Best of the AHA Scientific Sessions 2006

Highlights from the American Heart Association Scientific Sessions, November 12-15, 2006, Chicago, IL

[*Rev Cardiovasc Med.* 2007;8(1):25-35]

Key words: Carotid intima-media thickness • Medication adherence • Ventricular tachyarrhythmias • Stents • Percutaneous coronary intervention • Heart failure

The 2006 American Heart Association (AHA) Scientific Sessions was the scene of important clinical trial results that could have important implications for clinical care. Our board members discuss data regarding pioglitazone on carotid intima-media thickness (CIMT) in patients with type 2 diabetes, adherence to medications, prediction of ventricular tachyarrhythmias, stents, chocolate and the heart, use of percutaneous coronary intervention (PCI) for total occlusion of the infarct-related artery following acute myocardial infarction (MI), prediction of the development of heart failure (HF), and diagnosis of HF.

Reviewed by Premranjan P. Singh, MD, Richard W. Nesto, MD, FACC, David P. Faxon, MD, FACC, FAHA, Norman E. Lepor, MD, FACC, FAHA, FSCAI, Karol E. Watson, MD, PhD, Alice K. Jacobs, MD, FACC, FAHA, Peter A. McCullough, MD, MPH, FACC, FACP, FCCP, FAHA.

The CHICAGO Trial

Thiazolidinediones (TZDs) are effective agents to treat type 2 diabetes because they reduce insulin resistance and preserve beta cell function. Numerous studies utilizing in vitro data and animal models of atherosclerosis have demonstrated the potential anti-atherosclerotic effects of these drugs. TZDs have also shown beneficial effects on a variety of cardiovascular disease risk parameters in humans, such as lipid profiles, inflammatory biomarkers, and fibrinolytic factors. The clinical trial Carotid Intimal-Medial Thickness in Atherosclerosis using Pioglitazone (CHICAGO) extends this knowledge base by evaluating the effect of a TZD, pioglitazone, on CIMT in patients with type 2 diabetes.[1]

CIMT is a well-described marker for cardiovascular risk. Increased thickness of the carotid intima-media layer correlates not only with the presence and number of cardiovascular risk factors but also with the risk of future macrovascular events, such as MI and stroke.[2,3] Furthermore, an increase of merely 0.03 mm per year in CIMT has been associated with a twofold increase in relative risk of MI and cardiac death during 2 years of follow-up.[4] CIMT has a modest relationship with obstructive coronary artery disease (CAD) in nondiabetic[5,6] and diabetic[7] subjects, indicating that CIMT is a marker of atherosclerosis burden as well as an index of the severity of CAD. In a recent meta-analysis of 37,197 subjects followed for a mean of 5.5 years, Lorenz and coworkers[8] demonstrated that an absolute CIMT difference of 0.1 mm correlated with a 10% to 15% increase in the future risk of MI, and a 13% to 18% increase in stroke. They cautioned, however, that the relationship between CIMT and the

relative risk of vascular events is not strictly linear in most populations. Limited evidence exists with respect to the effect of pharmacologic interventions on CIMT in type 2 diabetes; antiplatelet therapy[9] and angiotensin-converting enzyme (ACE) inhibition[10] slow the progression of thickening, and amlodipine has been shown to reduce CIMT in a small group of patients with diabetes.[11]

Minamikawa and colleagues[12] reported a reduction in CIMT in Japanese subjects with type 2 diabetes mellitus who received troglitazone. A similar benefit of TZD on CIMT was demonstrated in another study[13] in which pioglitazone-treated diabetic patients had a significant decrease in CIMT after 3 months (−0.050 ± 0.019 mm vs 0.019 ± 0.009 mm; $P < .005$) and 6 months (0.084 ± 0.023 vs 0.022 ± 0.006 mm; $P < .001$) compared with the control group. In the group treated with pioglitazone, glycemic control (hemoglobin [Hb] A_{1c}) was significantly improved after 3 and 6 months (8.5 at baseline vs 7.5 and 7.3; $P < .001$) but no difference was seen in cholesterol, high-density lipoprotein (HDL), triglyceride, or blood pressure.[13]

Postprandial glucose levels are more strongly associated with CIMT than are levels of fasting glucose and HbA_{1c}.[14,15] The Campanian Postprandial Hyperglycemia Study demonstrated that the reduction of postprandial hyperglycemia in patients with type 2 diabetes mellitus was associated with regression of CIMT.[16] The beneficial effect of rosiglitazone on CIMT progression in CAD patients without type 2 diabetes has also been demonstrated. TZD-treated patients showed a mean reduction in progression of CIMT compared with the placebo group (mean CIMT change −0.012 mm/48 wk vs 0.031 mm/48 wk; $P = .03$).[17]

Langenfeld and colleagues[18] conducted a 24-week study of 173 patients with type 2 diabetes to examine whether pioglitazone therapy decreased CIMT compared with a glimepiride-based approach and whether the effect of the TZD was related to changes in cardiovascular risk parameters or was a potential direct effect of the drug. At 24 weeks, there were similar substantial decreases in A_{1c} in both the pioglitazone (−0.8 ± 0.9%) and glimepiride (−0.6 ± 0.8%) groups. However, after adjustment for the use of statins, ACE inhibitors, and angiotensin receptor blockers, the pioglitazone group showed a more pronounced decrease in CIMT (−0.054 ± 0.059 mm) compared with the glimepiride group (−0.011 ± 0.058 mm) ($P < .005$ between groups). Reduction of CIMT correlated with a reduction in insulin resistance ($r = 0.29$; $P < .0005$) and was independent of improvement in glycemic control ($r = 0.03$; $P = 0.68$), suggesting that TZD has a direct effect on vascular structure[18] (Table 1).

