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Clopidogrel Plus Proton-Pump Inhibitors

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Ho PM, et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA*. 2009;301:937-944.

SINCE THE RISK OF GASTROINTESTINAL BLEEDING IS INCREASED when clopidogrel is added to aspirin therapy in patients with acute coronary syndromes (ACS), many prescribe proton-pump inhibitors (PPIs) to reduce this risk. However, mechanistic studies suggest that PPIs may reduce the effectiveness of clopidogrel. Thus, Ho et al used a Veterans Affairs national cohort to compare rates of mortality and rehospitalization for ACS between patients taking clopidogrel alone vs. clopidogrel plus PPIs. This was a retrospective cohort study of all patients with ACS discharged from any VA hospital beginning in 2003 and ending in 2006 who were prescribed clopidogrel and who filled the prescription; pharmacy refill data was used to see if the patient was on PPIs over the course of the study. Of the 8,205 identified patients on clopidogrel, 64% were given PPIs. The latter patients were older and had more co-morbidities. During a median follow-up of 521 days, 21% were re-admitted for ACS without PPIs vs. 30% on PPIs (OR 1.25, 95% CI 1.11-1.41). Also, mortality was significantly higher in the clopidogrel plus PPI group (20% vs. 17%, $p = 0.001$). Among those prescribed a PPI, 60% were given omeprazole and 37% were prescribed more than one PPI. Use of PPIs without clopidogrel in ACS patients was not associated with increased adverse outcomes. Ho et al concluded that the use of clopidogrel plus PPIs after discharge for ACS was associated with an increased risk of adverse outcomes vs. patients on clopidogrel alone.

■ COMMENTARY

The strength of this longitudinal observational study was that drug use was assessed over the duration of follow up, not just at hospital discharge, thus strengthening the conclusion that concomitant PPI and clopidogrel use after ACS leads to increased subsequent coronary

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events. Sensitivity analyses in this study also showed a consistent effect across subgroups. The most common event was re-hospitalization for ACS, which substantiates the mechanistic theory that PPIs affect clopidogrel's effectiveness as a platelet aggregation inhibitor. The presumed mechanism is that both drugs are metabolized by the liver CYP2C19 cytochrome P450 isoenzyme; mechanistic studies have demonstrated this drug interaction. Polymorphisms of the CYP2C19 gene have also shown reduced effectiveness of clopidogrel and increased cardiovascular events. Although platelet aggregation studies were not done in this large observational study, the results certainly make sense based upon what we know about these drugs.

Until more definitive studies are done, it would seem prudent to not use PPIs prophylactically for dual antiplatelet therapy but reserve it for those with other important indications. Alternatively, one could use hydrogen-blocking drugs, which do not use the P450 system, or pantoprazole, which also does not use the P450 system. Another confounding issue is that omeprazole is now available over the counter, so patients will need to be advised about indiscriminant use of this drug. Finally, if the new thienopyridine prasugrel is approved by the FDA, it may avoid this issue because it does not use the P450 system. ■

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Management of Asymptomatic Severe Mitral Regurgitation

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Kang DH, et al. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. *Circulation.* 2009;119:797-804.

THE OPTIMAL TIMING OF SURGERY FOR ASYMPTOMATIC severe mitral valve regurgitation (MR) is unclear. Thus, Kang et al from South Korea studied the outcomes of patients treated with early surgery to those treated more conservatively in a prospective observational study. The treatment was at the discretion of the attending physician. Conventional treatment was selected in 286, and early surgery was selected in 161 who met inclusion criteria. Severe MR was defined as a PISA radius > 8 mm. All patients had marked mitral-valve prolapse or flail leaflet. Symptomatic patients, those with a left ventricular (LV) ejection fraction < 60%, LV diameter > 45 mm, atrial fibrillation, significant aortic valve disease, systolic pulmonary artery pressure > 50 mmHg, age > 85 years, or who were not candidates for surgery due to comorbidities were excluded. Patients in whom MR was clearly due to ischemic heart disease also were excluded. Vasodilator drugs were not given to the conservative management group unless another clear indication for them, such as hypertension, was present. Among the surgical group, 94% had mitral valve repair and the remainder had valve replacement. Coronary bypass surgery was done in 19 patients, and all but one patient undergoing valve repair had an annuloplasty ring placed.

