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INSIDE

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Atorvastatin Reload Prior to PCI for Patients on Chronic Statin Therapy

ABSTRACT & COMMENTARY

By Andrew J. Boyle,, MD

Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

Dr. Boyle reports no financial relationships relevant to this field of study.

Source: Di Sciasio G, et al. Efficacy of Atorvastatin Reload in Patients on Chronic Statin Therapy Undergoing Percutaneous Coronary Intervention. Results of the ARMYDA-RECAPTURE (Atorvastatin for Reduction of Myocardial Damage During Angioplasty) Randomized Trial. *J Am Coll Cardiol.* 2009;54:558-565.

THE ARMYDA (ATORVASTATIN FOR REDUCTION OF MYOCARDIAL Damage During Angioplasty) series of randomized, controlled trials has assessed the role of atorvastatin loading prior to percutaneous coronary intervention (PCI) in both stable and unstable coronary syndromes. In patients who are naïve of statin therapy, a loading dose of atorvastatin prior to PCI reduces the incidence of periprocedural myocardial infarction (MI). However, many patients referred for PCI already are receiving statin therapy. Whether a repeat loading dose of atorvastatin in patients who are on chronic statin therapy also reduces periprocedural events was not known. In the latest of the series, the ARMYDA-RECAPTURE study, the authors addressed this issue, performing a multi-center, randomized, controlled trial of atorvastatin reload versus placebo prior to PCI in patients on chronic statin therapy.

Patients who were taking any type of statin therapy at any dose for at least 30 days, and who were referred for PCI for either stable angina or ischemia or non-ST elevation acute coronary syndromes (ACS), were screened. Exclusion criteria included ST elevation, ACS with high-risk features, requiring emergency coronary angiography, abnormal liver function tests, left ventricular ejection fraction < 30%, renal failure with serum creatinine > 3mg/dL, or a history of muscle or liver disease. Patients were randomized to either atorvastatin (80 mg loading given 12 hours before coronary angiography,

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with a further 40 mg dose approximately two hours before the procedure, n = 192) or placebo at the same times (n = 191). All patients received aspirin 100 mg/day and clopidogrel 600 mg before the procedure, and continued aspirin indefinitely and clopidogrel 75 mg daily for at least one month, but for 12 months for those receiving a drug-eluting stent or presenting with ACS. All patients received atorvastatin 40 mg/day regardless of treatment assignment or prior statin therapy. The primary endpoint was 30-day incidence of MACE (major adverse cardiac events), defined as cardiac death, MI, or target vessel revascularization. Secondary endpoints were MI, serum C-reactive protein (CRP) levels, and MACE in prespecified subgroups.

The baseline characteristics were well matched between cohorts and were typical of coronary intervention trials, being predominantly male, mean age 66 years, and a 36% diabetes prevalence. Nearly half the patients (46%) presented with ACS. The mean duration of statin therapy prior to the procedure was nine months in both groups. The primary endpoint of 30-day MACE occurred in 3.7% in the atorvastatin group and 9.4% of the placebo group ($p = 0.037$). This was primarily driven by higher rates of periprocedural MI (3.7% vs. 8.9% respectively). Patients with ACS had lower MACE rates with atorvastatin reload (3.3% vs. 14.8%; $p = 0.015$), but patients with stable angina did not (4.0% vs. 4.9%; $p = 0.98$). CRP levels did not differ between groups before or after PCI. The authors performed multivariable analysis to identify predictors of risk of 30-day MACE. Atorvastatin reload was associated with a 50% reduction in relative risk of MACE ($p = 0.039$), and there was no difference in the benefit found when adjusting for the type of stent or antithrombin used during the index procedure. Logistic regression revealed an 82% relative risk reduction in MACE with atorvastatin reload in patients presenting with ACS (OR 0.18, 95% CI 0.10 to 0.83; $p = 0.027$) but no reduction in patients with stable angina (OR 0.74, 95% CI 0.20 to 2.9; $p = 0.70$). DiSciasio et al conclude that reloading with high-dose atorvastatin improves the clinical outcome of patients on chronic statin therapy undergoing PCI.

■ **COMMENTARY:**

Patients on chronic statin therapy presenting with ACS had reduced incidence of periprocedural MI with atorvastatin reloading. This finding is in keeping with the results of previous ARMYDA studies, and has direct clinical relevance. While the exact mechanism by which atorvastatin reduces periprocedural myocardial necrosis remains unknown, DiSciasio et al postulate several possible mechanisms. These include a reduction in inflammatory cytokine release, possible antiplatelet effects of atorvastatin, and recruitment of endothelial progenitor cells to the site of injury to stimulate the healing response. Whatever the mechanism, the results of the present study are consistent with prior studies in statin-naïve patients with ACS who also derive benefit from atorvastatin loading before PCI. Importantly, the authors noted no benefit from atorvastatin reload in patients on chronic statin therapy who presented with stable angina or ischemia.

Notably, the use of glycoprotein IIb/IIIa inhibitors was low in this study (12%), despite the fact that half the patients presented with acute coronary syndromes. It is not known if these results would hold true if more patients received IIb/IIIa inhibitors. Thus, the results may not be directly applicable in the United States, where IIb/IIIa inhibitor use is much more common. ■

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New data on Warfarin Therapy for Atrial Fibrillation

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Singer DE, et al. The net clinical benefit of warfarin anti coagulation in atrial fibrillation. *Ann Int Med*. 2009; 151:297-30 5.