The CHICAGO trial was presented at this year's AHA scientific sessions.[1] The CHICAGO trial is the largest and longest clinical trial of the effect of TZD therapy on subclinical carotid atherosclerosis. CHICAGO was a

Table 1
Clinical Trials Showing Effect of Statin and TZD on CIMT

Study	Subjects	Treatment	Follow-up	Result/Change in CIMT
ARBITER[36]	161 (without type 2 DM)	Atorvastatin 80 mg/d vs pravastatin 40 mg/d	1 year	−0.034 ± 0.021 mm/yr vs 0.025 ± 0.017 mm/yr
Sidhu JS et al[17]	92 (without type 2 DM)	Rosiglitazone 4 mg/d to 8 mg/d vs placebo daily	48 weeks	−0.012 mm/48 wk vs 0.031 mm/48 wk
Langenfeld MR et al[18]	173 (with type 2 DM)	Pioglitazone 45 mg/d vs glimepiride 2.7 mg/d ± 1.6 mg/d	24 weeks	−0.054 ± 0.059 mm/24 wk vs −0.011 ± 0.058 mm/24 wk
Hanefeld M et al[37]	132 (with impaired glucose tolerance)	Acarbose 100 mg tid vs placebo daily	3.9 years	dIMT + 0.007 (0.019) mm/yr vs dIMT + 0.013 (0.018) mm/yr
CHICAGO[1]	462 (with type 2 DM)	Pioglitazone 15 mg/d to 45 mg/d vs glimepiride 1 mg/d to 4 mg/d	18 months	−0.001 mm/18 m vs +0.012 mm/18 m

TZD, thiazolidinediones; CIMT, carotid intima-media thickness; DM, diabetes mellitus; d, difference.

randomized, double-blind, multicenter study comparing the effects of pioglitazone versus those of glimepiride on CIMT in 462 patients with type 2 diabetes. Subjects were randomized to 15 mg/d to 45 mg/d of pioglitazone versus 1 mg/d to 4 mg/d of glimepiride, with a target HbA_{1c} of less than 7%, and were treated for 18 months. Inclusion criteria included age 45 years to 85 years and a baseline HbA_{1c} of 6.5% to 9% on antidiabetic therapy or 6.5% to 10.0% if not on medication. Exclusion criteria included symptomatic cardiovascular disease or peripheral arterial disease, insulin therapy alone, New York Heart Association (NYHA) class III or IV HF or a left ventricular ejection fraction (LVEF) of less than 40%, recent TZD therapy, significant valvular disease, triglycerides exceeding 500 mg/dL, or body mass index higher than 45 kg/m^2. The primary endpoint of the study was the change in mean posterior wall intima-media thickness of the right and left common carotid arteries (CIMT) as measured by carotid ultrasound. Secondary endpoints included the change in maximal CIMT, markers of glucose and lipid control, and a composite cardiovascular disease endpoint. Baseline characteristics in both groups were similar. The study subjects were an ethnically diverse group, and 50% to 60% were taking a statin during the course of the trial. At the final visit, the change from baseline in mean CIMT was −0.001 mm in the pioglitazone group and +0.012 in the glimepiride group, for an overall difference of −0.013 mm (95% confidence interval [CI], −0.024-0.002; $P = .02$). The change in maximal CIMT was also significantly different between the groups (−0.024 [95% CI, −0.042 to −0.006]; $P = .008$).

There were between-group differences in several metabolic parameters, including HbA_{1c} (−0.3%; $P = .002$), HDL cholesterol (+6 mg/dL; $P < .001$), and triglycerides (−16%; $P < .001$), all in favor of pioglitazone. Prespecified subgroup analyses showed that the change in CIMT favored pioglitazone irrespective of age, gender, and duration of diabetes, body mass index, HbA_{1c}, or statin use. Because of the small number of clinical events, it is difficult to evaluate the effect of treatment on the composite cardiovascular outcome. There were 10 such events in the glimepiride group (mostly revascularizations) and 4 in the pioglitazone group. A single HF hospitalization occurred with pioglitazone. Other adverse events were similar between the groups. Overall weight gain was 3.2 kg with pioglitazone and 1.0 kg with glimepiride. Edema occurred more frequently in subjects randomized to the TZD (13% vs 7%).

Conclusion

This report adds to a growing body of literature suggesting that TZDs possess significant antiatherosclerotic effects. The main questions at this time include the following 1) Are such small changes in CIMT clinically meaningful? 2) Is the change in CIMT a direct effect of the drug on the vessel wall? 3) Or is the change an indirect effect mediated by metabolic parameters such as age, sex, total cholesterol, systolic blood pressure, body mass index, blood sugar, and HbA_{1c}.