Results: Comparing baseline data between the two groups, the surgical cohort had more flail leaflets, a larger effective regurgitant orifice area (EROA), and larger LV diameters. Operative mortality was zero. After a median follow-up of more than 1,900 days, there were no cardiac deaths in the surgical group and 12 in the conventional therapy group ($p = 0.008$). Cardiac causes of death were heart failure (6), sudden death (4), and endocarditis (2). The composite primary endpoint of operative mortality, cardiac death, repeat surgery, and hospitalization for heart failure occurred in 1% of the operated group and 12% of the conservative group. Using propensity matching, 127 pairs of patients emerged. In this cohort, seven-year, event-free survival was 99% in the surgical group vs. 85% in the conservative group ($p = 0.007$). In the conservative group, 28% developed criteria for surgery during follow-up. Multivariate analysis showed

that pulmonary hypertension, age, and EROA were independent variables that predicted the development of surgical indicators or heart failure. Kang et al concluded that compared to conservative management, early surgery for asymptomatic severe MR decreased cardiac mortality and hospitalization for heart failure.

■ COMMENTARY

The timing of surgery in patients with MR remains controversial. This paper, the latest observational study (randomized, controlled trials are unlikely to ever happen) makes several interesting points. First, in this select group of patients, operative mortality and seven-year post-operative mortality were zero. Who were these select patients? They were young; mean age was 52 years. Most had no significant coronary artery disease or other serious comorbidities for surgery. They had truly severe MR (EROA averaged 0.79 cm^2), and 39% had flail leaflets. Left ventricular function was preserved, and none had a pulmonary systolic pressure > 50 mmHg. Also, transesophageal echo was preformed in most, and the likelihood of being able to do a repair rather than valve replacement was high since 94% had a repair.

Second, among the conservatively managed patients, factors that increase the operative risk were likely to develop. Heart failure developed in 12% of the conservative group. Most developed pulmonary hypertension, and a few developed infective endocarditis. Third, among the conservatively managed patients who ultimately went to surgery (28%), post-operative LV size was larger than that observed with the early surgery group, even though ejection fraction was not significantly different. This suggests that LV remodeling may have occurred, which could portend a reduced long-term survival.

These results are in contrast to a smaller and shorter follow-up study by Rosenhek et al (*Circulation*. 2006;113: 2238-2244) of conservatively managed patients who were similar to those in this study (mean age 55 years). They found that survival over 62 months was no different from expected. Surgical criteria developed in 29%; mostly symptoms and post-operative LV function was preserved in all. However, surgical-free survival at six years was only 65%.

What do we do with this data? In an asymptomatic patient with severe MR or a flail leaflet, who is an excellent operative candidate, and TEE demonstrates that repair is feasible, surgery is the best option. In doing second opinions on such cases, my biggest area of disagreement with the primary physician is in the rating of the severity of MR. This study used sophisticated echo techniques to quantitate MR severity. This must be done! If the degree of MR is borderline or the patient is reluctant to have surgery, then watchful waiting is acceptable as long as careful follow-up can be achieved. ■

PCI vs. CABG for Severe CAD: The SYNTAX Study

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

Source: Serruys PW, et al. Percutaneous coronary intervention versus coronary artery bypass grafting for severe coronary artery disease. *N Engl J Med*. 2009;360:961-972.

Revascularization, in conjunction with optimal medical therapy, remains a critical component in therapy for patients with obstructive coronary artery disease (CAD). Coronary artery bypass graft surgery (CABG) initially showed benefit over medical therapy and, subsequently, over percutaneous transluminal coronary angioplasty (PTCA) as well. Studies comparing percutaneous coronary intervention (PCI) in the era of bare-metal coronary stents (BMS) with CABG suggested CABG remained superior to PCI. However, PCI techniques have advanced rapidly over recent years, including the introduction of drug-eluting stents (DES), allowing more complex patient and lesion subsets to be treated percutaneously than in the past. Recent studies suggest that patients with multivessel CAD can be treated relatively safely with DES, albeit at higher risk for needing repeat revascularization than patients treated with CABG. Accordingly, the SYNTAX trial randomized patients with severe CAD to CABG or PCI with DES to determine the optimal approach to these patients.

