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Tirofiban vs. Abciximab During PCI

ABSTRACT & COMMENTARY

The do tirofiban and reopro give similar efficacy? (target) Trial, was the first (and thus far, the only) trial to directly compare 2 glycoprotein IIb/IIIa inhibitors in a "head-to-head" fashion.[1] The study was designed to include a broad range of patients undergoing percutaneous coronary intervention (PCI). Any patient at a participating institution without ST-elevation myocardial infarction (MI), or cardiogenic shock, and a > 70% coronary lesion with morphology amenable to stent implantation could be considered for enrollment. In this study, 4809 patients undergoing coronary stent implantation were randomized to receive either abciximab (ReoPro) or tirofiban (Aggrastat). The primary end point of TARGET was a composite of death, nonfatal MI, or urgent target vessel revascularization (TVR) at 30 days. The study was designed and statistically powered to demonstrate "noninferiority" of tirofiban when compared with abciximab. However, the primary end point occurred more frequently in the tirofiban group than in the abciximab group (7.6% vs 6.0%; $P = 0.038$), resulting in a 1.6% absolute risk reduction and a 20% relative risk reduction with abciximab therapy. The difference in the primary end point was driven largely by higher rates of MI in the tirofiban group (6.9% vs 5.4%). Therefore, the TARGET investigators concluded that tirofiban offered less protection from major ischemic events than did abciximab for patients undergoing PCI.

The latest report from the TARGET investigators was presented at this year's ACC meeting and is currently available as a "rapid track" electronic publication on the *Circulation* web site (www.circulationaha.org). It will be published in an upcoming print issue of the journal. In this report, Stone and colleagues provide information about outcomes beyond the 30-day primary end point extending to 6 months of follow-up. In addition, they evaluate outcomes when patients are stratified with respect to the acuity of the clinical syndrome at entry into the study. Of the 4809 patients randomized, 3025 presented with an acute coronary syndrome (ACS), defined as recent Q-wave MI, recent non-Q-wave MI, or unstable angina, the remaining 1784 patients presented with non-ACS, including stable angina, silent ischemia, or "other" clinical syndromes.

Volume 21 • Number 5 • June 2002 • Pages 41-48

INSIDE

As would be expected, the ACS patients constituted an overall higher-risk group, with a higher percentage of females, smokers, left ventricular dysfunction, and prior MI included in the group. When compared with the stable subgroup, patients with ACS in this study had higher rates of death or MI at 30 days and 6 months, and higher rates of TVR at 6 months as well. The presence of ACS was an independent predictor of adverse outcomes at 6 months.

Of the ACS patients, 1511 received abciximab and 1514 received tirofiban. The demographic, clinical and anatomic characteristics, and procedural success rates were similar between the 2 groups, though the ACS patients receiving abciximab were slightly older and more likely to have left anterior descending coronary artery disease with PCI. Patients with ACS treated with abciximab had lower rates of the composite primary end point (death, MI, or urgent TVR) at 30 days when compared to those receiving tirofiban (6.3% vs 9.3%; P = 0.002). The difference in outcomes for ACS patients was again almost entirely attributable to lower rates of MI in patients receiving abciximab (5.8% vs 8.5%; P = 0.004), as there were no significant differences in rates of death or TVR between the 2 groups at 30 days. Of the stable, non-ACS patients, 900 received abciximab and 884 received tirofiban. In contrast, the non-ACS patients did not demonstrate improved outcomes with abciximab when compared to tirofiban therapy, either in terms of the composite primary end point (5.6% vs 4.5%; P = 0.32) or in any individual component of the composite end point.