Several outcome studies such as the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medications (DREAM) trial, the Prospective Pioglitazone Clinical Trial in Macrovascular Events (ProACTIVE), and A Diabetes Outcome Progression Trial (ADOPT) have highlighted the importance of intervention at the earliest possible stage in dysglycemia to inhibit disease progression by decreasing insulin resistance and preserving beta cell function, ultimately with the hope that cardiovascular disease will be reduced. Additional ongoing studies such as Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI2D), Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE), Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD), and Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in diabetes with Cardiovascular History (APPROACH) will help examine the critically important question of whether TZDs can reduce cardiovascular events.

[Premranjan P. Singh, MD, Richard W. Nesto, MD, FACC]

Adherence to Medications: Results of the FAME Trial

Compliance with chronic medication continues to be a serious problem that limits effectiveness of therapy and is felt to contribute to unnecessary morbidity and mortality. The problem is most serious in elderly patients, who frequently take more than 4 chronic medications and often suffer from dementia that complicates their care and medication adherence. Effective ways of improving compliance with medication are limited and have not been well studied in part because the problem is complex and multifactorial. The Federal Study of Adherence of Medications (FAME) trial was presented by Dr. Allan J. Taylor (Walter Reed Army Medical Center, Washington, DC) at the late-breaking trials.[19]

The study enrolled 200 patients older than 65 years who were on at least 4 chronic medications and who were living independently without any serious medical conditions that would limit their life expectancy. The

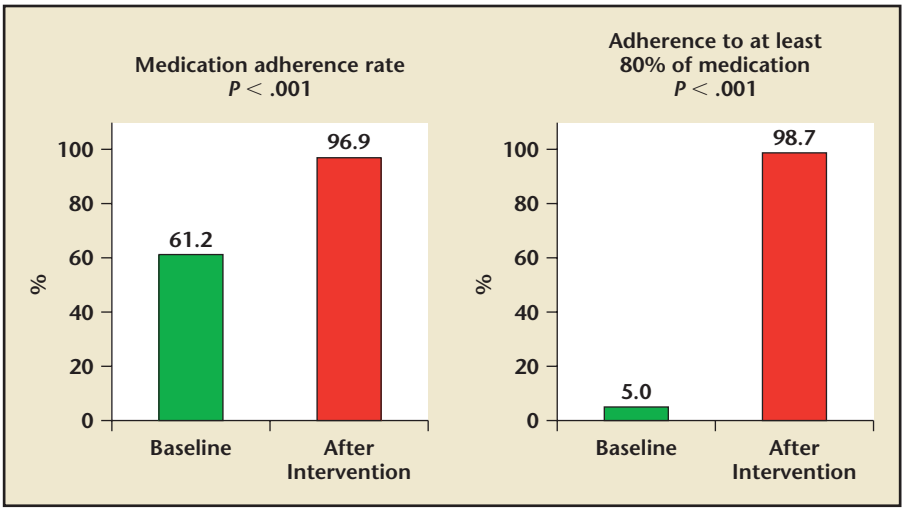


Figure 1. *Primary outcome of the observational phase of the Federal Study of Adherence of Medications (FAME) trial. Data from Taylor A.*[19]

trial was conducted in the federal health care system, which allowed coordination between the pharmacy and patients. The study aim was to compare usual care with a pharmacy intervention group. Following an initial run-in phase for 2 months to ascertain baseline medication compliance, all the patients were placed into an observation phase for 6 months. In this phase, medications were dispensed in specially designed blister packs with all medication needed for each time point packaged together. In addition, there was an education program on medication use and systematic pharmacy follow-up. At the end of this observation phase, patients were randomized to continue in the intervention group or to return to usual care for an additional 6 months. The primary endpoint was change in medication use over baseline and medication use after 6 months in the randomized phase of the study. The secondary endpoints were changes in blood pressure and low-density lipoprotein (LDL) cholesterol levels at the 2 time points.

At the study onset, medication use was what might be expected: 80% of patients were on statins and 50% were on ACE inhibitors and beta-blockers. The mean medication adherence in the initial run-in phase was 61.2%. At the end of the observational period during which the intervention was used in all patients, the rate of medication adherence increased to 96.9% ($P < .001$). The number of patients who took at least 80% of all their medication rose from 5% at baseline to 98.7% at the end of the observational period (Figure 1). This change was associated with a small but significant decrease in systolic blood pressure from 133.2 mmHg to 129.9 mmHg ($P = .02$) and a reduction in LDL cholesterol from 91.7 mg/dL to 88.8 mg/dL ($P = .001$). An important component of the trial was the validation of the observation study performed in the randomized phase. During this phase, medication adherence in the usual care group fell to 69.1%, a level close to that on entry, whereas the intervention group maintained compliance at 95.5% ($P = .001$). The adherence rate of taking at least 80% of all medication was 21.7% in the usual care group versus 97.4% in the intervention group ($P = .001$). Like the observational phase, the randomized phase showed a significantly greater fall in systolic blood pressure. Interestingly, there was no difference in the reduction in LDL cholesterol.