Current recommendations for stroke prophylaxis with warfarin for patients with atrial fibrillation do not take into account the risks of hemorrhage. Thus, Singer et al from Kaiser Permanente studied more than 13,000 patients with non-valvular atrial fibrillation to estimate the net clinical benefit of warfarin therapy for atrial fibrillation (reduction in thromboembolism minus the increase in intracranial hemorrhage). The mean age of the subjects was 73 years, and 20% had no major risk factors for stroke based upon CHADS2. At entry, about half the patients were receiving warfarin, and tended to have a higher prevalence of stroke risk factors, except for those age > 75 years. Over a median follow-up of six years, there were 1,092 embolic events (1,017 strokes) and 299 intracranial hemorrhage events (193 on warfarin). The annual rate of stroke or systemic embolic events was 2.1% in those not on warfarin and 1.3% in those on warfarin. The annual rate of intracranial hemorrhage was 0.32% in those not on warfarin and 0.58% in those on warfarin. The adjusted net clinical benefit of warfarin was 0.68 adverse events prevented per 100 person years. The benefits of warfarin were observed to increase as the risks for thromboembolism increased, but harm increased only modestly. Prior stroke was the strongest risk factor for subsequent stroke and intracranial hemorrhage. The net clinical benefit increased with the presence of any risk factor except hypertension. Also, net clinical benefit increased with age, being near zero at ages < 75 years and as the CHADS2 score increased above one. Singer et al concluded that a risk assessment that includes the risk of thromboembolism and intracranial hemorrhage provides a better basis for decisions regarding warfarin therapy in patients with non-valvular atrial fibrillation.

■ COMMENTARY

When faced with starting a patient with atrial fibrillation on warfarin, many physicians demur for a variety of reasons. One is fear of major bleeding. The downsides to warfarin therapy are often applied irrationally to our decision making, as there is no equivalent of the CHADS2 score for the risk of warfarin. Thus, this analysis of the Kaiser Permanente database on warfarin therapy for atrial fibrillation is of interest because it estimates net clinical benefit of warfarin by subtracting the risk of intracerebral hemorrhage, the most serious major bleeding event, from the predicted benefits of treatment based on CHADS2.

There are several clinically useful points made by this analysis. First, the risk of stroke in non-valvular atrial fibrillation is lower now than that observed in the up to 20-year-old prior studies (2% vs. 5%). This makes consideration of adverse effects even more compelling. Second, the risk of stroke increases considerably with increasing CHADS2 score: one point each for congestive heart failure, hypertension, age > 75 years, and diabetes, and 2 points for prior stroke. However, the risk of intracerebral hemorrhage is relatively constant across CHADS2 scores. Thus, the higher the CHADS2 score, the greater the net clinical benefit. In their data, a CHADS2 score of two or more would seem worth considering warfarin therapy. Finally, the net benefits of warfarin increase significantly over age 75 years. Treatment with warfarin should seriously be considered in such individuals, unless there are contraindications to its use.

The strengths of this study include the large population, with ample numbers of events and a relatively long follow-up period. Also, the events were carefully validated. This study represents best practices because in this closed population, INRs were tightly controlled to minimize complications. The major weakness is that it is a non-randomized, observational study. Hence, it is likely that patients at higher risk of stroke and with fewer potential contraindications were treated with warfarin, exaggerating the benefits and minimizing the risks, which will confound the results. Also, concomitant aspirin or other antiplatelet drug use was not recorded for this study, but is estimated to be about half the subjects. Finally, no specific predictors of intracranial bleed were identified, so an estimated net clinical benefit cannot be calculated for each individual. Prior stroke carries a two-point weight in the CHADS2 scoring system because it carries the highest risk of stroke, but this study showed it also carried the greatest risk of an intracranial hemorrhage on warfarin; the proverbial double-edged sword.

My take on this study is that the risk vs. benefit of warfarin is much narrower than previously thought, but warfarin should be seriously considered in those > 75 years old or with a CHADS2 score of two or more, unless they have a prior stroke; then, consultation with a neurologist should be sought before starting warfarin. ■

An Alternative to Warfarin Therapy for Atrial Fibrillation

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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Dr. DiMarco is a consultant for Novartis, and does research for Medtronic and Guidant.

Source: Holmes DR, et al. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomized non-inferiority trial. *Lancet*. 2009;374:534-542

Stroke is the most dreaded complication of atrial fibrillation. The left atrial appendage is thought to be the source of many of the emboli in patients with atrial fibrillation. Although anticoagulation with warfarin is effective, warfarin therapy can be difficult to many patients due to unstable INR levels and increased risk for bleeding. This paper describes the use of a new device for occlusion of the left atrial appendage in patients with atrial fibrillation.

The WATCHMAN device is an expandable, nickel titanium (nitinol) frame structure with fixation barbs and a permeable polyester fabric cover. The devices are implanted percutaneously via a transseptal approach to seal the ostium of the left atrial appendage. The PROTECT AF study, reported here, was a randomized trial comparing the efficacy and safety of percutaneous closure of the left atrial appendage with this device compared to chronic warfarin therapy.

Adult patients with paroxysmal persistent or permanent nonvalvular atrial fibrillation were eligible for enrollment if they had one or more risk factors for stroke. All patients had to be eligible for warfarin therapy. Patients were randomly assigned to the intervention or control groups in a 2:1 ratio. Patients allocated to left atrial appendage closure had a WATCHMAN device implanted in the catheterization laboratory. Implantation was guided by fluoroscopy and transesophageal echocardiography (TEE) to ensure proper positioning and stability. After implantation, intervention patients were treated with warfarin for 45 days. TEE imaging was performed at 45 days, 6 months and 12 months to assess residual peri-device leakage, device stability, and position. Patients with complete closure of left atrial appendage documented were allowed to stop warfarin. They were then treated with clopidogrel and aspirin until the six-month visit, and aspirin thereafter. Patients in the control group received warfarin for the duration of the study, with a target INR between 2.0 to 3.0. Both groups were seen in follow-up at 45 days and at 6, 9, and 12 months after randomization. Neurologic assessments were performed at baseline, 12 months, and 24 months. The study was a non-inferiority comparison of warfarin to the WATCHMAN device for the composite endpoint of stroke, cardiovascular or unexplained death, or systemic embolism. The primary composite safety endpoint consisted of bleeding events or procedure-related complications.