At 6-months follow-up, there was no statistically significant reduction in the composite end point attributable to abciximab therapy in either the ACS (15.5% vs 18.0%; P = 0.056, with a strong trend favoring abciximab) or the non-ACS (13.4% vs 10.3%; P = 0.056, with a strong trend favoring tirofiban). Of interest, the MI rates at 6 months remained lower only in the ACS patients who received abciximab (7.2% vs 9.8%; P = 0.013). Conversely, TVR rates at 6 months were somewhat higher in the non-ACS patients who received abciximab when compared to those receiving tirofiban (8.4% vs 5.8%; P = 0.04). However, it is interesting to note that neither of these differences translated into a reduction in mortality at 6 months, which was equivalent for abciximab or tirofiban therapy for the ACS, as well as the non-ACS patients. For the ACS and non-ACS groups alike, abciximab resulted in significantly higher rates of thrombocytopenia and higher rates of minor bleeding. However, no differences in major bleeding or transfusion were noted with abciximab administration in either group. (Stone GW, et al. *Circulation*. 2002; 105:r87-r94.)

COMMENT BY SARAH M. VERNON, MD

There is an extensive body of clinical trial data demonstrating the efficacy of glycoprotein IIb-IIIa inhibitors in the reduction of ischemic complications in patients with ACS and in patients undergoing PCI. Taken in total, these trials demonstrate that these drugs, as a class, are particularly useful is improving outcomes in the highest-risk populations of patients they are applied to, namely those with acute MI, with ACS (particularly in the presence of elevated biomarkers or ST depression), and in diabetics. Consequently, the use of glycoprotein IIb-IIIa inhibitors in coronary care units and cardiac catheterization laboratories is widespread, but particularly in the United States where it has been estimated they are used in 80-90% of PCI procedures. With contemporary dosing and adjuvant anticoagulation regimens, these drugs have proven to be safe, but for any individual patient the risk of complications, such as bleeding or thrombocytopenia, is real. In addition, these drugs, as a class, are extremely expensive to administer. Therefore, a strategy for their cost-effective use, including patient selection, choice of agent, dosing and duration, and adjuvant therapy is worthy of ongoing refinement in light of new data as it becomes available.

Despite the results of the initial study demonstrating

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superiority of abciximab at 30 days, the latest analysis of data from TARGET suggests that, for patients without ACS, there is no clear advantage to abciximab, and that at 6 months, tirofiban may provide equivalent, if not improved outcomes for these patients. There may be a role for tirofiban in the treatment of patients undergoing PCI after all, namely those patients presenting with a stable coronary syndrome. Stone et al acknowledge the limitations of the present study and state that these data should be interpreted with caution. This is a post-hoc analysis, as syndrome acuity was neither predefined nor prespecified for subgroup analysis, and probably not adequately powered to definitively evaluate the ACS and non-ACS populations separately. Nonetheless, these results are intriguing and suggest that there may be a relationship between syndrome acuity and response to individual glycoprotein IIb-IIIa inhibitors that could have "important implications for cost-effective medical practice."

There are significant theoretical differences between the drugs in terms of their pharmacology. For example, the monoclonal antibody derived agent, abciximab, binds the MAC-1 and vitronectin receptors of the vascular endothelium, while the small molecule agents, tirofiban and eptifibatide, specifically bind the platelet glycoprotein IIb-IIIa receptor only. Whether this feature of abciximab translates into clinically meaningful differences in its effectiveness remains open to speculation. In addition, many questions remain about optimal dosing for all of these agents to potentially enhance their efficacy and minimize risk. "Point-of-care" measurement of the actual degree of inhibition of platelet aggregation will likely lead to a better understanding of how each of these agents should be administered in a given patient. Direct comparison between the available agents has essentially been limited to TARGET, with the remainder of clinical trial data being placebo controlled or open label. Comparisons between clinical trials can provide some information, but understanding the details of patient selection, dose, duration, and specific definitions of outcomes needs to be taken into account. It is also important to remember that we have little data suggesting that these drugs, as a class, offer significant benefit to low-risk patients with stable syndromes. With these limitations, in clinical practice the selection of the most appropriate and most cost-effective agent for a given patient in many cases becomes a leap of faith. For example, tirofiban has become "dead in the water" for many interventional operators, who may opt for eptifibatide when selecting a small molecule GP IIb-IIIa agent, on the basis of data from the original TARGET trial combination with ESPRIT[2] (a placebo-controlled trial of showing the benefit of eptifibatide in PCI). This has become common practice in many laboratories despite the fact these 2 studies hardly provide a direct comparison between the small molecule agents. The most recent results from the TARGET trial shed no further light on this specific issue. We still don't know which is the superior glycoprotein IIb-IIIa inhibitor (if any) in a clinically stable patient, but perhaps if we ask the right questions it will eventually become clear. ■

References

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2. The ESPRIT Investigators. *Lancet*. 2000;356: 2037-2044.