This trial demonstrated that a rather simple program that utilized improved education, medication packaging, and pharmacy oversight can significantly improve adherence to chronic medication use in the elderly. The strength of the study was not only the findings in the observational phase but the validation in the randomized component. It is disturbing, however, that the education that occurred in the open-label observation period did not change behavior during the randomized phase. This finding suggests that merely educating patients on medication use once or even multiple times is not enough; the influence wears off. This result strongly supports the need for an ongoing program. Finally, the reduction in blood pressure and LDL demonstrates the clinical effectiveness of such a program (Figure 2). The study was small and conducted in a federal health care system, where patients may differ from those in a private setting. Despite these limitations, the study provides convincing evidence that improved systems of care can make a difference in medication adherence and clinical outcome. [David P. Faxon, MD, FACC, FAHA]

Defining the Risk of a Ventricular Tachyarrhythmic Event in Patients With Ischemic Cardiomyopathy

The Alternans Before Cardioverter Defibrillator (ABCD) trial was presented by Dr. Ottorino Costantini (Case Western Reserve University, Cleveland, OH).[20] The purpose of the study was to compare microvolt T-wave alternans (MTWA)–directed therapy with electrophysiological study (EPS)–directed therapy in

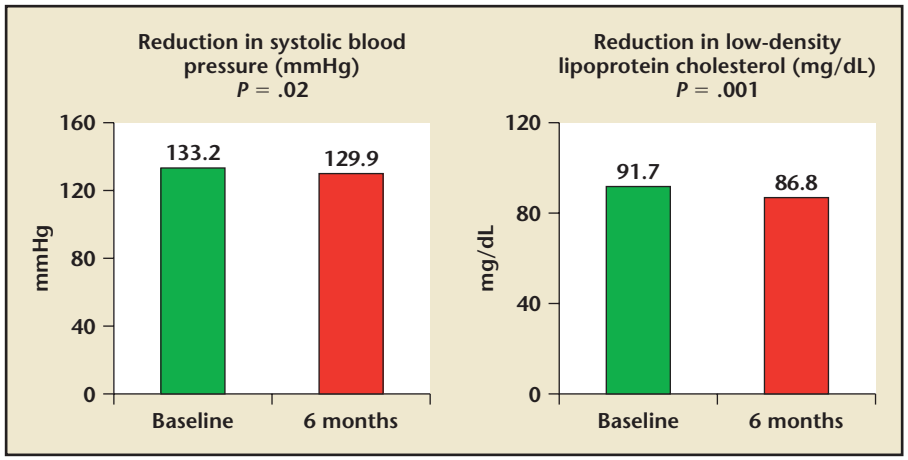


Figure 2. *The differences in blood pressure and low-density lipoprotein cholesterol between the baseline and the observational phase of the Federal Study of Adherence of Medications (FAME) trial. Data from Taylor A.*[19]

predicting ventricular tachyarrhythmias in patients with ischemic cardiomyopathy without known history of ventricular tachyarrhythmias. Patients were excluded if they had a prior cardiac arrest or sustained ventricular arrhythmia, used antiarrhythmic drugs, or had NYHA class IV HF. The mean LVEF at baseline was 28%, with the majority of patients in NYHA HF class II (51%) or class I (30%) and 19% in class III.

The highest event rate (12.6%) was among those patients who were MTWA-positive and EPS-positive, and the lowest event rate (2.3%) was among those who were MTWA- and EPS-negative. Patients who were MTWA-negative but EPS-positive had an intermediate event rate (7.5%). Patients who were MTWA-positive but EPS-negative had an event rate of 5.0% (Figure 3). MTWA was predictive early on in the study but only through 12 months, whereas EPS was predictive from 9 months onward but not earlier.

This study shows the complementary nature of EPS and MTWA in defining the risk of a ventricular tachyarrhythmic event in patients with ischemic cardiomyopathy. Those patients who have abnormal EPS and MTWA would seem to be a population that should receive the highest priority for implantable cardioverter-defibrillator insertion. Patients who are EPS- and MTWA-negative are a low-risk population in whom an expectant approach to implantable cardioverter-defibrillator insertion may be appropriate.

A Cobalt Chromium Stent Versus an SES

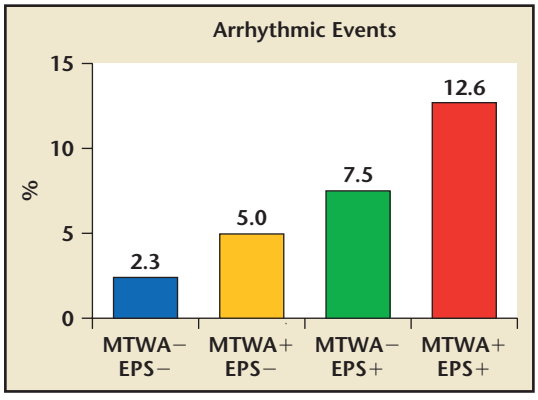
The MISSION trial compared the efficacy of the cobalt chromium stent (VISION® [Guidant Corporation, St. Paul, MN]) with that of the sirolimus-eluting stent (SES) (Cypher® [Cordis Corporation, Miami Lakes, FL]) among 316 patients with ST-elevation MI.[21] The subjects, ages 18 to 80 years, had clinical and electrocardiographic evidence of ST-elevation MI, directed treatment of the de novo culprit lesion, and a reference vessel diameter of 2.25 mm to 3.75 mm. Patients were randomized to a particular stent after the lesion was crossed with a guidewire.