This was a multi-center, randomized trial conducted at 85 sites, recruiting consecutive patients with severe, previously untreated CAD (triple-vessel or left-main disease) who could be treated with either PCI or CABG. Eligible patients were assessed by an interventional cardiologist and a cardiac surgeon at their local site. Those suitable for inclusion were then randomized to undergo CABG or PCI with DES, with the aim of complete revascularization of all vessels at least 1.5 mm in diameter and with at least 50% stenosis severity. Symptomatic angina, or ischemia, was an inclusion criterion. Exclusion criteria were history of prior PCI or CABG, acute myocardial infarction, and the need for concomitant cardiac surgery. For the CABG patients, internal mammary artery grafting of the left anterior descending artery was recommended and, in patients younger than 70 years of age, arterial revascularization was recommended; all other surgical techniques were at the surgeon's discretion. In the PCI arm, standard PCI

techniques were recommended and clopidogrel was preloaded and continued for at least six months.

After screening 4,337 patients, 1,800 patients were randomized to receive PCI (n = 903) or CABG (n = 897). The baseline characteristics were well matched between groups, with mean age 65 years, 77% male, 25% diabetics, and BMI 28 in each group. The only differences were slightly more patients with hypertension in the PCI arm and more patients with elevated triglycerides and low HDL in the CABG arm. Time-from-randomization, procedure duration, and length of hospital stay after the procedure were significantly longer in the CABG arm, with complete revascularization achieved more often (63% vs 57%; $p = 0.005$). Both the PCI and CABG arms enrolled high-risk patients, with no differences seen in terms of euroSCORE, Parsonnet score, or SYNTAX score between the groups. A mean of 4.4 lesions per patient were treated in both groups. In the CABG group, 97.3% of patients had arterial grafts, with an average of 2.8 conduits and 3.2 distal anastomoses per patient. In the PCI group, more than four stents were placed per patient on average; 14% had staged procedures and 63% had at least one bifurcation or trifurcation lesion.

The primary outcome was 12-month major adverse cardiac or cerebrovascular event (MACCE) rate, which included death, myocardial infarction (MI), stroke, and revascularization. CABG had a lower rate of the primary endpoint than PCI (12.4% vs. 17.8%, $p = 0.002$); thus, the non-inferiority endpoint for PCI was not met and CABG was considered superior. Similar MACCE rates were observed when analysis was performed on an as-treated and intention-to-treat basis. There was no difference between the rates of death (4.4% vs. 3.5%; p = NS) or MI (4.8 vs. 3.3; p = NS) between PCI and CABG, respectively. CABG resulted in a significantly higher stroke rate than PCI (2.2% vs. 0.6%; $p = 0.003$), and PCI resulted in a higher rate of revascularization (13.5% vs. 5.9%; $p < 0.001$), which was the primary driver of the higher overall MACCE rate with PCI. The rates of symptomatic graft occlusion and stent thrombosis were similar. When outcomes were analyzed based on the complexity of the coronary artery disease, as assessed by the SYNTAX score, CABG performed well regardless of the complexity of the disease. PCI, on the other hand, had higher MACCE rates in patients with a high SYNTAX score, compared to those with a low or intermediate score. Similarly, PCI resulted in similar rates of MACCE compared to CABG in patients with low or intermediate SYNTAX scores, although CABG performed better in those with high SYNTAX scores. Serruys et al concluded that CABG, as compared to PCI, is associated with a lower rate of MACCE at one year among patients with three-vessel or left-main CAD (or both) and should, therefore, remain the standard of care for such patients.

■ COMMENTARY

The SYNTAX study provides important new insights into the most appropriate methods for revascularization for patients with severe CAD. CABG continues to be an excellent choice for revascularization, providing low adverse event rates and freedom from the need for repeat revascularization. PCI with DES performed well in this all-comer design trial in severe CAD. This study gives us more detail to discuss with patients when deciding on the options of CABG or PCI for severe CAD. Both therapeutic options are likely to results in similar rates of death or MI; CABG is likely to reduce the need for repeat revascularization, and PCI is likely to result in a lower rate of stroke. Importantly, the decision of which option to pursue was not made on the cath lab table. The procedure was stopped after the diagnostic angiogram, and discussion occurred between the cardiologist and the cardiac surgeon. Now we are able to allow patients to make a more informed decision, but only after a comprehensive discussion has occurred.

It should be noted that the trial was sponsored by the manufacturer of paclitaxel-eluting stents, and yet, the study was, if anything, biased against PCI by inclusion of revascularization as an endpoint. Why this combined endpoint was chosen is not immediately clear. Furthermore, all stents used in this study were paclitaxel-eluting stents, and the results may not exactly extrapolate to other stent types. In fact, other stent types may have lower rates of revascularization based on previous clinical trials.