Sudden Cardiac Death in Cardiomyopathy

ABSTRACT & COMMENTARY

Synopsis: The surprisingly low mortality in the patient population prevented their ability to demonstrate any benefit of ICD therapy in this group.

Source: Bansch D, et al. *Circulation*. 2002;105: 1453-1458.

Bansch and coworkers from germany report the results of a trial of ICD therapy in patients with nonischemic dilated cardiomyopathy (DCM). Patients were eligible for inclusion if they were between 18 and 70 years of age, had recent onset (less than or equal to 9 months), symptoms due to nonischemic DCM, and a left ventricular ejection fraction (LVEF) less than or equal to 30%. Patients had to be in New York Heart Association functional class II or III. Patients who had a history of symptomatic bradycardia or ventricular arrhythmias or those who were listed for heart transplantation were excluded. All patients underwent physical examination, baseline ECG, exercise testing, and echocardiography. Each patient underwent a 24-hour ambulatory ECG and an electrophysiologic study to determine if ventricular arrhythmias were inducible. Patients were then randomized to either receive standard therapy or insertion of an implantable cardioverter defibrillator (ICD). Patients who received an ICD had a VT/VF detection zone programmed to 200 bpm. Patients were followed every 3 months.

The pretrial estimate for mortality in this group was 30% in the first year with 40% of these deaths being sud-

den. The study planned to enroll 1348 patients. After 1 year of follow-up, an interim blinded survival analysis was performed. This indicated that the overall 1-year mortality was only 5.6%. At this point, randomization was stopped due to futility and the patients were then followed throughout an additional 5.5 ± 2 years.

Between July 1991 and March 1997, 104 patients were enrolled in the trial with 50 randomly assigned to ICD treatment and 54 to the control group. The group was 80% male with a mean age of 52 ± 11 years. Two thirds of the patients were in NYHA class II and one third in NYHA class III. The mean ejection fraction (EF) was 24 ± 7%. On a baseline 24-hour Holter monitor, 53% of the patients had nonsustained ventricular tachycardia (VT). Electrophysiologic study induced monomorphic VT in 3 patients and inducible ventricular fibrillation in 10 patients. Ninety-six percent of the patients received an ACE inhibitor. Only a few patients (3.8%) received a beta blocker.

All-cause mortality rates did not differ between the ICD group and the control group after either 1 year (the primary end point) nor after long-term follow-up. After a mean follow-up of 5.5 ± 2 years, 13 patients in the ICD group and 17 in the control group died. Cumulative survival was 92%, 86%, and 73% in the ICD group vs. 93%, 80%, and 68% in the control group after 2, 4, and 6 years, respectively (log rank, $P = 0.554$). Total mortality was highest in those with an EF less than or equal to 21%, intermediate for those with an EF of 22-27%, and lowest for those with an EF greater than or equal to 28%. There were 11 patients who received ICD therapy for VT greater than 200 bpm. Survival in these was diminished compared to those who had no VT documented.

Bansch et al conclude that the surprisingly low mortality in the patient population prevented their ability to demonstrate any benefit of ICD therapy in this group.