Repeat angiography and intravascular ultrasound were performed at 9 months. The primary endpoint of in-segment late loss at 9-month angiographic follow-up was lower in the SES group compared with the bare-metal (VISION®) group (0.12 mm vs 0.68 mm; $P < .001$), as was percent diameter stenosis (24% vs 41%; $P < .001$). Binary stenosis occurred less frequently in the SES group (3.8% vs 22.8%; $P < .01$). At 1 year, target vessel revascularization was performed in 13.3% of the bare-metal stent group and 5.1% of the SES group ($P = .01$). There was no difference in death (2.7% vs 1.3%) or MI (9.3% vs 5.7%). Stent thrombosis occurred in 2.0% of the bare-metal stent group and 1.3% of the SES group ($P =$ NS). This study illustrates the efficacy and safety of an SES compared with a bare-metal stent in patients presenting with ST-elevation MI.

Treatment of In-Stent Restenosis by Paclitaxel-Coated PTCA Balloons

The Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis (PACCOCATH ISR) trial compared

Figure 3. *Results from the Alternans Before Cardioverter Defibrillator (ABCD) trial. MTWA, microvolt T-wave alternans; EPS, electrophysiological study. Data from Costantini O.*[20]



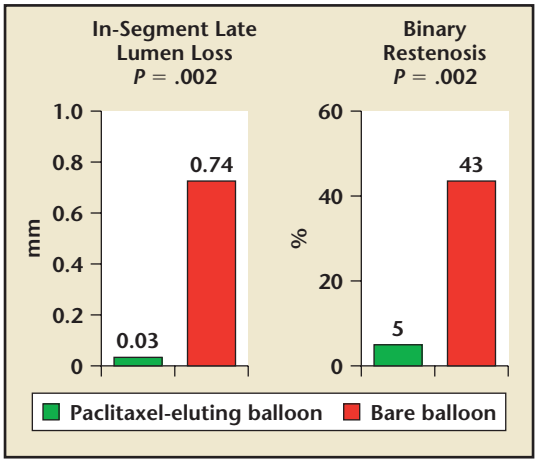


Figure 4. *Results from the Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis (PACCOCATH ISR) trial. Reprinted with permission from Scheller B et al.*[22]

the safety and efficacy of a paclitaxel-eluting percutaneous transluminal coronary angioplasty (PTCA) balloon catheter with those of a non-eluting balloon catheter among patients with coronary in-stent restenosis.[22] Patients were randomized in a double-blind manner to 1 of 2 balloon treatment regimens: either a paclitaxel-eluting balloon catheter (n = 26) or a non-eluting balloon catheter (n = 26). The primary endpoint of in-segment late lumen loss was smaller in the paclitaxel-eluting balloon group (0.03 ± 0.48 mm vs 0.74 ± 0.86 mm; P = .002), with less binary restenosis in the paclitaxel-eluting balloon group than in the non-eluting balloon group (5% vs 43%; P = .002) (Figure 4).

This small pilot study shows the potential for a paclitaxel-eluting balloon to limit recurrent in-stent restenosis. If larger trials show similar results in this cohort as well as in the primary treatment of coronary stenosis, the use of a drug-eluting balloon that may be able to treat lesions that are more difficult to access will be a nice addition to the armamentarium of PCIs.
[Norman E. Lepor, MD, FACC, FAHA, FSCAI]

Chocolate at the Heart

Over the years, chocolate has been criticized as being harmful for vascular health, mostly because of concern over its saturated fat and sugar content. There has also been, however, evidence for some time that the antioxidant flavonoids present in chocolate might be beneficial for cardiovascular health. A 1992 review by Kris-Etherton and Keen, which evaluated evidence from 66 published studies, supported the view that consumption of flavonoid-rich tea and/or chocolate was associated with reduced risk for cardiovascular disease.[23] Much of this benefit was felt to be due to the antioxidants present in chocolate.

Another proposed mechanism of a cardiovascular benefit is that chocolate might have an antiplatelet effect. New data regarding this hypothesis were presented at the AHA meeting by Dr. Diane M. Becker of the Johns Hopkins School of Medicine (Baltimore, MD).[24]

Casual Chocolate Consumption and Platelet Activity

The data presented at the AHA were from a substudy of a larger trial of 1535 people, funded by the National Heart, Lung, and Blood Institute, intended to investigate the genetics of aspirin responsiveness. Subjects in the study were instructed to avoid chocolate, tea, strawberries, and red wine, substances that have been associated with antiplatelet activity. Some of the subjects, however, admitted to consuming chocolate. Dr. Becker analyzed the urine and platelets of these 139 subjects in comparison to those from subjects who had not consumed chocolate.

Testing of platelet samples from both groups showed that chocolate eaters were found to have reduced aggregability, on average taking 130 seconds to clot as compared to 123 seconds in the subjects who did not eat chocolate. In another test of platelet reactivity, urinary thromboxane (11-dehydro-thromboxane B_2) was measured. Dr. Becker found that chocolate eaters showed less activity, with 177 nanograms per millimol of creatinine versus an average of 287 nanograms per millimol of creatinine in the group that abstained from chocolate, indicating that the chocolate eaters had less platelet reactivity.