The trial randomized 707 patients, with 463 assigned to device closure of the left atrial appendage and 244 assigned to chronic warfarin therapy. Device implantation was attempted in 449 patients, but 41 did not have a successful implantation. At the 45-day follow-up, 349 (86%) of the 408 patients who actually had an implanted device met TEE criteria for left atrial appendage closure and were able to stop warfarin. By six months, 92% of these 408 patients had met criteria for closure. In the control group, therapeutic INRs were achieved in 66% of the study visits. Left atrial appendage closure was non-inferior to warfarin in terms of the primary efficacy endpoint. This was 3.0 per 100 patient years in the intervention group vs. 4.9 per 100 patient years in the control group. At two years, the cumulative primary event rate for the intervention group was 5.9%, compared with 8.3% for the control group. Subgroup analysis showed consistent results across all subgroups. Additional observations were reported. The rate of ischemic stroke was higher in the intervention group than in the control group, primarily due to five patients who had periprocedural events related to air embolism. After the immediate periprocedure period, ischemic stroke rates were similar, with 1.3 events per 100 patient years in the intervention group compared with 1.6 events per 100 patient years in the control group. There were five hemorrhagic strokes in the control group, compared to only one hemorrhagic stroke in the intervention group. The latter occurred during the 45-day post-implant period while the patient was on warfarin. There were 21 deaths in the intervention group and 18 deaths in the control group. The cumulative mortality rates for the intervention and control groups were 3.0% vs. 3.1% at one year and 5.9% vs. 9.1% at two years.

Major complications were noted in the intervention group. A serious pericardial effusion occurred in 22 (4.8%) of the patients. Of these, 15 were treated with pericardiocentesis and seven required surgical drainage. Device embolization was noted in three patients. Pericardial effusions that did not require drainage were noted in eight additional patients. One patient in the intervention group suffered an esophageal tear and one had a procedure-related arrhythmia. Major bleeding was noted in 4.1% of the patients in the control group vs. 3.5% in the intervention group. Device-related complications decreased with operator experience.

Holmes et al concluded that percutaneous closure of the left atrial appendage using the WATCHMAN device was non-inferior to warfarin in terms of stroke, cardiovascular death, and systemic embolism. Although there were

a significant number of periprocedural adverse complications, long-term outcomes were similar.

■ **COMMENTARY**

It is well established that warfarin markedly reduces the risk of stroke in patients with nonvalvular atrial fibrillation. However, up to one-third of patients are not candidates for warfarin because of risk factors for bleeding at baseline. If warfarin is started, major bleeding occurs in up to 5% to 10% of patients during the first months of therapy and then at a rate of at least 25 per year. The genetic variability in warfarin metabolism, and a high potential for food and drug interactions, make chronic warfarin therapy inconvenient and challenging.

For these reasons, development of a simple and safe method that would reduce stroke risk in patients with atrial fibrillation without the need for warfarin would be highly attractive. This paper describes an initial experience with an innovative device. Although placement is technically difficult and, in this early series, was associated with a significant risk for complications, it is highly likely that increased operator experience and modifications of the device itself will increase the safety profile over time. Long-term follow-up, however, will be necessary to ensure that the promising results seen in this paper are maintained during truly long-term therapy. ■

A New Antiplatelet Agent for Patients with ACS

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MD, PhD

Source: Wallentin L, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:e-pub ahead of print.

Dual antiplatelet therapy with aspirin and clopidogrel has become the standard of care for patients suffering an acute coronary syndrome (ACS). However, there remains a significant incidence of recurrent ACS and mortality even in patients treated with dual antiplatelet therapy. Furthermore, clopidogrel is an irreversible platelet inhibitor, and patients requiring urgent surgery are at higher risk of bleeding if operated on within 5-7 days of clopidogrel use. There remains a need for more effective platelet inhibition with a reversible antiplatelet agent. Ticagrelor is an orally active antiplatelet drug that acts on the P2Y12 ADP receptor on the platelet surface (the same receptor targeted by clopidogrel) to produce a more efficient platelet inhibition than clopidogrel, which is also reversible. Wallentin et al performed a large, multi-center, randomized, controlled, double-blind trial, the PLATO study, to compare ticagrelor and clopidogrel in patients presenting with ACS.

Enrollment criteria were ST elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTEACS) with high-risk features. High-risk NSTEACS were ones with at least two of the following: ST segment deviation, elevated biomarkers, or at least one risk factor (age > 60, prior myocardial infarction [MI], CABG or stroke, known coronary artery disease [CAD] or cerebrovascular disease with > 50% stenosis, diabetes, peripheral arterial disease, or chronic renal impairment). Exclusion criteria were contraindication to antiplatelet therapy, need for anticoagulation, increased risk of bradycardia, and concomitant therapy with strong cytochrome P450 3A inhibitors or inducers. Patients were randomly assigned to receive ticagrelor (180 mg loading dose, followed by 90 mg bid; n = 9,333) or clopidogrel (300 mg loading dose if naïve, followed by 75 mg daily; n = 9291). Medications were administered a median of five hours after admission and 11 hours after onset of symptoms. All patients also received aspirin (preferred loading dose 325 mg, followed by 75-100 mg daily). Those undergoing percutaneous coronary intervention (PCI) received an extra dose of drugs at the time of the procedure (ticagrelor 90 mg or clopidogrel 300 mg).