■ COMMENT BY JOHN P. DiMARCO, MD, PhD

The study by Bansch et al provides an interesting look at ICD therapy as primary prevention of sudden death in patients with idiopathic DCM. There are now 2 randomized trials of primary ICD therapy in patients with ischemic cardiomyopathy that have shown benefit among those randomized to receive an ICD. In both the Multicenter Automatic Defibrillator Implantation trial (MADIT) and its follow-up MADIT II, a significant improvement in survival was seen after ICD implantation. The cardiomyopathy trial reported here suggests that as much benefit may not be seen in patients with idiopathic dilated cardiomyopathy. Two other studies are now underway that also address this question. The Sudden Cardiac Death-Heart Failure trial enrolled patients with both ischemic and nonischemic cardiomyopathy. This trial which enrolled 2500 patients is still in the follow-up phase. Another study, the DEFINITE trial, has enrolled more than 400 patients with nonischemic cardiomyopathy. This trial also continues in follow-up. Another study, the AMIOVIRT trial from the University of Michigan, has presented a preliminary report showing no improvement with ICD therapy vs. amiodarone therapy in nonischemic cardiomyopathy.

Why should the defibrillator work in ischemic cardiomyopathy but not in dilated cardiomyopathy? The most obvious reason is that therapy for dilated cardiomyopathy has improved dramatically in the last few years. The widespread use of ACE inhibitors, beta blockers, and other interventions has lowered the overall mortality in dilated cardiomyopathy with many deaths now occurring in the terminal stages of hemodynamic deterioration. Amiodarone may also be more effective in patients with nonischemic cardiomyopathies as opposed to those with ischemic cardiomyopathy. Both the GESICA trial and the CHF-STAT trial reported decreased mortality with amiodarone therapy in patients with nonischemic cardiomyopathy. If amiodarone even produces a relatively small benefit, it will be difficult to show benefit from ICD therapy in DCM patients except in a large trial.

This paper also highlights one of the difficulties in planning large-scale mortality trials. Survival estimates made during the planning phase of a trial will often change as therapy for the underlying condition improves. If effective therapy is added, this will lower the event rate and may make it more difficult or impossible to show benefit from the intervention under study. ■

Amiodarone vs. Lidocaine for Shock-Resistant Ventricular Fibrillation

ABSTRACT & COMMENTARY

Synopsis: The use of amiodarone results in a better outcome than use of lidocaine in patients with shock resistant out-of-hospital cardiac arrest.

Source: Dorian P, et al. *N Engl J Med*. 2002;346: 884-890.

Dorian and colleagues performed a double-blind, clinical trial comparing amiodarone with lidocaine in patients with out-of-hospital ventricular fibrillation. Adults with out-of-hospital cardiac arrest in

whom ventricular fibrillation was documented were potential candidates. If ventricular fibrillation was resistant to 3 shocks from an external defibrillator followed by 1 dose of intravenous epinephrine and a fourth defibrillator shock, they were then eligible for entry into the trial. Drug administration kits were distributed to ambulances in a balanced randomized order in blocks of four. A double-blind, double-dummy technique was used. Each kit contained either active amiodarone and a lidocaine placebo or active lidocaine and an amiodarone placebo. Amiodarone was administered at a dose of 5 mg/kg of estimated body weight. Lidocaine was given at a dose of 1.5 mg/kg estimated body weight. Both drugs were infused rapidly into a peripheral vein and then further defibrillator shocks were delivered as necessary. If ventricular fibrillation persisted after the next shock, a second dose of the study drug could be administered (1.5 mg of lidocaine per kilogram or 2.5 mg of amiodarone per kilogram) together with placebo, and attempts at resuscitation were continued. The primary study end point was survival to admission to the hospital intensive care unit. Patients who died in the field or in the emergency department were not considered to have been admitted. Secondary end points included survival to discharge from hospital and adverse events.

Between November 1995 and April 2001, 347 patients were enrolled in the trial. The mean interval from the time at which the paramedics were dispatched to the scene and their arrival at the patient's side was 7 ± 3 minutes and the mean interval from dispatch to the time of drug administration was 25 ± 8 minutes. The group was approximately 80% male with a mean age of 67 years. Sixty percent of the patients had a history of prior cardiac disease. The cardiac arrest had been witnessed in 77% of the patients. Twenty-seven percent of the patients had received bystander cardiopulmonary resuscitation. Before receiving the study drug, patients had received 5 ± 2 shocks. Twenty-four patients in the amiodarone group (13%) and 11 (7%) in the lidocaine group had manifested a transient return of spontaneous circulation before receiving study drug. Eighty seven patients in the amiodarone group and 86 patients in the lidocaine group received a second dose of the study drug.