Implications

Although this study is small, nonrandomized, and not a prespecified analysis, it can lend important insight into the effects of chocolate on cardiovascular disease. This study also highlights the potential impact that small dietary habits can have on cardiovascular health. Now, no one is suggesting that eating chocolate should be recommended as a preventive practice, for several reasons: chocolate is typically quite high in sugar and calories; commercially available chocolate varies greatly in composition and will presumably vary in beneficial effects as well; and the antiplatelet effect of chocolate is rather modest, and significant amounts of chocolate would need to be consumed to approximate the antiplatelet effects of aspirin. Nonetheless, emerging evidence suggests that chocolate may not be the cardiovascular villain previously believed.
[Karol E. Watson, MD, PhD]

Table 2
Four-Year Cumulative Event Rates in OAT

Outcome	PCI (%)	Medical (%)	Hazard Ratio	95% CI	*P* Value
Death, MI, HF	17.2	15.6	1.16	0.92-1.45	.20
All MI	7.0	5.3	1.36	0.92-2.00	.13
Nonfatal MI	6.9	5.0	1.44	0.96-2.16	.08
NYHA class 4 HF	4.4	4.5	0.98	0.64-1.49	.92
Death	9.1	9.4	1.03	0.77-1.40	.83

OAT, Occluded Artery Trial; PCI, percutaneous coronary intervention; CI, confidence interval; MI, myocardial infarction; HF, heart failure; NYHA, New York Heart Association. Data from the OAT trial.[28]

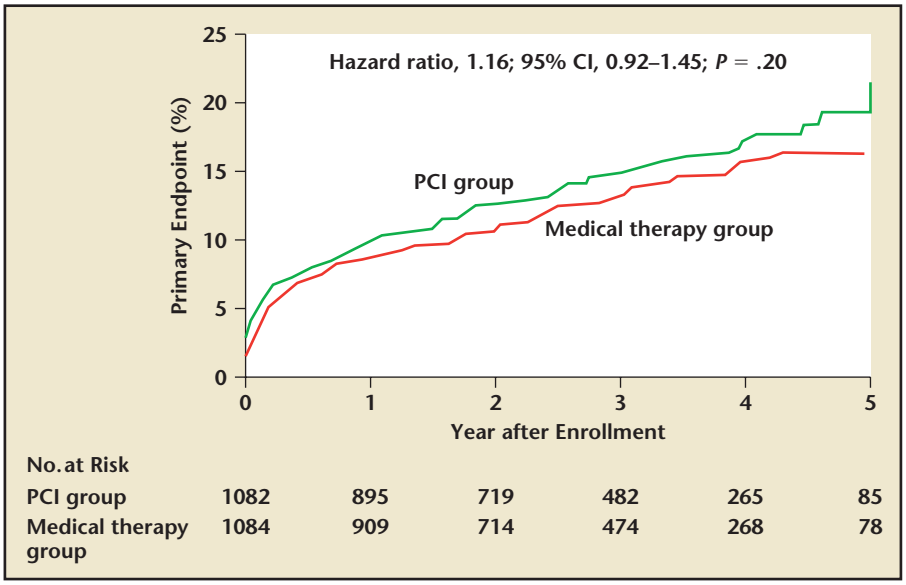
Occluded Artery Trial (OAT)

Numerous observational studies have suggested that following MI, patency of the infarct-related artery (in comparison to persistent occlusion) is associated with lower subsequent event rates.[25-27] Yet, it has been unclear whether *restoring* patency of the artery with PCI would be beneficial late after MI, when salvage of myocardium is no longer possible. The Occluded Artery Trial (OAT), funded by the National Heart, Lung, and Blood Institute, tested the hypothesis that a strategy of routine PCI for total occlusion of the infarct-related artery following acute MI would reduce the incidence of a composite endpoint of death, reinfarction, and NYHA Class IV HF.[28] Accordingly, between February 2000 and December 2005, 2166 patients without severe ischemia 3 days to 28 days following MI at 217 clinical sites in 27 countries were randomly assigned to PCI using stents (n = 1082) or optimal medical therapy (n = 1084). Eligible patients were hemodynamically stable with Thrombolysis In Myocardial Infarction (TIMI) flow 0 or 1 in the infarct-related artery and were considered high risk due to an LVEF of less than 50% or proximal occlusion of the infarct artery. In a subgroup of 381 patients, coronary angiography was repeated at 1 year as part of an ancillary study.[29]

The results of OAT were presented by the principal investigator, Dr. Judith S. Hochman (New York University, New York, NY), at a late-breaking trials session. As expected, baseline clinical and angiographic characteristics were similar between the groups, including the interval between MI and randomization, with the exception of a higher prevalence of diabetes in the medical therapy group. In the PCI group, procedural success was 87%. Stents were used in 87% (drug-eluting in 8%), and glycoprotein IIb/IIIa receptor antagonists were used in 72%. In the subgroup of patients who underwent repeat angiography at 1 year, infarct artery patency was 89% in the PCI group and 25% in the medical therapy group ($P < .001$). At discharge, use of therapy recommended by the American College of Cardiology/AHA guidelines was high in both groups, with a thienopyridine administered to significantly more patients in the PCI group and anticoagulants, nitrates, and hypoglycemic agents administered to significantly more patients in the medical therapy group. Of note, 9% of patients in the medical therapy group crossed-over to PCI.