The primary endpoint, a composite of vascular death, MI, and stroke, occurred in 9.8% of the ticagrelor group and 11.7% of the clopidogrel group at 12 months (hazard ratio 0.84; $p < 0.001$). There were multiple predefined secondary endpoints in this study. For patients undergoing invasive management strategy, ticagrelor resulted in lower primary endpoint (8.9% vs. 10.6%; $p = 0.003$), and lower rate of stent thrombosis (1.3% vs. 1.9%; $p = 0.009$). Compared to clopidogrel, ticagrelor resulted in lower rates of MI (5.8% vs. 6.9%; $p = 0.005$), vascular death (4.0% vs. 5.1%; $p = 0.001$), and total mortality (4.5% vs. 5.9%; $p < 0.001$). There was no difference in stroke rate between groups, but a trend toward higher hemorrhagic stroke in the ticagrelor group (0.2% vs 0.1%; $p = 0.10$). There was no difference between groups in major bleeding, fatal or life-threatening bleeding. However, the ticagrelor group had higher non-CABG-related major bleeding (4.5% vs 3.8%; $p = 0.03$)

and fatal intracranial bleeding (0.1% vs. 0.01%; p = 0.02). On the other hand, the ticagrelor group had fewer episodes of other types of fatal bleeding (0.1% vs. 0.3%; p = 0.03).

Ticagrelor was not without side effects. Dyspnea was more common with ticagrelor (13.8% vs. 7.8%; $p < 0.001$), as was a rise in serum creatinine (11% vs. 9%; $p < 0.001$) and serum uric acid (15% vs. 7%; $p < 0.001$). There was also an increase in ventricular pauses > 3 seconds in the first week (5.8% vs. 3.6%; p = 0.01), but this was no longer apparent at 30 days, and there was no difference in the rates of bradycardia, syncope, heart block or requirement for pacemaker. Discontinuation of the drug for adverse effects was more common with ticagrelor (7.4% vs. 6.0%; $p < 0.001$). Wallentin et al conclude that in patients presenting with ACS, with or without ST elevation, treatment with ticagrelor compared to clopidogrel significantly reduced the rate of death from vascular causes, MI, or stroke without an increase in the overall incidence of bleeding, but with an increase in the rate of non-procedure-related bleeding.

■ COMMENTARY

The results of the PLATO study presented at the recent European Society of Cardiology meeting, and simultaneously published in the *New England Journal* of Medicine, demonstrate a significant reduction in the incidence of vascular death, MI, and stroke, with no appreciable increase in bleeding risk using ticagrelor compared to clopidogrel in patients with ACS. This is a very large study (> 18,000 patients) with robust endpoints that were consistent across multiple subgroups tested. Multiple secondary and exploratory endpoints were also consistent. With recent concerns regarding clopidogrel resistance, we welcome newer therapies that can reduce ischemic complications in patients presenting with ACS. Importantly, those undergoing invasive or non-invasive strategies seemed to benefit to similar degrees with the use of ticagrelor over clopidogrel. These results challenge the doctrine that more effective antiplatelet action must be accompanied by increased bleeding risk.

Although the reduction in ischemic endpoints is promising, several issues should be noted. Firstly, in subgroup analysis, the benefits of ticagrelor over clopidogrel appeared to be attenuated in the North American cohort for unknown reasons. Secondly, ticagrelor can produce bradycardia, so patients at risk for bradycardia were excluded from the study, as were patients taking strong cytochrome P450 inhibitors or inducers. However, the use of ticagrelor did not translate into a higher rate of bradycardia, and similar numbers of patients were able to be treated with beta-blockers in each group. Thirdly, Ticagrelor was associated with a higher discontinuation rate for adverse events and patient preference. In addition, it is a twice-daily drug, which may also lower patient compliance. Caution must be exercised in patients in whom poor compliance may be catastrophic, such as those at high risk for stent thrombosis with multiple drug-eluting stents. Fourthly, the mean exposure to the study drug was only 277 days in each group; thus, the long-term differences between ticagrelor and clopidogrel remain unknown. Finally, ticagrelor does not have FDA approval for use in the United States at this time. ■

AED Placement and Effectiveness

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Folke F, et al. Location of cardiac arrest in a city center. Strategic placement of automated external defibrillators in public locations. *Circulation*. 2009;120:510-517

Folke et al from Copenhagen, Denmark, studied the consequences of automatic external defibrillator (AED) placement in a large metropolitan area. The study involved the placement and use of AEDs in Copenhagen, a city with a population of 600,000 and an area of 97 km^2. The central part of the city is served by a single emergency medical services (EMS) system with physician-staffed ambulances. The survey covers data from January 1994 through December 2005. During this period, there were 1,274 cardiac arrests in public areas, 26% of the total number of cardiac arrests to which EMS responded. During 2005, the final year of the study, 104 AEDS were placed in municipal or public buildings throughout the city. No data were used to guide the initial placements. A plot of AED location vs. cardiac arrest location within a 100-meter radius was then generated. Cost-effectiveness also was estimated. Each AED was assigned a cost of $2,000 and assumed to have an expected useful life of 10 years. Prior to AED placement, the cardiac arrest survival rate in Copenhagen had been 13.9%. Cost-effectiveness was estimated based on a projected increase in survival to 25%.