In the amiodarone group, 41 of 180 patients (22.8%) survived to hospital admission as compared with 20 of 167 patients (12%) in the lidocaine group ($P = 0.009$). In addition to treatment with amiodarone, other factors that significantly influenced survival to hospital admission were the length of time to the administration of the drug and the presence or absence of a transient return of spontaneous circulation before the administration of the study drug. The adjusted odds ratio for survival to hospital admissions in recipients of amiodarone as compared with recipients of lidocaine was 2.49 ($P = 0.007$). There were no differences between the treatment groups in the proportion of the patients who needed treatment of bradycardia or hypotension. Asystole was more common in the lidocaine group (40 of 142 patients, 28.9%) than in the amiodarone group (28 of 152, 18.4%). Among the 41 patients who received a hospital admission in the amiodarone group, 9 (5%) survived to hospital discharge as compared with 5 of the 20 initial survivors in the lidocaine group (3% of the entire group).

Dorian et al conclude that the use of amiodarone results in a better outcome than use of lidocaine in patients with shock resistant out of hospital cardiac arrest.

COMMENT BY JOHN P. DiMARCO, MD, PhD

Although lidocaine has traditionally been the intravenous antiarrhythmic drug of choice in the treatment of shock-resistant ventricular fibrillation, there are few data supporting a role for lidocaine in this setting. It has remained in resuscitation algorithms mostly by default since no other agent had been shown to be superior. Several years ago the amiodarone in out-of-hospital resuscitation of refractory sustained ventricular tachycardia (ARREST) study (*N Engl J Med*. 1999;341:871-878) showed improved survival to hospital admission when amiodarone was compared to placebo in patients with shock-resistant ventricular fibrillation. The current study confirms the benefit of amiodarone over lidocaine in this setting.

The mechanism by which amiodarone produces its effect is uncertain. Amiodarone has complex electrophysiologic properties including: noncompetitive beta-adrenergic blockade, calcium channel blockade, sodium channel blockade, and prolongation of the action potential. However, in studies looking at the onset of these effects after IV administration, beta-adrenergic blockade has been the effect seen first. It is possible that what we are seeing here is an early effect due to noncompetitive beta-adrenergic blockade on either the tendency to re-fibrillate after an initial defibrillation or an effect on defibrillation threshold itself. However, it should be remembered that chronic amiodarone therapy does not lower defibrillation thresholds.

Intravenous amiodarone is relatively costly and has a short shelf life. In its current formulation, which requires a solubilizing agent, it may cause hypotension and phlebitis after peripheral injection. These factors argue against its inclusion early in a resuscitation algorithm. An effective alternative to amiodarone would be of value. If the results seen in this trial and in the ARREST study are really due to beta-adrenergic blockade, then

use of other less toxic and more readily available intravenous beta-adrenergic blockers might produce similar results.

It is also important to note that amiodarone did not improve survival to hospital discharge. This is not an unexpected finding since the mean time for administration was 25 minutes after collapse. The patients who received the drugs earlier after arrest seemed to do better. Further trial in out-of-hospital resuscitation should seek to improve survival to discharge, the most meaningful clinical measurement of drug efficacy. ■

Hypertension Therapy—Becoming More Interesting!

ABSTRACTS & COMMENTARY

Synopsis: In patients with hypertension and LVH, despite equal blood pressure lowering effects, losartan reduced cardiovascular events more than atenolol. These effects were more pronounced in diabetics.

Sources: Dahlof B, et al. *Lancet.* 2002;359:995-1003; Lindholm LH, et al. *Lancet*. 2002;359:1004-1010.