The 4-year cumulative primary event rate (Table 2, Figure 5) was 17.2% in the PCI group and 15.6% in the medical therapy group (hazard ratio for death, reinfarction, or HF in the PCI versus medical therapy group, 1.16; 95% CI, 0.92-1.45; $P = .20$). Rates of myocardial reinfarction were 7.0% and 5.3% in the 2 groups, respectively (hazard ratio, 1.36; 95% CI, 0.92-2.00; $P = .13$), with only 6 (0.6%) reinfarctions related to the PCI procedure. Rates of death (9.1% vs

Figure 5. *Data from the Occluded Artery Trial (OAT). Kaplan-Meier curves for the primary endpoint, according to the intention-to-treat analysis. Reprinted with permission from Hochman JS et al.[28] Copyright © 2006 Massachusetts Medical Society. All rights reserved.*



9.4%) and NYHA Class IV HF (4.4% vs 4.5%) were similar between the groups. There was no interaction between treatment effect and any subgroup variable, including age, sex, ejection fraction, and diabetes. The investigators concluded that PCI did not reduce the occurrence of death, reinfarction, or HF, and there was a trend toward excess reinfarction at 4 years of follow-up in stable patients with an occluded infarct-related artery 3 days to 28 days after MI.

This landmark trial, which will certainly influence clinical practice, supports the routine use of aggressive secondary prevention without percutaneous coronary intervention as the preferred strategy for stable patients with an occluded infarct artery late following myocardial infarction.

Comment

This landmark trial, which will certainly influence clinical practice, supports the routine use of aggressive secondary prevention without PCI as the preferred strategy for stable patients with an occluded infarct artery late following MI. These unexpected results are contrary to the study hypothesis, despite high PCI procedural success, contemporary use of stents and adjunctive therapy, and sustained infarct artery patency. They raised additional concern about the trend for harm based on increased rates of reinfarction in the PCI group. The reason for this difference in (nonfatal and fatal) reinfarction between the groups is unclear, but it was speculated to be due to the loss of rapidly recruitable collateral flow after patency of the infarct artery was restored in the PCI group. This effect could predispose to reinfarction in the event of spontaneous reocclusion of the infarct artery, particularly in view of the sufficient viability present in 69% of a subgroup that underwent viability scanning. In fact, the potential benefit of attenuation of left ventricular remodeling of an open artery (the premise upon which the trial was based) may be diminished by an excess of nonfatal reinfarction. Indeed, OAT reminds us of the importance of testing conventional wisdom that is fortified by a belief in what seems intuitive, by providing evidence collected from well-designed randomized clinical trials.

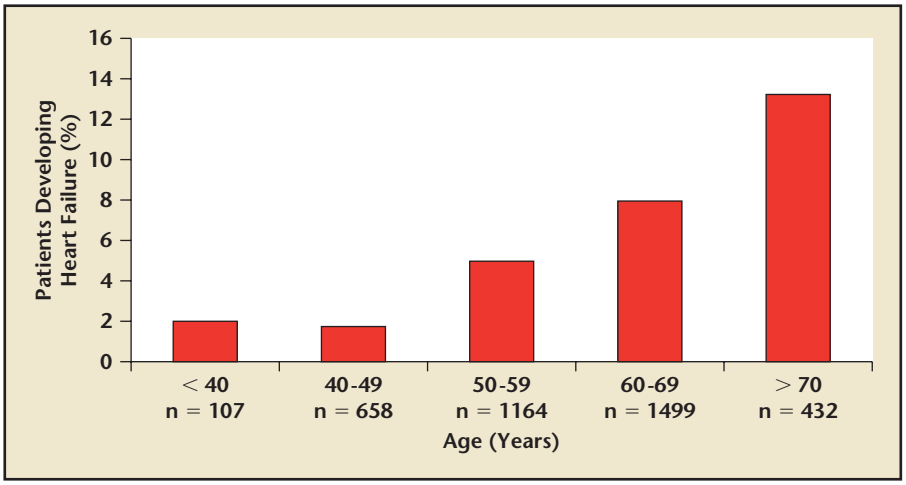
[Alice K. Jacobs, MD, FACC, FAHA]

Prediction of the Development of Heart Failure

In a symposia session, Dr. Marc A. Pfeffer (Brigham and Women's Hospital, Boston, MA) reviewed available data from the International Verapamil-Trandolapril Study (INVEST) of hypertensive patients with CAD.[30,31] The presence of chronic kidney disease was one of the strongest baseline predictors of increased risk, which also included prior HF, diabetes, older age, prior MI, peripheral vascular disease, and smoking. Researchers pooled data from 4 community-based longitudinal studies: the Atherosclerosis Risk in Communities Study (ARIC), the Cardiovascular Health Study (CHS), the Framingham Heart Study, and the Framingham Offspring Study. They found a greater risk for the composite endpoint (incident MI, fatal coronary heart disease, all-cause mortality, and fatal and nonfatal stroke) among patients with chronic kidney disease than without (30.1% vs 13.2%).

Recently, 4098 patients with previous MI who were enrolled in the Cholesterol and Recurrent Events (CARE) Trial were evaluated for chronic kidney disease, which was defined as an estimated glomerular filtration (eGFR) rate of less than 60 mL/min/1.73 m^2 and proteinuria ($> 1+$ protein) on dipstick urinalysis.[32] A total of 371 participants died during about 60 months of follow-up. Compared with patients without proteinuria or impaired kidney function, subjects with both characteristics were at high risk of mortality (hazard ratio 2.39; 95% CI, 1.72-3.30), whereas those

Figure 6. *The impact of age on the development of heart failure after a myocardial infarction in the Cholesterol and Recurrent Events (CARE) trial. Reproduced with permission from Lewis EF et al.*[33]



with only proteinuria or only impaired kidney function were at intermediate risk (hazard ratio 1.69; 95% CI, 1.32- 2.16; hazard ratio 1.41; 95% CI, 1.12 to 1.79, respectively). The results were similar for CV outcomes, including new cases of HF, stroke, and coronary death or nonfatal MI. A graded increase in all-cause mortality risk was seen for severity of renal impairment and degree of proteinuria by dipstick.