During the study period, there were 1,274 cardiac

arrests in public places. The highest density of cardiac arrests was in the city center and along major traffic routes. There were 73 cardiac arrests in grids containing a major train station, 175 in grids containing a high-density public area, 118 in grids containing a supermarket, 164 in grids containing a large industrial business, and 54 in grids containing a high school or primary school. The observed annual rate for cardiac arrest was highest in train stations, high-density public areas, shopping malls, bus terminals, and sport centers. High-incidence grids, designated by a probability of one arrest every five years within a 100-meter radius, included 10.6% of the total study area but 66.8% of all the public cardiac arrests. The results of unguided AED placement were disappointing. Not one of the 104 unguided AEDs had been used during the year they were in place and would potentially cover only 29 of the cardiac arrests in the entire study period. Calculated cost estimates of AED placement showed that cost per quality of life increased from $41,000 to $51,200 to $68,300, respectively, as the probability of AED use every five years fell from 100% to 80% to 60%, respectively.

Folke et al conclude that their data show that a high proportion of public cardiac arrests can be covered by strategic placement of AEDs within a limited portion of a city center with acceptable cost. Most arrests will be covered if AEDs are placed in a 100-meter radius of areas expected to have a cardiac arrest every five years. Strategic EMS initiatives focusing on selective placement of AEDs in areas with high incidence of cardiac arrests are needed.

■ COMMENTARY

For the effectiveness of public access AEDs to be optimal, the devices will need to be placed in areas where cardiac arrests occur with some reasonable frequency and where the arrests are witnessed by willing bystanders. They have been shown to be highly effective in casinos, airports, and on planes. This paper analyzes optimal placement on a citywide basis. Areas with dense pedestrian traffic were shown to be the best sites for AED placement, and an intelligent analysis of cardiac arrest incidence data would allow the most efficient use if only a limited number of AEDs were available. However, as more AEDs are used, costs per unit should drop and many private businesses or individuals may consider purchasing one. A network of AEDs purchased by public agencies, commercial firms, and private individuals will likely provide much better coverage in the future than we have now. ■

Improved Outcomes and Reduction of CV Risk in Diabetes Remains Problematic

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

Dr. Abrams serves on the speaker's bureau for Merck, Pfizer, and Parke-Davis.

Source: Preis Sr, et al. Trends in cardiovascular disease risk factors in individuals with and without diabetes mellitus in the Framingham Heart Study. *Circulation*. 2009; 120:212-220.

Do patients with diabetes share in the reduction of cardiovascular (CV) risk factors as much as non-diabetics? That question is the subject of an analysis of data from the most recent Framingham Heart Study (FHS). The report consists of outcomes in the FHS Third Generation Cohort: 4,950 children and spouses enrolled in 2002 who attended their first examination. The data were derived from the 50- and 60-year-old individuals with and without diabetes from 1970 to 2005. Continuous risk factors in the 50- and 60-year-old cohorts were BMI, blood pressure, total and LDL cholesterol, and diabetes. The prevalence of each risk factor over a 35-year period was calculated for each 10-year interval; secondary analyses included diabetic status and mean CVD risk factor levels by decade.

Results: Systolic and diastolic blood pressure fell equally in diabetics and non-diabetics. The magnitude of decline in systolic and diastolic blood pressure was similar in diabetics and non-diabetics. The prevalence of hypertension treatment increased from 21% to 53% among those without diabetes and from 26% to 63% among those with diabetes. Hypertension prevalence decreased in the 60-year-old group without diabetes mellitus (DM) with no change in the diabetics; treatment and control were similar in diabetics and non-diabetics in the 60-year-old cohort. Treatment of high blood pressure increased with and without diabetes. Treatment control of high blood pressure increased in subjects with and without diabetes.

BMI increased 0.39 kg/m^2 in non-diabetics and a mean of 2.52 kg/m^2 in diabetics per decade. Obesity increased markedly in the 50-year-old individuals: 17%-24% in non-diabetes and 36%-62% in diabetic subjects.

LDL cholesterol fell from a mean of 141 to 119 mg/dL in non-diabetics, a decline of 7.43 mg/dL per decade, whereas the diabetics had a decrease in LDL cholesterol from 161 to 111 mg/dL (15 mg/dL per decade). For all of the above, the direction of the trends for those with diabetes relative to those without diabetes was similar for 60-year-olds. The LDL cholesterol treatment and control increased markedly for those with and without diabetes, but only about 20% in either group achieved LDL control in 2000-2005. Results overall were similar in both the 50- and 60-year-old cohorts. Prevalence of high LDL decreased in non-diabetics, with no change in the diabetics. In 50- to 60-year-old subjects, high blood pressure prevalence decreased in those without diabetes, but there was no change in the diabetic cohort.

Preis et al concluded that diabetic subjects have not experienced the same magnitude of cardiovascular risk reduction as their non-diabetic cohorts.

■ COMMENTARY

This report helps us to understand why diabetes is such a serious clinical problem. When I went to medical school, and for many years thereafter, diabetes was a problem solely for the endocrinologist. Slowly and subsequently, with great speed over recent years, diabetes has also been recognized as a vascular, cardiovascular, renal, and endocrine problem. The understanding of insulin resistance is critical in dealing with diabetes therapy. Furthermore, several recent studies assessing the impact of diabetes on CV disease patients have been surprisingly negative, emphasizing the complexity of insulin resistance and hyperglycemia.

These data, gleaned from the large cohort of participants in the Third Framingham Heart Study population of almost 5,000 subjects, confirms yet again that diabetes is bad news for vascular health but, perhaps, more selective than we had thought. The resulting different medical problems (i.e., hypertension, obesity, renal disease, dyslipidemia) reflect the widespread presence of insulin resistance in type II diabetic individuals.