Two new publications suggest that specific choice of agent for control of blood pressure may be more important than previously believed. One of the largest trials in hypertension therapy, cardiovascular morbidity and mortality in the losartan intervention for endpoint reduction in hypertension study (LIFE), a randomized trial against atenolol, tested the hypothesis that interference with the renin-angiotensin system (RAS) may be as important as blood pressure control in reducing cardiovascular morbidity and mortality. The primary hypothesis of this study is that a selective angiotensin-II type 1 receptor blocker (ARB) would be more effective in reducing cardiovascular (CV) morbidity and mortality than the beta blocker atenolol in hypertensive patients with ECG evidence of left ventricular hypertrophy (LVH). The study was multinational, and enrolled 9193 subjects age 55-80 with essential hypertension, randomized to either losartan or atenolol. "Entry" baseline sitting blood pressure (BP) was 160-200/95-115 mm Hg. Patients had to have ECG LVH. The primary end point was a combination of CV death, myocardial infarction (MI), and stroke. Other secondary end points were assessed. Trial duration was a minimum of 4 years. Initiation of drug therapy was stepwise; all patients received hydrochlorothiazide (HCTZ) 12.5 mg. If blood pressure control was not adequate on the maximum dose of each drug (losartan or atenolol 100 mg daily plus HCTZ up to 25 mg), other agents could be added. A substudy indicated that most individuals had LVH on echocardiography. The trial was stopped when sufficient prespecified primary end points occurred. Patients enrolled between 1995-1997 from all Scandinavian countries, Iceland, the United Kingdom, and the United States. The 2 groups were closely matched in all characteristics; mean follow-up was 4.8 years. More than 80% of individuals were maintained on the initial study drug. The daily mean dose of losartan was 82 mg; atenolol 79 mg.

Results: Blood pressure was reduced in both groups to a comparable level by 40/17 mm Hg. Blood pressure at the last visit was 144/81 in both groups. Half of all subjects had a final sitting BP of ≤ 140/90. The adjusted primary end point demonstrated a 13% risk reduction with losartan, with curve separation beginning early and continuing in year 5-6, $P = 0.02$. Stroke outcome was robustly reduced by losartan with a 25% RR decrease, $P = 0.001$. ECG LVH was decreased more with losartan. Of interest, the ARB reduced the incidence of new diabetes during the study by 25%. Overall event rates were more than 2% per year, (11% for losartan and 15% for atenolol); thus, these subjects meet high-risk criteria defined by the NCEP-ATP-III scoring system. MI was not reduced in the ARB group. Dahlof and colleagues believe that LIFE is the first study to demonstrate a major clinical end point difference between 2 active treatment groups in hypertension, and stress that the comparable BP lowering effects within the 2 cohorts indicate that the ARB has additional protection against stroke beyond reducing BP. They state that although MI incidence did not differ between the 2 groups, atenolol presumably provided the cardioprotection common to all beta blockers, thus indicating an equivalent ARB protective effect. They suggest that the benefit of losartan "could result from increased protection against the detrimental effects of angiotensin II."

In a companion report, the LIFE investigators analyzed the large number of diabetics in the study. These results are actually more robust than those in the primary study. In this study, 1195 diabetics (13% of entire study) who met LIFE criteria were enrolled. Mean age was 67 and blood pressure was 177/96. At follow-up of 4.7 years, BP reduction was comparable of 18/11 mm Hg, to a mean final pressure of 147/79. The primary end point was reduced by 24%, $P = 0.031$. Cardiovascular mortality was reduced by 37%, $P = 0.028$, and all-cause mortality by 39%, $P = 0.002$. Compared to the majority of LIFE subjects without diabetes, the diabetic patients had a higher BMI, coronary risk score, and prevalence of

cardiovascular disease. In addition, baseline BP was slightly higher. A primary end point occurred in 20% of the diabetics. Reduction of stroke or MI was not different between the 2 groups. Heart failure admissions were reduced by 41% with losartan, $P = 0.019$. As in the entire LIFE study, fewer adverse events occurred with losartan. Albuminuria was less frequent in the ARB group. In addition, ECG LVH was considerably less with losartan than atenolol. Lindholm and associates note that in the 20% of diabetics not previously with hypertensive therapy, the results were even more impressive. They suggest that "lowering blood pressure may be even more important than glucose control in diabetics." Other studies in diabetics, but not all, including CAPPP and HOPE, are compatible with these results. Lindholm et al again stress the detrimental role of angiotensin II, and note that LVH is a risk marker for increased morbidity and mortality in diabetic patients.

