stent released 75% of the drug in 2 days and 100% in 10 days. By contrast, the Cypher stent releases 75% of the drug in 10 days and 100% in 30 days. Multiple previous trials have confirmed that the elution profile dictates the effectiveness of the system. In trials such as DELIVER, the drug was released extremely rapidly and the clinical benefit was minimal. Another DES system by Abbott Laboratories [Abbott Park, IL] will explore the use of a slower-release kinetics system using ABT-578 in the upcoming ZOMAXX clinical trial.

The Endeavor stent will be effective against restenosis in most coronary lesions. However, it is unclear whether it will perform as well in high risk lesions (lesions in diabetic subjects, small and long lesions). Regardless, ENDEAVOR II adds to the clinical database of how we can evaluate DES systems and how we can apply this knowledge to interventional management of coronary artery disease.

[Alan C. Yeung, MD]

Anti-Platelet Therapy

Many important new developments in anti-platelet therapy were highlighted at the 2005 ACC Scientific Session, including several presented elsewhere in this report. We have seen clinical trial data showing the importance of the adenosine diphosphate blocker clopidogrel in preventing subacute stent thrombosis and as an adjuvant to lytic therapy for the treatment of acute MI. However, our enthusiasm is sobered by the growing awareness of a population resistant to the actions of clopidogrel and aspirin, and at higher risk of thrombotic complications following PCI. This has fueled the effort to identify newer compounds that can more effectively inhibit platelets.

Prasugrel (CS-747, LY640315) is a novel thienopyridine platelet inhibitor that has been shown to be more potent than clopidogrel in preclinical studies. Asai and colleagues[6] from the Sankyo Company, Tokyo, Japan, presented the results of a double-blind, placebo-controlled, multiple oral drug dose study in 30 healthy male volunteers, comparing the effects of prasugrel to clopidogrel. Subjects were randomized into 5 groups: Prasugrel (5 mg, 10 mg, and 20 mg), clopidogrel (75 mg), and placebo. Effect of these compounds and doses were compared using pharmacodynamic measures of platelet aggregation (turbodometric) in response to adenosine diphosphate (ADP) and collagen as well as bleeding times. See Table 2 and Figure 6 for results.

The results of this trial showed that in healthy male volunteers, prasugrel was safe, well tolerated, and had a dose-dependent effect on bleeding time at doses up to 20 mg per day for 10 days. Prasugrel is at least 10-fold more potent than clopidogrel and at a dose of 10 mg

Table 2
Effect of Prasugrel on Bleeding Time Following 10th Daily Dose

	Placebo	Prasugrel, 5 mg	Prasugrel, 10 mg	Prasugrel, 20 mg	Clopidogrel, 75 mg
Bleeding Time (sec)*	231 ± 26.0	308 ± 42.5	1072 ± 379.3	1128 ± 270.3	422 ± 40.8
P vs Placebo	—	0.38	< .001	< .001	.021
P vs Clopidogrel	.021	0.15	0.31	0.18	—

*Mean ± standard error; n = 6, all groups.

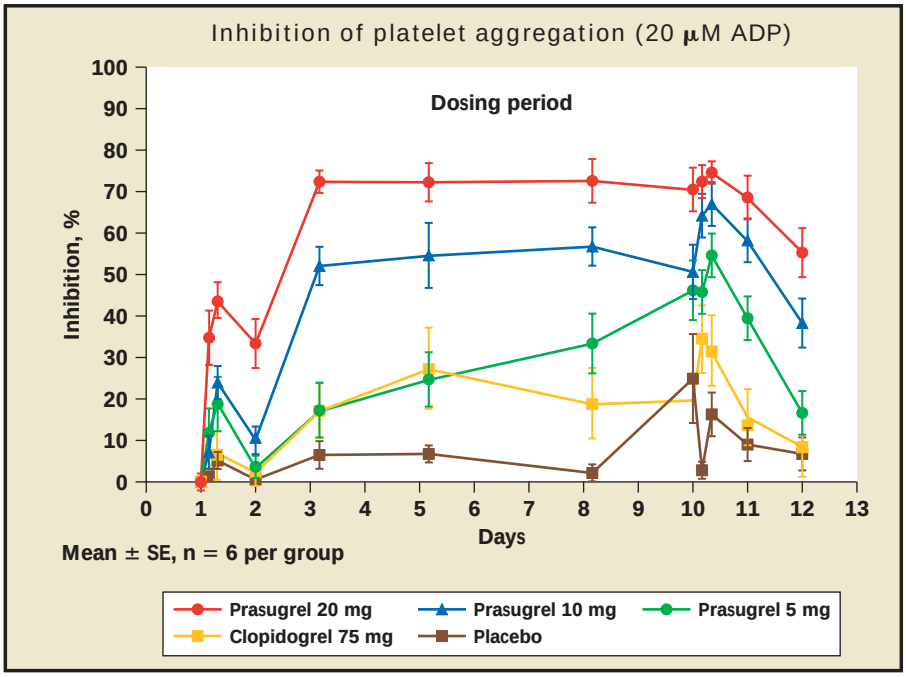


Figure 6. *A comparison of 3 doses of prasugrel (5 mg,10 mg, 20 mg) to clopidogrel (75 mg) and placebo for the inhibition of platelet aggregation. Reproduced with permission from Asai et al.*[6]

provides greater and more consistent platelet aggregation than clopidogrel at 75 mg per day.

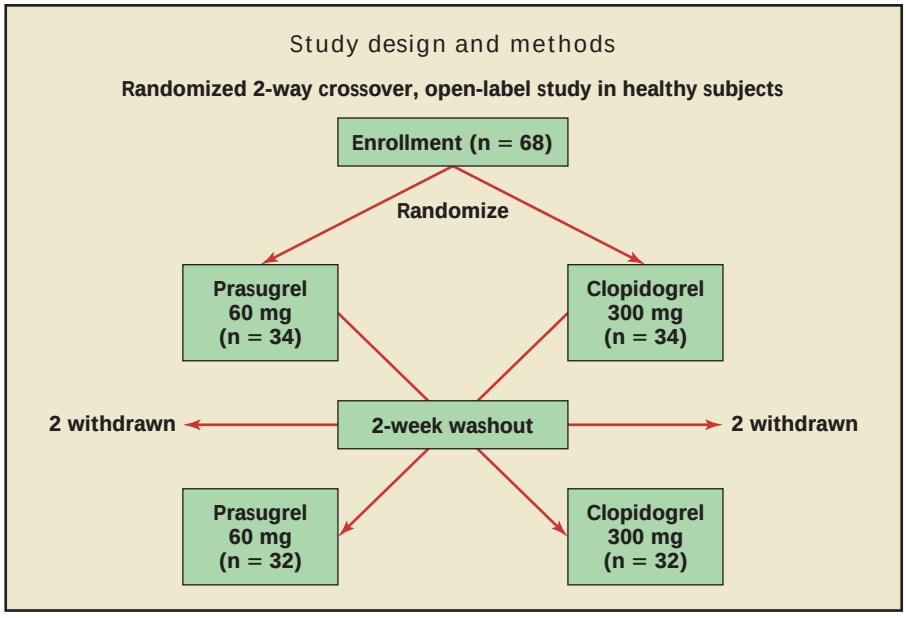
An additional trial on the same drug was reported on by Brandt and colleagues[7] from Eli Lilly & Company, Indianapolis, IN. Study design is described in Figure 7. Turbidimetric platelet aggregation in response to 20 μM ADP was performed prior to dosing and at 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 9 hours, 12 hours, and 24 hours post dosing, with laboratory personnel blinded to treatment. The maximal platelet aggregation (MPA) response within 8 minutes following addition of 20 μM ADP was determined. Responders were prospectively identified via 2 methods:

1. Inhibition of platelet aggregation (IPA) >25% at both 4 hours and 24 hours post-dose, which occurred in 43.4% of patients receiving clopidogrel and 100% of patients receiving prasugrel ($P < .01$).
2. Greater than 10% decrease in MPA at both 4 hours and 24 hours post-dose, which occurred in 100% of patients receiving prasugrel and 68.2% of patients receiving clopidogrel ($P < .01$).