Clearly, the body responds differently in the presence of insulin resistance and/or diabetes. For instance, diabetes and hypertension impose risk on patients with diabetes equally vs. non diabetics, although diabetes is a major risk factor when compared to smoking. These data are most remarkable when looking at the large increase in BMI over the years.

Finally, it is clear that an increased knowledge about diabetic therapy and/or treatment guidelines in diabetics vs. non-diabetics is highly recommended for our diabetic patients, with specific attention paid to each major CV risk factor separately and/or in conjunction with other risk markers. ■

CME Questions

19. Warfarin therapy for atrial fibrillation should be considered if:
a. age is < 65 years.
b. CHADS2 score is 2 or more.
c. there is prior intracerebral bleed.
d. All of the above

20. Which of the following administered prior to PCI improves ACS outcomes?
a. Atorvastatin
b. Clopidogrel
c. Abciximab
d. All of the above

21. New and improved antiplatelet drugs include:
a. prasugrel.
b. ticagrelor.
c. ranexa
d. A & B

22. The placement of AEDs is best determined by:
a. highest density of people.
b. highest incidence of cardiac arrest.
c. availability of trained personnel.
d. who is paying for the device.

23. Alternatives to warfarin therapy for atrial fibrillation are:
a. aspirin.
b. clopidogrel.
c. left atrial appendage closure device.
d. All of the above

24. The increased risk of cardiovascular disease in diabetics is partly due to:
a. associated genetic abnormalities.
b. toxic effects of high blood glucose.
c. reduced response to risk-reduction strategies.
d. All of the above

Answers: 19. (b); 20. (d); 21. (d); 22. (b); 23. (d); 24. (c)

CME Objectives

The objectives of *Clinical Cardiology Alert* are to:

• present the latest information regarding illness and treatment of cardiac disease;

• discuss the pros and cons of these interventions, as well as possible complications;

• discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• present the current data regarding outpatient care of cardiac patients. ■

Clinical Briefs in
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By Louis Kuritzky, MD
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The short-term risks of bariatric surgery

Source: The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium; et al. *N Engl J Med* 2009;361:445-454.

Long-term benefits from bariatric surgery have been definitely established. Nonetheless, perioperative risks associated with bariatric surgery are not insignificant, especially since persons undergoing bariatric surgery often suffer comorbidities of diabetes, hypertension, and dyslipidemia.

The LABS Consortium performed an observational study of short-term outcomes subsequent to bariatric surgery in the United States. From 2005 to 2007, data supplied by 10 different clinical sites (combined total n = 4776 first-time bariatric surgical procedures) provided information on the composite endpoint of 30-day major adverse outcomes (death, DVT, postoperative intervention, and extended hospital stay). Roux-en-Y bypass was performed on approximately 70% of subjects; the majority of the other patients underwent gastric banding.

Death occurred in 0.3% of subjects within 30 days; an additional 4% of subjects experienced at least one adverse event included in the composite primary endpoint. A previous history of DVT was associated with greater likelihood to incur a postoperative adverse event; additionally, the higher the BMI (mean BMI in this report = 46.5 kg/m^2), the greater the frequency of adverse events.

Bariatric surgery has significant associated risks. For most appropriately selected patients, the long-term benefits far outweigh these risks, but patients need to be informed of the potential for serious adverse outcomes. ■

Parsing the death toll of COPD

Source: Zvezdin B, et al. *Chest* 2009; 136:376-380.

Worldwide, COPD is the fourth leading cause of death; unless current trends reverse, the toll will rise. Mortality rates associated with hospitalized acute exacerbations of COPD have been as high as 30%; the mortality in the 1 year after hospitalization is as high as 43%. Some of this mortality is directly attributable to COPD; however, other prominent comorbidities (e.g., CVD, pulmonary embolism) are also responsible. Often, because post-mortem examination is limited, the cause of death can only be opined. To provide greater clarity, Zvezdin et al report on autopsies of 43 patients who died within 24 hours of COPD hospital admission.

The mean age of the study subjects was 70. According to autopsy results, more than half of the deaths were attributed to diagnoses other than COPD: heart failure (in 37%) and pulmonary embolism (in 21%). The authors also separate pneumonia as a "non-COPD" cause of death (occurring in 28%), defining COPD death as those individuals who die of respiratory failure due to COPD progression (14%).

If these results (from a Serbian tertiary care university hospital specializing in pulmonary diseases) are generalizable to U.S. populations, clinicians will need to exercise greater vigilance, enhanced preventive techniques, and intensified intervention for potentially fatal comorbidities when patients are admitted for acute COPD exacerbation. ■

Vardenafil and premature ejaculation

Source: Aversa A, et al. *Int J Impot Res* 2009;21:221-227.

Although clinicians are much more familiar with erectile dysfunction, over the lifespan premature ejaculation (PEJ) is more common. A much smaller percentage of men with PEJ seek help, attributable to factors such as embarrassment, absence of available FDA-approved medications, and lack of public awareness of PEJ as an important sexual health dysfunction.

The technical definition of PEJ is a matter of controversy, although most experts agree that consistent unintended/unwanted ejaculation within 1 min that causes distress is satisfactory for the diagnosis.

The most commonly used metric for measuring PEJ is intravaginal ejaculatory latency time (IELT), or the time after vaginal intromission at which ejaculation occurs. Population studies have suggested that in established heterosexual couples, typical IELT is 6-10 min. Subjects enrolling in PEJ trials typically have an IELT of 30-90 sec, or even ejaculation ante portis (prior to intromission). The above definition would, by construction, seem to exclude gay men or ejaculation involving other orifices/body parts, but the similarities of diagnosis and management of PEJ in gay couples suggest that IELT, while at times anatomically inconsistent, incorporates the broader concepts

of early ejaculation in a variety of sexual settings.