■ COMMENT BY JONATHAN ABRAMS, MD

LIFE is a landmark study in some respects, as it convincingly demonstrates that an agent that interferes with the angiotensin cascade with equivalent BP lowering to a beta blocker, has no downside and confers a small but definite reduction in morbidity, most of which is stroke. The data in the diabetics are even more robust, and consistent with the results of captopril in diabetic patients in CAPP. The HOPE study also enrolled a larger number of diabetics, not all hypertensive, who had an additional major CAD risk factor. In HOPE, patients at high vascular risk responded favorably to interference with the RAS provided by the ACE inhibitor ramipril. HOPE was not a comparative trial with another active agent, but did demonstrate that in high-risk patients, interfering with A-II is a big plus!

There was no reduction in MI in either the main cohort or in the diabetic subanalysis. The primary end point was reduced to 18% with losartan vs. 23% with atenolol; the CV mortality was 6% vs. 10%; both statistically significant. These data support that standard treatment of hypertension should include an ACE inhibitor or ARB based on the HOPE and LIFE trials. In the hypertensive diabetic, using either of these drug classes would appear to be mandatory, and HOPE suggests that an ACE inhibitor should also be used for diabetics those who do not have hypertension. Approximately half of type II diabetics will have hypertension, which imparts a substantial augmentation of CV risk. Dahlof et al's contention that equivalence of MI events between the 2 drugs suggests that losartan is cardioprotective is interesting. Stroke reduction is an important end point itself, and LIFE is very good news in this regard. Diabetics in LIFE were at an even greater risk, as indicated by their higher event rates compared to nondiabetics. The reduction of new diabetes in LIFE and in HOPE suggests possible improvement of insulin resistance and/or anti-inflammatory actions are features of these 2 related drug classes. ■

Genetic Variance in the Response to Diuretic Therapy for Hypertension

ABSTRACT & COMMENTARY

Synopsis: Diuretics are safe and effective in preventing complications of hypertension and are "the preferred first-time medication" for treatment of hypertension.

Source: Psaty BM, et al. *JAMA*. 2002;287: 1680-1689.

A recent report suggests that pharmacogenetic analysis may be used in the future in drug selection for common conditions. This study, from the Cardiovascular Health Research Unit in Seattle, asked the question whether a genetic variance in α-adducin, a gene associated with renal sodium balance, might result in different responses to a diuretic in carriers of a variant allele in whom high rates of renal tubular sodium reabsorption have been documented. The Gly460Trp variant of the α-adducin gene has been associated with renal sodium retention and salt-sensitive hypertension. A polymorphism has been described as a potential cause of hypertension in some populations. Psaty and colleagues hypothesized that carriers of 1 or 2 copies of the variant allele, who have increased renal sodium reabsorption, would have an augmented response to diuretics. They further asked whether the phenotype of salt-sensitivity, independent of blood pressure, might be related to events. This is a population-based case-control study in hypertensive patients, using an analysis of hypertension agents. The primary hypothesis is that pharmacologic treatment of hypertension with a diuretic would have a lower event rate in carriers of the α-adducin variant compared to normal, wild-type subjects. Cases from the Group Health Cooperative (GHC) in Seattle were identified with treated hypertension that had survived a myocardial infarction (MI) or stroke between 1995 and 1998. Controls were identified using a stratified random sample, and were matched with the MI cases by age, sex, and year of the index event. Controls were enrolled