Prasugrel inhibited platelet aggregation at a significantly greater rate than clopidogrel, from 30 minutes to 24 hours following oral administration (Figure 8). Even among clopidogrel non-responders, there seemed to be a significant anti-aggregatory platelet response to prasugrel. This important finding offers the hope that it may be possible to overcome clopidogrel resistance in affected patients with the administration of prasugrel (Figure 9).

The investigators concluded that compared to a 300 mg loading dose of clopidogrel, a 60 mg loading dose of prasugrel resulted in a higher level of inhibition of platelet aggregation, more consistent inhibition of platelet aggregation, more rapid onset of inhibition of platelet aggregation, and a superior response rate. Results of the on-going randomized TIMI 38 phase III trial are eagerly awaited, to help determine the role of prasugrel in patients undergoing percutaneous coronary stent implantation, as a possible replacement for clopidogrel.

Figure 7. *Study design of the trial comparing loading dose effects of prasugrel (60 mg) and clopidogrel (300 mg).*



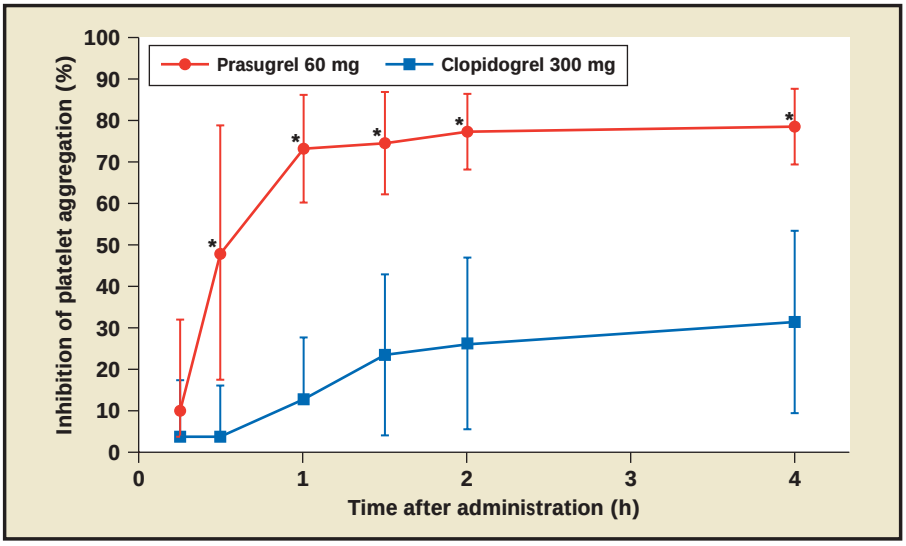


Figure 8. *The greater platelet-inhibiting effect of the prasugrel 60 mg loading dose versus the clopidogrel 300 mg loading dose.*

Anti-Anginal Therapy

Ranolazine has been shown to have anti-anginal properties as well as an ability to suppress the arrhythmic activity of a number of drugs that prolong the QT interval. Previous electrophysiologic studies have shown that ranolazine reverses the action potential duration (APD), prolongation, and proarrhythmic effects of a late I_{Na} enhancer, ATX-II, and the I_{Kr} blocker, E-4031. Using a high-resolution optical mapping system allowing for the simultaneous recording of 256 epicardial sites, Kozhevnikov and associates[8] determined the effect of ranolazine on APD, APD gradient (transepicardial dispersion of APD), and the activation pattern in the absence and presence of the late I_{Na} enhancer ATX-II and the I_{Kr} blocker E-4031.

The investigators found that ATX-II and E-4031 significantly increased the mean APD_{90} by 124% and 58%, respectively, above control level, whereas ranolazine alone caused only a moderate increase in APD_{90} at the highest concentration used and did not change the transepicardial ADP gradient at all. Ranolazine in a concentration-dependent fashion reduced APD_{90} and APD gradient increases caused by ATX-II and E-4031 (Figure 10). The investigators concluded that ATX-II and E-4031, but not ranolazine, increased the ventricular transepicardial gradient of APDs, that ranolazine reversed ATX-II, and E-4031 induced APD prolongation and increases in transepicardial APD gradients but did not affect ventricular activation.

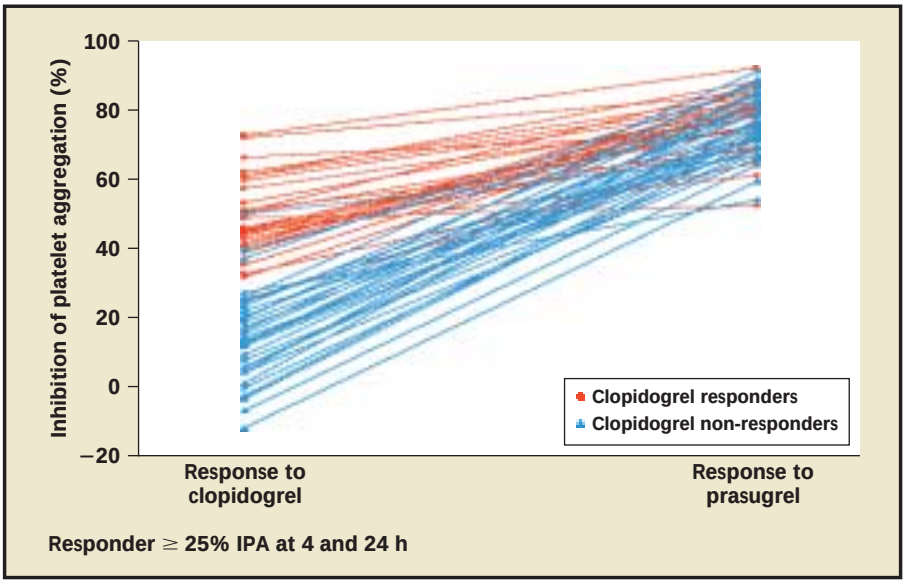
Heart Failure

ADHERE Substudy

In an abstract presentation by Heywood and coworkers,[9] the investigators attempted to determine if a temporal relationship existed among changes in the utilization of intravenous vasoactive therapy in hospitals and hospital mortality, proportion of patients in the ICU, and the need for mechanical ventilation.