SSRIs have an established role in management of PEJ. Success with SSRIs is greatest when taken on a maintenance schedule; however, patients would generally prefer as-needed administration, all things being equal.

Aversa et al studied men with PEJ (n = 42), all of whom consistently experienced IELT < 1 min. Patients were randomized (double-blind) to placebo or vardenafil 10 mg administered 15-30 min before sexual activity. The primary outcome was change in IELT.

Use of vardenafil provided a significant improvement in IELT (from 36 sec to 4.5 min) compared with placebo (IELT went from 42 sec to 54 sec). The tolerability of vardenafil is well established. Vardenafil appears to be a viable option for PRN treatment of PEJ. ■

Testosterone, depression, and hypogonadal men

Source: Shores MM, et al. *J Clin Psychiatry* 2009;70:1009-1016.

SUBTHRESHOLD DEPRESSION (sDEP), also known as minor depression, occurs in as many as 1 of 4 elderly patients. Although by definition the symptom burden of sDEP is less than major depressive disorder (MDD), it is more common than MDD and is still associated with diverse negative outcomes including decreased quality of life and function, and increased morbidity, mortality, and health care utilization.

Symptoms of hypogonadism include fatigue, decreased libido, and dysphoria, any of which may also be manifestations of depression. Shores et al studied the impact of testosterone replacement in hypogonadal men (total testosterone < 280 ng/dL) meeting DSM-IV criteria for sDEP.

This double-blind trial randomized adult men (n = 33) to testosterone gel 7.5 g/d or placebo for 12 weeks. The primary outcome was change in the HAM-D depression score.

At the end of the trial, testosterone-treated men had a significantly improved HAM-D score compared to placebo, and the percent with remitted sDEP was dramatically different (52.9% vs 18%) favoring testosterone.

No serious testosterone-attributable adverse effects were seen. Testosterone replacement shows benefit for improving sDEP in hypogonadal men. ■

Aspirin after colon cancer diagnosis

Source: Chan AT, et al. *JAMA* 2009; 302:649-658.

MOST COLORECTAL CANCERS OVEREXPRESS cyclo-oxygenase 2 (COX-2). Primary prevention with aspirin (ASA) is associated with reduced risk for colon cancer and colonic adenoma. Secondary prevention with ASA (and celecoxib) is effective in reducing risk of new adenomas in persons who have been previously diagnosed with colonic neoplasia. Because ASA has recognized toxicities, including cerebral hemorrhage and GI bleeding, it is important to determine whether use of ASA in high-risk subjects (persons previously diagnosed with colon cancer) provides net benefit for overall and/or colon cancer-specific mortality.

The Physicians' Health Study and the Nurses' Health Study are observational studies, providing a window of observation for the role of ASA in both primary and secondary prevention. A cohort within both populations took maintenance ASA prior to any diagnosis of colon cancer, and further information about effects of ASA in persons who developed colon cancer and continued with ASA subsequent to the cancer diagnosis (vs subjects who did not take ASA after a diagnosis of colon cancer) is presented here.

Of subjects who developed colon cancer (n = 1279) in these two study populations (combined), there were statistically significant differences in total mortality (35% vs 39%) and colon cancer-related mortality (15% vs 19%) favoring use of ASA. Concordant with current thinking on the putative mechanism of ASA benefit, the risk reduction was greatest in persons whose colon cancer overexpressed COX-2. Despite these favorable results, the authors caution that routine utilization of ASA post colon cancer might be considered premature since these data are observational; placebo-controlled randomized trials are needed for confirmation. ■

The Emperor's new vertebroplasty?

Source: Buchbinder R, et al. *N Engl J Med* 2009;361:557-568.

VERTEBROPLASTY (VERT) HAS RECENTLY enjoyed increased popularity as treatment for painful osteoporotic vertebral fractures. Observational or open-label studies have provided most of the supportive information. Enthusiasm for other previously popular surgical procedures has been dampened when double-blind randomized trials have failed to confirm positive outcomes: Two randomized trials in the last 7 years comparing arthroscopy for knee osteoarthritis found no outcomes difference when compared to placebo.

Buchbinder et al performed a randomized, double-blind, sham procedure-controlled trial of VERT for painful osteoporotic fracture in 78 participants. The primary outcome was pain reduction, which did not differ at weeks 1, 3, or 24 after treatment between intervention and sham intervention.

The Buchbinder study was published immediately preceding another VERT trial in the *New England Journal of Medicine* examining pain and disability at 1 month post intervention, which similarly did not find positive outcomes. These trials call for closer evaluation of the (potential) value of VERT. ■

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WHO Issues Global Alert on Antiviral Use

In this issue: WHO recommendations for antiviral use for H1N1 flu; antibiotic use trends for acute respiratory tract infection; denosumab clears FDA Expert Panel; FDA Actions.