at a ratio of 2-to-1 for men and 3-to-1 for women. Careful review of the GHC outpatient medical records, blood sampling, and medical interview were carried out using the GHC computerized pharmacy database information on anti-hypertensive therapy. Users of a specific drug had to be taking the agent for at least 30 days prior to the index event date; the majority of subjects used these agents for years. Compliance was assumed to be 100%. Hypertensive drugs analyzed included diuretics, beta blockers, ACE Inhibitors, calcium channel blockers, and other vasodilators. The adducin-variant was assayed by using standard PCR techniques. Participants were classified as either homozygote carriers of the adducin-wild-type genotype (normals) or those with 1 or 2 copies of the α-adducin-variant TRP460 allele. Odds ratios were subsequently calculated for cases and controls. The primary analysis consisted of 206 MI cases, 117 stroke cases, and 715 controls. There were same baseline differences between cases and controls, with a greater burden of CAD risk factors in those who had an MI. The frequency of the adducin-gene variant was > 35% in both groups. Current users of a diuretic had over 10 years of exposure vs. 3.7 years for noncurrent users.

Results: Among the wild-type carriers, ie, normals, the use of diuretics for hypertension was not associated with an increased risk of MI or stroke. For prior users, the adducin-variant was associated with a modest increase in risk (odds ratio [OR], 1.56; confidence interval [CI], 1.09-23). However, for adducin-variant carriers who took diuretics, the odds ratio was reduced by 33% (CI, 0.51-1.17). Diuretic therapy in the 385 carriers of the adducin-variant was associated with a markedly lower risk of major vascular events, but there was no association of such events with other hypertensive drugs. The risk reduction OR was 0.49; CI 0.32-0.77. The data were comparable for both stroke and MI. Other medications did not influence the results, and "the interaction between diuretic use and the adducin-variant was specific to diuretics," and was more pronounced in the homozygotes. In fact, homozygotes that took diuretics had no history of an MI or stroke. Psaty et al conclude that there is a significant interaction with the adducin-Trp460 variant and use of diuretics with respect to the risk of a combined outcome of first nonfatal MI or stroke, whereas among carriers of the wild-type genotype, diuretic therapy was not associated with any effect on risk. Risk reduction among the carriers was robust at approximately 50%, and was the specific to diuretic therapy. Psaty et al admit that the mechanism by which diuretic use reduces the risk of MI or stroke is uncertain, but is in some way related to the effects of diuretics on sodium excretion and absorption. Diuretics should reverse the physiologic status of the variant patients who have an increased sodium reabsorption state. "Salt-sensitivity, independent of blood pressure, has been associated with an increased risk of cardiovascular events." Psaty et al point out that other genetic polymorphisms have been associated with increased rates of hypertension. They believe that identification of various genes involved in blood pressure control may ultimately result in novel drug class design. Future research may improve "the safety and efficacy profile of commonly used medications." They suggest that if this data can be validated, future efforts to screen hypertensive patients for selective genetic polymorphisms might be a practical way to individualize drug treatment and maximize effectiveness as well as safety. Finally, they conclude that diuretics are safe and effective in preventing complications of hypertension and are "the preferred first time medication" for treatment of hypertension.

■ COMMENT BY JONATHAN ABRAMS, MD

I believe that this is an exciting study, as it appears to suggest a major role for pharmacogenetics influencing physician choice of drug therapy for hypertension. Mechanistically, there are little data available; the study suggests that individuals carrying 1 or 2 copies of the variant gene, when exposed to a diuretic for a protracted period of time, have a decreased risk in developing an MI or a stroke. There was no relationship found for the gene polymorphism for any other class of hypertensive agent. Other genetic variants have been identified, particularly the angiotensin insertion-deletion variant polymorphism, which has been extensively studied. The concept that a "simple drug" such as a diuretic might have different long-term effects on major vascular events, depending on a particular genetic variant is both fascinating and stimulating. In that the individuals with the gene variant are common and had a 50% lesser likelihood of having a stroke or MI during the observational period if treated with a diuretic, it seems clearly worth confirming these data. If these turn out to be valid, this data would predict a major role for genotyping to guide hypertension therapy in the near future. ■

CME Question

22. New evidence suggests that abciximab during PCI is superior to tirofiban for:

a. acute coronary syndromes.
b. reducing mortality.
c. reducing instent restenosis.
d. minor bleeding complications.