In investigating data from 273 US hospitals over 8 quarters as reported in the Acute Decompensated Heart Failure Registry (ADHERE®), researchers found that the use of intravenous inotropes decreased by 25% and intravenous nitroglycerin use decreased 5%, whereas the use of nesiritide increased by 238%. During this period, the need for mechanical ventilation decreased 21% and the proportion of patients in the ICU decreased by 9%. In-hospital mortality decreased from 4.5% to 3.9% (RR 0.86, $P = .03$). Changes in intra-

Figure 9. *Both clopidogrel responders and non-responders experienced a similar level of platelet inhibition with prasugrel. IPA, intravascular platelet activity.*



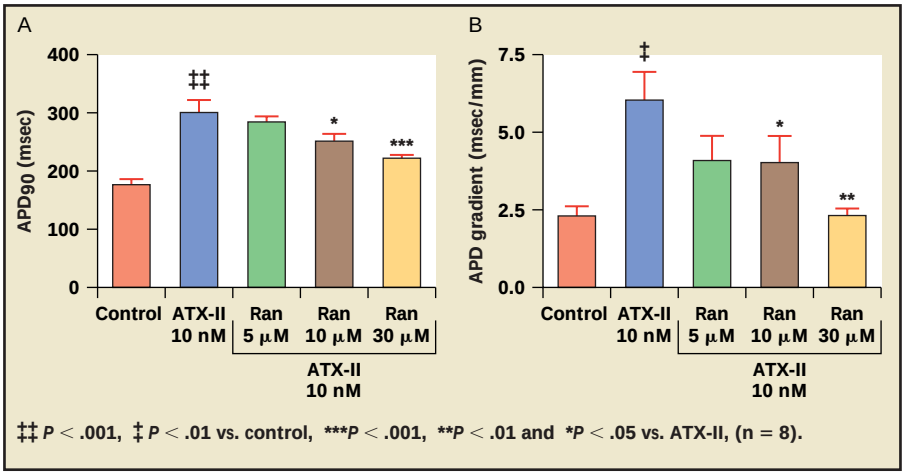


Figure 10. *Reversal by ranolazine (Ran) of ATX-II induced prolongation and increase in dispersion of ventricular action potentials. ATX-II at a concentration of 10 nM prolonged the action potential duration $(APD)_{90}$ by 71% above control, which was reversed by ranolazine in a concentration-dependent manner* **(A)**. *Ranolazine (30 μM) also normalized the ATX-II-induced increase in APD gradient* **(B)**.

venous therapy alone explained 6%, 16%, and 22% of variability in per hospital changes in mortality, mechanical ventilation, and proportion of ICU patients.

The investigators conclude that reductions in intravenous inotrope and nitroglycerin use and an increase in nesiritide use occurred over time, concurrent with the reductions of per hospital changes in mechanical ventilation requirement and proportion of patients in an ICU. They suggest that the changes in intravenous vasoactive therapies may partially explain the observed improvements in outcome. The potential for an agent such as nesiritide to reduce the need for ICU admission and for mechanical ventilation represents a strong argument for the use of this agent in patients presenting with acute decompensated heart failure.

PEECH Trial

The Prospective Evaluation of Enhanced External Counterpulsation in Congestive Heart Failure (PEECH) trial was performed to determine the role of Enhanced External Counterpulsation Therapy (EECP) in patients with NYHA Functional Class II and III heart failure. Dr. Arthur Feldman of Thomas Jefferson University in Philadelphia, PA, reported that ischemic etiology was present in about two thirds of the patients enrolled, with a baseline ejection fraction of 26%. EECP was administered in 35 1-hour sessions over the course of 7 weeks. All patients received optimal heart failure therapy. Patients were randomized, 93 to EECP plus optimal pharmacologic therapy and 94 to the control group, receiving optimal pharmacologic therapy alone.

An increase in exercise duration of at least 60 seconds occurred more frequently in the EECP group compared to the control (35.4% vs. 25.3%, $P = .016$) at the 6 month endpoint. Exercise duration was increased by 24.7 seconds in the EECP group and decreased by 2.9 seconds in the control group. There was also a greater change from baseline in the Minnesota Living With Heart Failure Score at 1 week and 3 months, but not at 6 months, with EECP. There was no difference in the co-primary endpoint of increase in peak VO_2 of at least 1.25 mL/min/kg.

In conclusion, in patients with symptomatic systolic, stable heart failure, on optimal pharmacologic therapy, use of EECP was associated with improvements in exercise capacity, NYHA classification, and quality of life, but provided no difference in peak VO_2. A sustained clinical improvement out to 6 months is difficult to attribute purely to a placebo effect. Because improvement in the quality of life of heart failure patients represents an important clinical endpoint, it would be reasonable to use a safe treatment such as external counterpulsation therapy in the patient on maximal medical therapy who remains symptomatic from heart failure. Because it is likely that the benefits of counterpulsation therapy are related to optimal use of this technology, both in terms of patient selection and appropriate technique, its use should probably be restricted to cardiologists who have received thorough training.

Rosiglitazone and Diabetics With Heart Failure

In an abstract presented by Dargie and colleagues[10] from the Western Infirmary, Glasgow, United Kingdom, evaluated the effect of the thiazolidinedione agent rosiglitazone on cardiac structure and function as determined by echocardiography in type 2 diabetics with Class I/II heart failure. A significant proportion of patients with congestive heart failure are diabetic, and therefore the safety of these agents in this population is an important issue.

The investigators randomized 224 diabetic patients with NYHA Class I or II heart failure to receive rosiglitazone (4-8 mg per day) or placebo with background antidiabetic medications up-titrated to a target fasting plasma glucose level less than 126 mg/dL. With similar ejection

fractions in both groups of 35% at baseline, there was no significant difference in ejection fraction or structure following 52 weeks of treatment. During this period, there were no differences in the frequency of worsening or possible worsening of heart failure in the 2 groups, though the rosiglitazone group did experience more edema (26% vs 9% in the control group) as well as increased dyspnea and the requirement for an increase in diuretic dose.

The investigators concluded that following 52 weeks of therapy with rosiglitazone, there were no adverse effects on cardiac structure and function. More fluid retention occurred in the experimental group but not enough to lead either to study withdrawal or hospitalization. It is clear that the thiazolidinediones are an important pharmacologic treatment for diabetic patients and that they seem to have positive effects on metabolism, coagulation, and endothelial function. Their use in patients with NYHA Class I and II heart failure seems to be safe and effective. We look forward to randomized, clinical trial data that will quantitate the potential benefit of this drug class in patients with diabetes who suffer from either mild heart failure or coronary artery disease.

It is clear that the thiazolidinediones are an important pharmacologic treatment for diabetic patients and that they seem to have positive effects on metabolism, coagulation, and endothelial function.

Contrast-Induced Nephropathy

Contrast-induced nephropathy (CIN) remains an issue of paramount concern to the interventional cardiologist and radiologist. Contrast nephropathy is associated with high short-term and long-term mortality and morbidity and seems to be most common in patients with diabetic nephropathy. With the advent of new noninvasive methods of coronary angiography using CT imaging, the use of radiocontrast agents will continue to grow, and protocols to prevent nephropathy in these populations are critical. Besides the use of saline and iso-osmolar contrast agents, clinical trials evaluating approaches including the use of N-acetylcysteine have had mixed outcomes.