Antiviral Recommendations for H1N1

The World Health Organization (WHO) has issued a global alert and response regarding the use of antivirals for pandemic H1N1 flu, reiterating that antivirals should be used to prevent severe illness and death in children and adults. The neuraminidase inhibitor oseltamivir (Tamiflu®) is recommended for patients who initially present with severe illness or whose condition begins to deteriorate. H1N1 remains sensitive to the neuraminidase inhibitors such as oseltamivir despite isolated reports of resistance earlier this year. The WHO recommends that clinicians in communities where the virus is circulating widely assume that patients with flu-like symptoms have H1N1 and not wait for laboratory confirmation. Most patients with pandemic flu experience typical flu symptoms and recover within a week. These patients do not need antivirals. But in patients with severe illness, studies have shown that early treatment, within the first 48 hours, is associated with better clinical outcomes. WHO also states that if oseltamivir is unavailable zanamivir (Relenza®) may be used in its place. This recommendation applies to all patient groups including children and pregnant women. The WHO statement comes in response to an article in the *British Medical Journal* suggesting neuraminidase inhibitors provide minimal benefit for children with seasonal influenza and have little effect on asthmatic exacerbations or use of antibiotics (Shun-Shin M, et al. *BMJ* 2009;339:b3172). ■

Antibiotic Use Declines Overall, While Use of Broad-Spectrum Increases

Physicians are prescribing fewer antibiotics for acute respiratory tract infections (ARTIs), but if an antibiotic is used, it is more likely to be a broad-spectrum drug. Using data from 1995 to 2006, antibiotic trends were reviewed from a national database for ARTIs, which included otitis media (OM). Children younger than age 5 were seen less frequently for ARTI than in the past, and they were less likely to be prescribed an antibiotic (36% reduction; 95% confidence interval [CI], 26%-45%). Among children age 5 or older, ARTI visit rates remained stable but antibiotic prescription rates decreased by 18% (95% CI, 6%-29%). Excluding otitis media, antibiotic prescription rates decreased by 41% among all age groups. Prescription rates for a penicillin, cephalosporins, and sulfonamide/tetracycline decreased while the rate of prescriptions for azithromycin increased, making it the most commonly prescribed macrolide for ARTI and OM. Among adults, quinolone prescriptions also increased. The authors conclude that overall antibiotic prescription rates for ARTI decreased in the last 10 years; however, prescription rates for

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broad-spectrum antibiotics increased significantly (Grijalva CG, et al. *JAMA* 2009;302:758-766). This study points out the success of multiple campaigns to decrease antibiotic use for ARTIs, which are primarily caused by viruses. However the increasing use of broad-spectrum antibiotics is concerning. ■

Denosumab Receives Conditional Approval from FDA Expert Panel

Denosumab is a new human monoclonal antibody that suppresses osteoclast function and thus inhibits bone resorption. It is being evaluated by the FDA for treatment of osteoporosis in men and women, and although it has not yet been approved, a recent FDA Expert Panel has given conditional approval paving the way for full FDA approval this fall. Two recently published, industry-sponsored studies suggest the drug is effective in 2 different populations. In the first study, more than 1400 men receiving androgen-deprivation therapy for nonmetastatic prostate cancer were randomly assigned to receive denosumab 60 mg SQ every 6 months or placebo for 2 years. The primary endpoint was change in bone mineral density (BMD) at the lumbar spine, with secondary endpoints of change in BMD in the hip as well as fracture incidence. At 24 months, BMD increased in the lumbar spine with denosumab (5.6% increase vs 1% decrease for placebo; $P < 0.001$). BMD was also increased in the total hip, femoral neck, and distal radius, and the effect was maintained for 36 months. New fracture rate was also decreased with treatment (1.5% vs 3.9% with placebo; $P = 0.006$). Rates of adverse events were similar in both groups (Smith MR, et al. *N Engl J Med* 2009;361:745-755).

In the second study, 7868 postmenopausal women with low BMD were randomized to denosumab 60 mg SQ every 6 months or placebo for 36 months. The primary endpoint was new vertebral fractures. Denosumab was associated with a reduction in vertebral fractures (2.3% vs 7.2% placebo; $P < 0.001$), a reduction in hip fractures (0.7% vs 1.2% placebo; $P = 0.04$), and a smaller reduction in nonvertebral fractures. There was no increase in risk of cancer, infection, cardiovascular disease, delayed fracture healing, hypocalcemia, or osteonecrosis of the jaw in this study (Cummings SR, et al. *N Engl J Med* 2009; 361:756-765).

These last findings are important because the FDA's Expert Panel expressed concerns about infection and cancer data in giving a recommendation to approve denosumab when the FDA votes on the drug in October. If approved, which seem likely, denosumab will be marketed by Amgen under the trade name Prolia™. ■

FDA Actions

The FDA is requiring new boxed warnings on TNF-blockers regarding the risk of lymphoma and other malignancies in children and adolescents who have received the drugs. The new labeling will include warnings regarding cases of leukemia in adults, adolescents, and children, as well as new onset psoriasis. The labeling will also include a revised Medication Guide to reflect the safety information. Products subject to the new boxed warning are infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), and the recently approved agents certolizumab pegol (Cimzia®) and golimumab (Simponi™). These TNF-blockers are used to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis. The warning is based on reports of nearly 50 cases of various cancers associated with the drugs, of which half were lymphomas.

The FDA has approved a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Bristol-Myers Squibb and AstraZeneca's saxagliptin (Onglyza™) is the second DPP inhibitor approved after sitagliptin (Januvia®). It is the first drug approved since the FDA changed its standards for diabetes drug approvals, requiring evidence of cardiovascular safety. While saxigliptin has not shown evidence of higher rates of cardiovascular disease, the FDA is requiring post-marketing studies to specifically look at cardiovascular safety in high-risk populations. Saxigliptin is dosed once daily and is approved as monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones.

The FDA has announced that it is reviewing adverse event reports of liver injury in patients taking the weight-loss drug orlistat, marketed as the prescription drug Xenical® and over the counter as Alli®. The agency has received 32 reports of serious liver injury in patients taking the drug in the last 10 years. Of these, 6 resulted in liver failure. Almost all of the reports are from outside the United States. The FDA is not recommending patients discontinue the drug, but is suggesting that those who have used orlistat should consult a health care professional if they develop jaundice, fever, fatigue, brown urine, or other symptoms of liver injury. ■