Clinicians should be aware that an estimated glomerular filtration rate of less than 60 mL/min and the presence of microalbuminuria with a urine albumin:creatinine ratio higher than 30 mg/g identifies a patient with coronary artery disease at increased risk for heart failure and death.

In this analysis of the CARE trial, Dr. Eldrin F. Lewis (Brigham and Women's Hospital, Boston, MA) suggested that the best way to predict which post-MI patients are at greatest risk for developing HF is to examine the large databases of registry, population, and clinical trial data to determine which patients are surviving their MIs and subsequent discharge and then eventually progressing to HF.[33] In the CARE trial (n ~ 3860), subjects who had survived an MI for at least 3 months had 7 independent predictors of HF, with the most powerful being age (Figure 6). In general, for every 1-year increase in age, there is a 7% increase in risk of HF. The other clinical variables included hypertension, history of MI prior to index MI, diabetes, heart rate, and ejection fraction. The implications of these data are that one of the major age-related variables is a decrease in eGFR that occurs with age, and thus a variety of mechanisms may be at work to predispose to and worsen existing HF. Clinicians should be aware that an eGFR of less than 60 mL/min and the presence of microalbuminuria with a urine albumin:creatinine ratio higher than 30 mg/g identifies a patient with CAD at increased risk for HF and death. This patient should be considered a candidate for aggressive secondary prevention measures and requires strict attention to blood pressure control and frequent office follow-up.

Diagnosis of Heart Failure

The N-Terminal proB-type Natriuretic Peptide Improves the Management of Patients with Suspected Acute Decompensated Heart Failure: Primary Results of the Canadian Multicenter Improved Management of Patients with Congestive HF (IMPROVE-CHF) Study was a late-breaking clinical trials session presented by Dr. Gordon W. Moe (St. Michael's Hospital, Toronto).[34] Like mature B-type natriuretic peptide (BNP), the breakdown fragment N-terminal proB-type natriuretic peptide (NT-proBNP) is a biomarker associated with HF. NT-proBNP is cleared by the kidneys, so it also works as an indicator of mild renal dysfunction in

Main Points

- The clinical trial Carotid Intimal-Medial Thickness in Atherosclerosis using Pioglitazone (CHICAGO) adds to a growing body of literature suggesting that thiazolidinediones possess significant antiatherosclerotic effects.
- The Federal Study of Adherence of Medications (FAME) trial showed that a rather simple program that utilized improved education, medication packaging, and pharmacy oversight can significantly improve adherence to chronic medication use in the elderly.
- The Paclitaxel-Coated Balloon Catheter for In-Stent Restenosis (PACCOCATH ISR) trial, a small pilot study, shows the potential for a paclitaxel-eluting balloon to limit recurrent in-stent restenosis.
- In a substudy of data regarding genetics of aspirin responsiveness, patients who ate chocolate were found to have reduced aggregability, on average taking 130 seconds to clot as compared to 123 seconds in the subjects who did not eat chocolate.
- In the Occluded Artery Trial (OAT), data suggested that percutaneous coronary intervention did not reduce the occurrence of death, reinfarction, or heart failure, and there was a trend toward excess reinfarction at 4 years of follow-up in stable patients with an occluded infarct-related artery 3 days to 28 days after myocardial infarction.
- Data from the International Verapamil-Trandolapril Study (INVEST) of hypertensive patients with coronary artery disease showed that the presence of chronic kidney disease was one of the strongest baseline predictors of increased risk, which also included prior heart failure, diabetes, older age, prior myocardial infarction, peripheral vascular disease, and smoking.

patients with and without HF. This study consisted of 501 patients presenting to Canadian emergency departments with shortness of breath and suspected HF. Just over half of the subjects were men (52%), and the median age was 75 years. Physicians immediately committed to a diagnosis for each patient based on their clinical judgment. Those diagnoses were later judged and confirmed by cardiologists blinded to each patient's NT-proBNP results, which were measured in the emergency department and again at 72 hours following admission in those patients who were hospitalized. The patients were then randomized to receive either usual care or care guided by the NT-proBNP test results. The median level of NT-proBNP in the 227 patients with final diagnoses of HF was 3717 pg/mL, compared to 340 pg/mL in those without HF, levels that straddle the Food and Drug Administration (FDA)-approved cut-point for NT-proBNP of 450 pg/mL for individuals older than 75 years. At 60 days of follow-up, 114 subjects (23%) had died or were hospitalized, with no difference between groups for that combined endpoint. Every 10-fold increase in the NT-proBNP level in the emergency department was associated with a 41% increase in the combined risk of death or rehospitalization at 60 days. This study strongly supports the previously published B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) trial, which demonstrated improved emergency department and hospital efficiency with the routine use of BNP among patients in whom HF is suspected.[35] This trial should help erase any residual skepticism of the routine use of BNP by emergency department physicians in the evaluation of patients with suspected HF. ■

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

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