A poster presentation by Jo and colleagues[11] from the Seoul National University Hospital in Seoul, South Korea, reported a randomized, prospective, single-center study comparing the nephrotoxic effects of the iso-osmolar, non-ionic contrast agent, iodixanol, to the low-osmolar, ionic agent, ioxaglate, in 282 patients with a calculated creatinine clearance of 60 mL/min or less (calculated by Cockroft-Gault formula), who underwent coronary angiography.

Half saline was administered for 8 hours before and after the administration of the contrast agent. The primary endpoint was defined as an increase of greater than 25% in serum creatinine within 2 days of the coronary angiogram. Contrast nephropathy occurred in 6.1% of patients in the iodixanol group and 15.4% in the ioxaglate group ($P = .013$). The difference was more distinct in the diabetic population (5.8% vs 21.7%, respectively). This study reinforces previous clinical trial results showing that the incidence of CIN is lower with the use of the iso-osmolar contrast agent, iodixanol, than with the low-osmolar agent, ioxaglate, and supports the use of iodixanol, along with aggressive hydration, in patients at risk for CIN (creatinine clearance $<$ 60 mL/min) and undergoing contrast-requiring procedures.

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

The ASCOT Blood Pressure-Lowering Study

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was originally designed to address 2 questions. First, would a low-dose statin, in hypertensive patients who did not meet the usual criteria for receiving such treatment, reduce cardiovascular outcomes? Second, would there be any benefit to treating relatively high risk hypertensive patients with a regimen of newer antihypertensive agents (calcium channel blockers and angiotensin-converting enzyme inhibitors) versus a more traditional regimen (β-blockers, thiazide diuretics) to reduce major events?

The study was conducted in a 2×2 factorial trial design that could examine both these questions simultaneously. Approximately 2 years ago, the Data and Safety Monitoring Board (DSMB) stopped the part of the trial dealing with cholesterol-lowering therapy, when it became apparent that, compared with placebo, a low dose of atorvastatin significantly reduced clinical endpoints. More recently (at the end of November, 2004), the DSMB stopped the second part of the trial dealing with blood pressure therapy when, again, they thought it was unethical to continue the trial when 1 treatment arm was clearly doing much better than the other. It was these recent data, still in preliminary form, that were presented at the 2005 Annual Meeting of the American College of Cardiology by Björn Dahlöf, MD, of the Sahlgrenska University Hospital/Ostra in Goteborg,

Sweden, and Peter S. Sever, MB, BChir, PhD, of Imperial College, London, UK.

Hypothesis and Endpoints

The principal blood pressure hypothesis of ASCOT was that, for similar achieved blood pressures, the newer regimen of a calcium channel blocker (CCB) and angiotensin-converting enzyme (ACE) inhibitor would be superior to a β-blocker/thiazide regimen in preventing the primary combined endpoint of non-fatal myocardial infarction plus fatal coronary heart disease events. Major secondary endpoints included total cardiovascular events and procedures, total coronary events, all-cause mortality, cardiovascular mortality, fatal and non-fatal stroke, and fatal and non-fatal heart failure. In addition there were a group of tertiary endpoints, including new-onset diabetes mellitus. To effectively test the primary endpoint, the study was powered for 1150 primary events; however, due to the premature closure of the study recommended by the DSMB, there were only 869 events recorded.

Methods

To enter this hypertension trial, untreated patients were required to have a baseline blood pressure greater than or equal to 160/100 mmHg if previously untreated, or greater than or equal to 140/90 mmHg during previous treatment with 1 or more drugs. Age range required for entry was 40 to 79 years, and patients were excluded if they had any evidence of a previous myocardial infarction or were known to have any other current form of coronary heart disease. However, patients were required to have 3 or more risk factors for cardiovascular events; male gender was 1 of these factors.

The design of this blood pressure study was based on randomization of patients to treatment with either the CCB/ACE inhibitor regimen or the β-blocker/thiazide regimen. The goal of treatment in each arm was to reduce blood pressure below 140/90 mmHg in the majority of hypertensive patients, and below 130/80 mmHg in those with diabetes. Patients in the CCB/ACE inhibitor arm began treatment with amlodipine, 5 mg daily. If needed to achieve the treatment goal, this dose could be increased to 10 mg. If necessary, perindopril, 4 mg daily, was added, with the option of increasing to 8 mg daily. Finally, doxazosin, 4 mg daily, or, if necessary, 8 mg, could be added. Beyond this regimen, investigators could use additional drugs including moxonidine or spironolactone. For the β-blocker/thiazide arm, treatments started with atenolol, 50 mg daily, then 100 mg. If needed, bendroflumethiazide-K, 1.25 mg, then 2.5 mg, could be added. If control was still not achieved, doxazosin and other drugs could be added as in the other treatment arm.

The study used a prospective, randomized, open-label, blinded endpoints (PROBE) design. All events were carefully adjudicated by an independent endpoints committee.

The design of this blood pressure study was based on randomization of patients to treatment with either the CCB/ACE inhibitor regimen or the β-blocker/thiazide regimen.

Results

Altogether, 9639 patients were randomized to the CCB/ACE inhibitor arm and 9618 to the β-blocker/thiazide arm. Only about one quarter of the patients were women, reflecting the fact that male gender was counted as a risk factor in determining patient eligibility for the trial. Approximately one third of patients were smokers. The average age of participants was 63. Baseline blood pressure in both groups was 164/95 mmHg and their average body mass index was 28.7. As far as previous therapy was concerned, 19% of patients were receiving no antihypertensive therapy at study entry; 44% were on 1 drug and the remainder on 2 or more.

Blood Pressure. For the trial as a whole, blood pressure was reduced by 28/16 mmHg. Early in the trial, there was a greater decrease in the CCB/ACE inhibitor group, though this difference largely disappeared for most of the study. Overall, the mean trial difference between the 2 treatment arms was 2.9/1.8 mmHg.

Major Outcomes. There were a total of 869 primary events and 3192 secondary events. The major endpoint comparisons between the 2 treatment arms are shown in Table 3. Due to the reduced number of events caused by the early halting of the trial, the primary endpoint of non-fatal myocardial infarction and fatal coronary heart disease did not quite reach significance ($P = 0.12$). Other major outcomes, as shown in the table, show highly significant benefits for the CCB/ACE inhibitor treatment arm. All-cause mortality and cardiovascular mortality were both significantly reduced by this treatment (and were, in fact, the main reason cited by the DSMB for the prema-

Table 3
Preliminary Results of the ASCOT Trial: Hazard Ratios for Effects of CCB/ACE Inhibitor Versus β-Blocker/Diuretic Therapies

	Hazard Ratio	*P* Value	Confidence Interval
All-cause mortality	0.86	0.005	0.78-0.96
Nonfatal MI/fatal CHD	0.90	0.12	0.78-1.03
Total coronary endpoints	0.86	0.0048	0.78-0.96
Fatal/nonfatal stroke	0.77	0.0007	0.66-0.90
All CV events/revascularization	0.84	<0.0001	0.77-0.90
CV mortality	0.76	0.0017	0.65-0.91
New-onset diabetes	0.68	<0.0001	0.60-0.77

ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; MI, myocardial infarction; CHD, coronary heart disease; CV, cardiovascular.

ture discontinuation of the trial). Total coronary endpoints and all cardiovascular events and interventions were also significantly lower in the CCB/ACE inhibitor arm. Of interest, new-onset diabetes was reduced by 30% in the patients receiving the newer therapies.

Conclusions

This study has shown a clear advantage to the newer antihypertensive agents. The combination of a CCB and an ACE inhibitor, when compared to a traditional β-blocker and thiazide combination, is superior in preventing major cardiovascular events in high-risk hypertensive patients. In fact, this advantage in outcomes compelled the DSMB to recommend early cessation of the trial, thus limiting the number of primary endpoints and not allowing the investigators the power to adequately test their main hypothesis. Even so, assuming that the final results of the study—which will be presented in a few months once all patient visits are completed and the data fully collected—do not deviate materially from the present findings, it appears legitimate to claim that the newer drugs may be treatments of choice for most hypertensive patients.

The Blood Pressure Issue. It is recognized that even small differences in achieved blood pressures can affect clinical outcomes in hypertension. In the recent past, this has confounded interpretation of 2 major clinical trials: The Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial (ALLHAT)[12] and the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) Trial.[13] Indeed, the blood pressure issue in each of these trials made it virtually impossible to draw firm conclusions regarding the possible superiority of 1 regimen compared with another. The findings in ASCOT could also be explained, at least in part, by the greater blood pressure-lowering efficacy of the CCB/ACE inhibitor treatment arm. The principal investigator of this study, however, has pointed out that the difference in event rates between the 2 regimens consistently favored the CCB/ACE inhibitor regimen throughout the trial, not just in the early part when there was a relatively large blood pressure difference, but during the remainder of the trial when the blood pressure difference was minimal. Further analysis of these findings would be helpful in confirming the apparent advantage of this newer treatment approach. As a practical matter, it could also be concluded—at least as far as the predominantly Caucasian populations studied in this British and Scandinavian trial are concerned—that a regimen based on CCB/ACE inhibitor therapy might be the most efficacious way to maximize blood pressure control.

It is still too early to draw definitive conclusions from this work, and observers must await the formal publication of this study that is likely to appear in the latter part of 2005. However, it is becoming apparent that the results of ASCOT have thrown down a firm challenge to ALLHAT in terms of recommendations for optimal initial therapies for hypertension. Indeed, bearing in mind that the supposedly superior treatment regimen in ALLHAT was a diuretic/β-blocker combination, the fact that it was bettered in ASCOT by a CCB/ACE inhibitor combination indicates that recent guideline recommendations favoring the older therapies for initiating treatment[14] will now be strongly challenged.

The findings in ASCOT could also be explained, at least in part, by the greater blood pressure-lowering efficacy of the CCB/ACE inhibitor treatment arm.

It is interesting to speculate as to why the combination of a CCB and an ACE inhibitor, beyond evident

blood pressure-lowering efficacy, might convey particular advantages in cardiovascular protection. It is known that ACE inhibitors provide strong protection against such events in high-risk cardiovascular patients,[15,16] and have been shown to have some endpoint benefits when compared with diuretic-based therapy in hypertensive patients.[17] A recent trial with the CCB amlodipine, which was also the agent used in ASCOT, demonstrated clear endpoint benefits when compared with a placebo and, in addition, indicated a potentially beneficial impact on the progression of coronary atherosclerosis.[18] Of interest, in studies of vascular compliance, the effects of an ACE inhibitor and a CCB have been shown to be additive in improving the distensibility of the arterial wall.[19]

It is also possible to interpret ASCOT as a comparison not of individual drugs, but rather of competing combination therapies. It is now broadly recognized that most hypertensive patients will require at least 2 drugs to effectively manage their condition, thus making combination treatment a highly relevant concept. It will be of interest to see whether ASCOT accelerates the current trend toward the use of antihypertensive drug combinations for initiating treatment in hypertensive patients at risk.

[Michael A. Weber, MD]

The COMPASS-HF Trial

Does Heart Failure Management Guided by Remote Hemodynamic Monitoring Reduce Heart Failure Events?

Congestion contributes to symptoms, functional status limitations, hospitalization risk, and possibly, to mortality risk in heart failure (HF). Assessment of ventricular filling pressures and congestion through the evaluation of symptoms, weight, physical examination, and laboratories, even by HF specialists, remains challenging. Assessment by right heart catheterization is invasive, costly, adds significant risk, and cannot examine hemodynamics in everyday ambulatory conditions.

To provide remote access to hemodynamic measures, an implantable hemodynamic monitor has been developed (Chronicle;® Medtronic, Inc., Minneapolis, MN).[20] The Chronicle system consists of an implantable memory system, similar to the pulse generator of a pacemaker. The device has a pressure transducer lead that is placed in the right ventricular outflow track. Intracardiac pressures (right ventricular systolic, right ventricular diastolic, estimated pulmonary artery diastolic) are measured continuously and stored in the device.[20] Data are intermittently transmitted by the patient to a secure website accessible to treating clinicians. Information from the Chronicle system, together with other available, patient-specific data, such as symptoms, daily weight, and physical signs, can then be used to guide treatment decisions. The concept behind this strategy is that, with this additional information, the clinician can intervene early, before congestion results in worse symptoms and when it may be easier to resolve.

The Chronicle system consists of an implantable memory system, similar to the pulse generator of a pacemaker.

The Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial was designed to test whether information from this device could be used to improve outcomes of patients with HF. The primary endpoint of the trial was the composite of HF hospitalizations, HF-related emergency department visits, and unplanned HF clinic visits.

COMPASS-HF randomized 274 patients with chronic NYHA functional class III-IV HF, on standard medical therapy, with at least 1 prior HF hospitalization in the last 6 months. All patients were implanted with a Chronicle sensor, to have their management guided or not guided by the device's data output. HF patients with reduced or preserved systolic function could be enrolled. Clinicians had complete access to the data from patients in the first group and were blocked from access to data from patients in the other group, who served as controls. Data were transmitted at least once weekly and more often as needed. To maintain the blind, patients in the blocked access group received random calls about their status. Functional status was assessed by a blinded physician. A management guide for suggested responses to hypervolemia, optivolemia, and hypovolemia was provided to clinicians.

Results

The results of the COMPASS-HF trial were presented at a late-breaking clinical trial session by Robert Bourge, MD, of the University of Alabama at Birmingham. The trial entered 301 patients. Of these, device placement was attempted in 277 patients and was successful in 274, who were then randomized. Patients were of mean age 58, 35% women, 50% white, 85% NYHA functional class III, 15% functional class IV, 26% with LVEF less than 50%, 40% receiving

Table 4
COMPASS-HF: Primary Endpoint Outcomes

Outcome	Chronicle-Guided Overall, n = 134	Control Overall, n = 140	Chronicle-Guided NYHA Class III, n = 112	Control NYHA Class III, n = 122
HF-related event rate* at 6 months (%)	70	89	53	90

*Hospitalizations, emergency department visits, urgent clinic visits.
COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure; HF, heart failure; NYHA, New York Heart Association.

Table 5
COMPASS-HF: Heart Failure-Related Hospitalization

Group	HF-Related Hospitalization	*P* Value
All patients, RR (95% CI)	0.79 (0.64-0.98)	0.029
NHYA class III, RR (95% CI)	0.76 (0.60-0.97)	0.023

COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure.

other device therapy, 80% receiving β-blocker therapy, 80% receiving angiotensin converting enzyme inhibitor and/or angiotensin receptor antagonist therapy.

Primary endpoint outcomes are shown in Table 4. Therapy guided by the monitoring device was also associated with the following outcomes.

- 21% trend for reduction in the relative risk of HF hospitalization ($P = 0.27$)
- 33% reduction in the proportion of patients with worsening HF
- 22% reduction in HF events overall
- 41% reduction in HF-related events among the 85% of patients with NYHA class III HF ($P = .03$)

There were significantly fewer HF-related hospitalizations in patients treated with complete access to hemodynamic data as compared to the group where access was blocked. See Tables 4 and 5. Therapy guided by the hemodynamic monitoring device resulted in improved clinical status. The clinical composite score (Table 6) was significantly better in patients treated with complete access to the hemodynamic data as compared to patients where access was blocked.

Results of the COMPASS-HF trial demonstrate that the Chronicle system is safe and effective in the management of HF patients. Management strategy for HF, based on continuously monitored intracardiac pressures in patients already on the best available therapy, with care by expert HF physicians, significantly reduced patient morbidity compared to expert HF care without hemodynamic monitoring. This reduction in HF events was seen in patients already receiving best medical care by HF specialists and advance practice nurses. This study provides proof of the concept that effective evaluation of congestion and hemodynamics is important in managing HF patients. The Chronicle system represents an important new tool to manage moderate to severe HF patients by monitoring hemodynamics remotely.

[Gregg C. Fonarow, MD, FACC, FACP]

Table 6
COMPASS-HF: Change in Heart Failure Status Based on Clinical Composite Score*

Change	Chronicle-Guided (% Patients)	Control (% Patients)
Improving	46	35
No change	21	14
Worsening	34	51

*$P = .035$ vs. controls
COMPASS-HF, Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure.

The EVEREST I Trial

Efforts toward developing percutaneous techniques for cardiac valve replacement and repair continue to generate considerable interest in the cardiology community. There are several devices currently under active investigation for percutaneous aortic and pulmonic valve replacement and numerous devices being examined for mitral valve repair. These latter devices include those that reduce mitral annular size by cinching the annulus through either the coronary sinus or by way of transventricular approaches, as well as those that result in a double-orifice mitral valve, using edge-to-edge repair techniques. The edge-to-

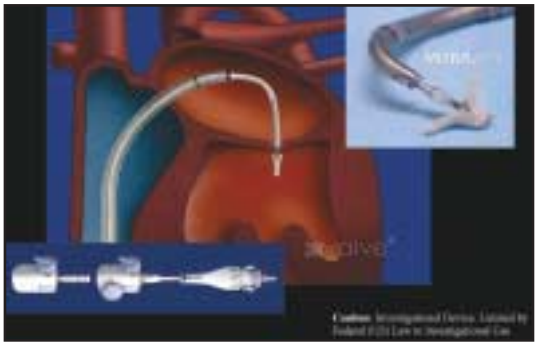


Figure 11. *Illustration showing the mechanism of action for percutaneous valve repair utilized in the EVEREST I trial.*

edge approach is similar to the surgical Alfieri procedure.

There are few human studies of any of these devices to date. The Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I is a phase 1 trial of safety using a percutaneously applied clip that holds the anterior and posterior mitral leaflets together as shown in Figure 11. The procedure results in a double-orifice mitral valve, as shown in Figure 12.

Methods and Results

EVEREST I is a prospective, multicenter feasibility and safety study in symptomatic patients or those with left ventricular (LV) end-systolic dimensions greater than 45 mm and of significant mitral regurgitation (MR). Exclusion criteria included those with an LV ejection fraction less than 30% or LV end-systolic diameter greater than 55 mm, those with renal insufficiency, and those with rheumatic heart disease or endocarditis. The study was presented at the 2005 ACC Scientific Sessions by Dr. Ted Feldman of Evanston Hospital and Northwestern University in Evanston, IL.[21]

Twenty-seven patients were enrolled, 25 with prolapse and 2 with ischemic MR. In 3 of the first 7, clips could not be placed. The other 4 required 2 clips each. A learning curve was evident with the time required for procedural completion dropping from about 220 minutes early to about 65 minutes later in the study. There were 2 in-hospital complications (1 required a blood transfusion and 1 had a partial clip detachment) with the average hospital stay of 2.5 days. At 30 days, 85% were free from events; there were a total of 3 partial clip detachments and 1 cerebrovascular accident after discharge. At 6-month follow-up, 82% were surgery free, with 4 patients eventually undergoing valve repair or replacement. MR was graded +1 to +2 in 64% at 6 months.

Conclusions and Comments

This study demonstrates that it is feasible to perform edge-to-edge percutaneous repair at low risk in selected patients with MR. As with all new technologies, there are many advances and modifications to the delivery system and the device design that are currently being investigated. The EVEREST I trial has led to US Food and Drug Administration approval for a randomized trial of percutaneous mitral repair versus surgery (EVEREST II). In this latter trial, similar patients will be sought with a randomization scheme of 2:1. Thirty centers have been recruited, though enrollment has yet to begin. A percutaneous approach to mitral regurgitation has great appeal for many patients. The generally positive results from this study have encouraged other investigators of percutaneous devices to continue to pursue this unique approach to MR. [Thomas M. Bashore, MD, FACC, FAHA]

This study demonstrates that it is feasible to perform edge-to-edge percutaneous repair at low risk in selected patients with MR.

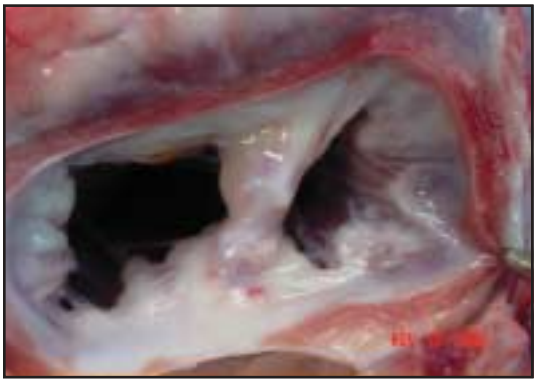


Figure 12. *Porcine model of resultant double-orifice mitral valve after percutaneous valve repair (6 months post-procedure), as practiced in the EVEREST I trial.*

GIPS-II Trial

Numerous experimental studies have suggested a role for metabolic support of the acutely ischemic myocardium. The early use of glucose–insulin–potassium (GIK) was based

on the rationale that insulin stimulates potassium reuptake through stimulation of sodium–potassium–ATPase while it stimulates glucose uptake for glycolytic energy production.[22] Indeed, over 35 years ago, Sodi-Pallares and colleagues reported that the systemic administration of GIK shortened the electrocardiographic evolution of an acute myocardial infarction (MI), reduced the incidence of ventricular ectopy, and improved early survival following acute MI.[23] More recent work has identified additional mechanisms by which GIK is protective of ischemic myocardium, including improving post-ischemic myocardial systolic and diastolic function as well as coronary vasodilation,[24] increasing glycolytic flux and glycolytic ATP synthesis,[25] and decreasing both circulating free fatty acid levels and myocardial free fatty acid uptake.[26]

These findings prompted early clinical studies that demonstrated the promise of GIK in the treatment of acute MI. A meta-analysis of trials performed in the pre-fibrinolytic therapy era revealed a reduction in in-hospital mortality following acute MI by 28% in patients receiving GIK.[27] Based on additional experimental and clinical evidence (in the setting of cardiac surgery), the Glucose–Insulin–Potassium Study (GIPS-I) was initiated at a single center where patients with ST-segment elevation MI (STEMI), treated with primary percutaneous coronary intervention (PCI), were randomized to GIK or to control.[28] Although there was no difference in overall mortality at 30 days between groups, there was a significant relative risk reduction of 72% in patients without congestive heart failure.

To confirm these finding, GIPS-II was designed to evaluate 1044 patients in 7 centers with STEMI without evidence of congestive heart failure, who were within 6 hours of symptom onset and who were eligible for reperfusion therapy. The results of this trial were presented on behalf of the investigators by Dr. Jorik Timmer of the Isala Klinieken in the Netherlands, at a late-breaking trial session of the 2005 ACC Scientific Session. Patients were randomly assigned to receive 20% glucose plus 80 mmol potassium per liter at 2 mL/kg/hr for 12 hours. Insulin was administered according to glucose levels and at 5 units per hour in normoglycemic patients. The power calculation was based on GIPS-I. A planned interim analysis after enrollment of 731 patients would dictate whether to stop the trial based on specified statistical parameters. The primary endpoint of the trial was mortality at 30 days and the secondary endpoint was infarct size estimated by peak creatine kinase (CK) level.

As expected, baseline characteristics did not differ between groups. The study was terminated following the planned interim analysis and total enrollment of 889 patients, 444 of whom were treated with GIK. There was no difference in mortality at 30 days: 2.9% (13/444) and 1.8% (8/445) in the GIK and control groups, respectively. Mean peak CK level was 1970 ± 1888 units/L in both groups, showing no difference between groups. See Figure 13. The authors concluded that GIK, as administered per this study design, does not decrease mortality at 30 days or enzymatic infarct size in patients with STEMI without congestive heart failure, treated with reperfusion therapy.

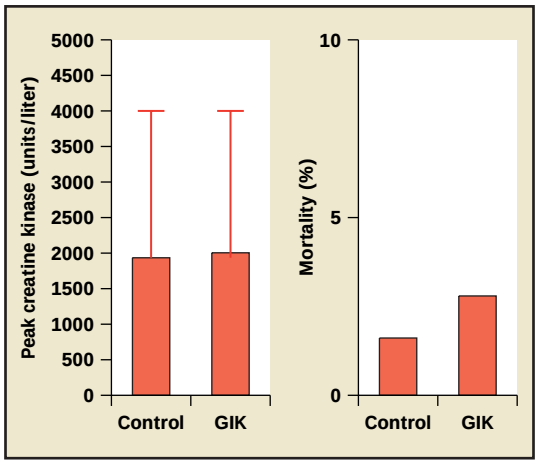


Figure 13. *Primary and secondary outcomes at 30 days in the GIPS-II trial. GIK, glucose-insulin-potassium.*

Comment

Dr. Thomas J. Ryan discussed the results of this trial and the disappointing outcome. The mal-distribution of anterior MIs and a longer ischemic time inherent to the GIK group were excluded as potential explanations for the unanticipated findings. Questions were raised as to what may have masked the potential efficacy of metabolic support. The reduced dose of GIK used in GIPS–II to decrease the potential for volume overload and subsequent congestive heart failure, the short overall ischemic time (owing to early reperfusion) that reduced the treatment time for GIK, in addition to an underpowered study and inadequate number of primary endpoints, all could have been factors. Given the negative results of the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment

Evaluation-Estudios Cardiologicas Latin America (CREATE-ECLA) Study Group 2 GIK Full Scale Trial[29] conducted in 20,201 patients, 1980 of whom reached the primary endpoint of death, it is likely there is little role for GIK in the treatment of acutely ischemic and reperfused myocardium. Yet, the 25% relative reduction in mortality in the subset of patients treated with primary PCI or tissue plasminogen activator in addition to GIK in CREATE-ECLA[30] may prompt investigators who remain convinced by the science to consider yet another trial in a group of patients treated with contemporary reperfusion therapy in whom very early (pre-hospital) administration of GIK could be achieved.

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

The TNT Trial

Is Less More?

Although the clinical benefits of low-density lipoprotein cholesterol (LDL-C) lowering for reduction of cardiovascular events has been demonstrated in several randomized trials, the precise LDL-C target level for therapy has remained somewhat uncertain. Recently, the PROVE-IT trial, involving patients with acute coronary syndromes, did show that treating to LDL-C levels substantially below 100 mg/dL (ie, approximately 70 mg/dL) was associated with a modest further absolute risk reduction compared to higher levels of LDL-C, suggesting that lower levels of LDL-C may be better for risk reduction. However in the PROVE-IT trial, 2 different statins, atorvastatin and pravastatin were compared, making it difficult to assess with certainty whether the lower risk observed with atorvastatin was due to lower LDL-C levels achieved or some properties unique to atorvastatin. Furthermore, this study involved patients with acute coronary syndromes and not patients with stable coronary artery disease (CAD), in whom the results could have been different.

At the 2005 ACC Annual Scientific Session, results of the Treating to New Targets (TNT) trial were presented by Dr. John LaRosa of the State University of New York Downstate Medical Center, Brooklyn, NY, in the late-breaking clinical trials session. The goal of TNT was to determine whether greater LDL-C lowering achieved with an 80 mg/day dose of atorvastatin (with the goal of achieving an LDL-C level of about 75 mg/dL) would achieve a greater cardiovascular risk reduction compared to more modest lowering of LDL-C, using 10 mg/day of atorvastatin (with the goal of achieving LDL-C levels of about 100 mg/dL), in patients with chronic stable CAD. A total of 18,469 patients were screened in 14 countries and 10,003 patients with LDL-C levels below 130 mg/dL (mean LDL-C level of 99 mg/dL) were randomized in a double-blind fashion: 5006 to atorvastatin 10 mg and 4995 to atorvastatin 80 mg. Patients were followed for a median of 4.9 years.

The atorvastatin 80 mg group achieved a mean LDL-C of 77 mg/dL, whereas the atorvastatin 10 mg group achieved a mean LDL-C of 101 mg/dL. The primary endpoint was a major cardiovascular event (death from CAD; nonfatal, nonprocedure-related myocardial infarction; fatal or non-fatal stroke; and resuscitation from cardiac arrest) whereas the secondary endpoint was a composite of the primary outcome and cardiovascular accident, hospitalization for CHF, peripheral arterial disease, death from any cause, any cardiovascular event, and any coronary event. The results have since been reported in the *New England Journal of Medicine*[31] and are summarized in Table 7.

Conclusions and Perspective

Overall results of the TNT trial show that higher dose atorvastatin (80 mg/day), achieving LDL-C levels of about 77 mg/dL compared to a 101 mg/dL level in the atorvastatin 10 mg group, reduces major cardiovascular events by an absolute number of 2.2 events per 100 patients (relative risk reduction of 22%), compared to lower-dose atorvastatin. The higher dose of atorvastatin was generally well tolerated with a low incidence of myalgias, rhabdomyolysis, and liver-function test abnormalities. Thus, the overall results from the TNT trial support the notion that in long-term, stable CAD patients, LDL-C levels substantially lower than 100 mg/dL do provide modestly greater absolute clinical benefit compared to LDL-C levels of 100 mg/dL, thereby extending the observations from the PROVE-IT trial involving acute coronary syndrome patients. It is interesting to note that with high-dose atorvastatin, there was no significant reduction in all-cause mortality, even though cardiovascular mortality was reduced. This interesting finding may have resulted from lack of statistical power to detect a reduction in all-cause mortality and/or the possibility that non-cardiac mortality may have increased to offset reduced cardiac mortality. In fact, there were 31 more non-cardiac deaths in the atorvastatin 80 mg group. Whereas this may have resulted from chance, it does raise a potential concern. Although the general concept that lower LDL-C levels may be beneficial is receiving support from clinical trials, several questions need to be addressed in the future.

1) Which subsets of patients have the most to gain from high-dose statin therapy, without incurring an increase in non-cardiovascular deaths?

Table 7
Estimated Hazard Ratio for Primary and Secondary Efficacy Outcomes in the TNT Trial

Outcome	10 mg of Atorvastatin (n = 5006)	80 mg of Atorvastatin (n = 4995)	Hazard Ratio (95% CI)	*P* Value
	no. with first event (%)			
Primary outcome				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69-0.89)	<0.001
Death from CHD	127 (2.5)	101 (2.0)	0.80 (0.61-1.03)	0.09
Nonfatal, nonprocedure-related myocardial infarction	308 (6.2)	243 (4.9)	0.78 (0.66-0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56-1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59-0.96)	0.02
Secondary outcomes				
Major coronary event†	418 (8.3)	334 (6.7)	0.80 (0.69-0.92)	0.002
Cerebrovascular event‡	250 (5.0)	196 (3.9)	0.77 (0.64-0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59-0.94)	0.01
Peripheral-artery disease§	282 (5.6)	275 (5.5)	0.97 (0.83-1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85-1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75-0.87)	<0.001
Any coronary event¶	1326 (26.5)	1078 (21.6)	0.79 (0.73-0.86)	<0.001

In each row, only the first event for each patient is counted.
† This was the original primary outcome (death from CHD, nonfatal nonprocedure-related myocardial infarction, or resuscitation after cardiac arrest).
‡ A cerebrovascular event was defined as fatal or nonfatal stroke or transient ischemic attack.
§ Peripheral-artery disease was defined as any new diagnosis of peripheral-artery disease, any admission related to its treatment, or any incidental discovery of plaques or stenosis.
¶ Any coronary event was defined as a major coronary event, revascularization procedure, procedure-related myocardial infarction, or documented angina.
CHD, coronary heart disease; TNT, Treating to New Targets. Reproduced with permission from LaRosa et al.[31]

2) Does it matter how lower LDL-C levels are achieved (eg, using high dose statin therapy vs diet and statin therapy vs statin plus other LDL-lowering drugs such as ezetimibe)?
3) How will the risk/benefit profile of high-dose statin therapy compare with lower dose statins coupled with high-density lipoprotein (HDL)-raising agents?
4) Are the benefits of high-dose atorvastatin due to lower LDL-C levels achieved or some other mechanism (eg, pleiotropic effects)?

My own belief is that the totality of evidence suggests that the clinical benefits of statin therapy are largely, if not entirely, due to LDL-C lowering effects and therefore, pending data to the contrary, it may be prudent to recommend that even for patients with chronic stable CAD, all attempts should be made to lower LDL-C levels to about 70 mg/dL. This could be achieved with high-dose statin therapy and/or combination drug/diet therapy. ■

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Main Points

- The Kidney Early Evaluation Program (KEEP), evaluated estimated glomerular filtration rate (GFR) based on measured serum creatinine, age, gender, race, and other factors in a randomized group of patients at risk for chronic kidney disease (CKD) and found that subjects with all of the 3 most prevalent CKD-related factors had a 35.8% rate of cardiovascular disease, indicating a need for further study of the hemodynamic, neurohormonal, metabolic, and hematopoietic aspects of CKD.
- Results from the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY-TIMI 28) trial showed a reduction in the rate of occluded coronary vessels at the time of angiography, death, or recurrent myocardial (pre-angiography) infarction with clopidogrel, a finding that was internally consistent among all prespecified subgroups and that extended benefit of reduced rates of death or MI at 30 days, thus supporting the use of early clopidogrel before angiography in those patients with ST-segment elevated myocardial infarction who receive lytic therapy.
- The REALITY, ISAR-DIABETES, and SIRTAX trials were consistent in finding lower late loss with the Cypher drug-eluting stent versus the TAXUS stent, but were not consistent as far as clinical outcomes were concerned, with only 1 trial showing a reduction in clinical restenosis.
- The ENDEAVOR II trial showed that the Endeavor drug-eluting stent system will be effective against restenosis in most coronary lesions. However, it is unclear whether it will perform as well in high-risk lesions (lesions in diabetic subjects, small and long lesions).
- Two studies examining the anti-platelet effects of the novel thienopyridine compound prasugrel showed it to be potent, consistent, and well tolerated, even in patients resistant to other anti-platelet agents. Patient reaction to prasugrel was dose dependent in daily regimens ranging from 5 mg to 20 mg and remained safe when administered in a loading bolus dose.
- Preliminary results of the ASCOT trial show that the combination of a calcium channel blocker and an ACE inhibitor, when compared to a traditional β-blocker and thiazide diuretic combination, is superior in preventing major cardiovascular events in high-risk hypertensive patients.
- The COMPASS-HF trial, which implanted hemodynamic monitoring devices in NYHA class III and IV heart failure patients and then randomized them to allow physicians access to monitor hemodynamic data for half of them, showed that treatment guided by complete access to hemodynamic data led to significantly fewer heart failure-related hospitalizations as compared to treatment when access to data was blocked.
- The EVEREST I trial demonstrates that it is feasible to perform edge-to-edge percutaneous repair at low risk in selected patients and has led to US Food and Drug Administration approval for a larger-scale, randomized trial of percutaneous mitral repair versus surgery (EVEREST II).
- The study authors for the GIPS-II trial concluded that GIK, as administered per their study design, does not decrease mortality at 30 days or enzymatic infarct size in patients with STEMI without congestive heart failure, treated with reperfusion therapy.
- Overall results of the TNT trial show that higher dose atorvastatin (80 mg/day), achieving LDL-C levels of about 77 mg/dL compared to a 101 mg/dL level in the atorvastatin 10 mg group, reduces major cardiovascular events by an absolute number of 2.2 events per 100 patients (relative risk reduction of 22%), compared to lower-dose atorvastatin.

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