The inclusion of the SYNTAX score is invaluable. This score gives a numerical value to the complexity of the coronary artery anatomy, something that is often overlooked in the debate between PCI and CABG. In a subgroup analysis, Serruys et al demonstrate that patients with less complex anatomy perform just as well with either PCI or CABG, but that CABG outperforms PCI in patients with more complex anatomy. Although that may seem self-evident, Serruys et al should be congratulated on formally studying this type of variable. The decision to pursue PCI or CABG on an individual patient can now be better informed, rather than considering one option superior to the other in all cases. The SYNTAX trail provides us with valuable new information in treating patients with severe CAD. ■

Dronedarone: New and Improved Amiodarone?

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: Hohnloser SH. Effect of dronedarone on cardiovascular events in atrial fibrillation. *N Engl J Med*. 2009;360: 668-678.

DRONEDARONE IS A NEW ANTIARRHYTHMIC DRUG WITH structural similarities to amiodarone. During development of the molecule, the steps included removal of the iodine atoms and making the compound more lipophilic; the latter produces a shorter elimination half-life and reduced tissue accumulation. The primary goal was to reduce the risk for organ toxicity, especially thyroid, pulmonary, and hepatic adverse events. The ATHENA trial was a placebo-controlled study designed to determine whether dronedarone would reduce cardiovascular hospitalizations and deaths in patients with atrial fibrillation.

Initially, patients were eligible for inclusion in the trial if they had a history of paroxysmal or persistent atrial fibrillation and were either at least 70 years old or younger but had a risk factor for stroke or death. Subsequently, however, the entry criteria were modified such that patients between 70 and 75 years of age had to have at least one additional risk factor. Patients older than 75 continued to be eligible even if they had no additional risks. Patients younger than age 70 were no longer eligible. Patients were excluded from the study if they had permanent atrial fibrillation, a recent episode of decompensated heart failure or current New York Heart Association class IV symptoms, acute myocarditis, or significant bradycardia. Patients could be either in sinus rhythm at the time of enrollment or have a cardioversion planned. The primary study outcome was a composite endpoint that included a first hospitalization due to a cardiovascular event or death from any cause. Unplanned hospitalizations were classified as cardiac or non-cardiac in a blinded fashion by an events committee. Secondary study outcomes were death from any cause, death from cardiovascular cause, and first hospitalization due to a cardiovascular event.

ATHENA enrolled 4,620 patients; 2,301 in the dronedarone group and 2,327 in the placebo group. The mean age was 71.6 years, and 47% of the patients were women. Hypertension was the predominant underlying cardiovascular disease seen in 87% of the patients. Although 21% of the patients had a history of New York Heart Association class II or III heart failure, only 11.9% and 3.9% of the patients had a left-ventricular ejection fraction below 45% or 35%, respectively.

The median duration of follow-up was 22 months. Dronedarone was superior to placebo in terms of the primary outcome event. Among patients who received dronedarone, 675 patients (29.3%) had their first cardiovascular hospitalization and 59 (2.6%) patients died without prior hospitalization. In the placebo group, there were 859 (36.9%) first cardiovascular hospitalizations and 58 deaths before hospitalization (2.5%). The hazard ratio (HR) for the composite primary outcome was 0.76 (95% confidence interval [CI] 0.69 to 0.84; $p < 0.001$). Subgroup analysis showed a consistent beneficial effect of dronedarone across several important subgroups. Analysis of the secondary endpoints also favored dronedarone. There was a trend toward reduced total mortality in the dronedarone group, with 116 (5%) deaths in that group compared to 139 (6.0%) in the placebo group (HR 0.84, $p = 0.18$). Cardiovascular deaths were significantly reduced.

In the dronedarone group, there were 63 cardiovascular deaths (2.7%), compared to 90 cardiovascular deaths in the placebo group (HR 0.71, 95% CI, 0.51 to 0.98; $p = 0.03$). There were no significant differences between the groups in deaths resulting from cardiac arrhythmia. Atial fibrillation recurrence was not an endpoint, but the reduction in cardiovascular hospitalization was driven mainly by a reduction in the number of hospitalizations for atrial fibrillation. There were 510 hospitalizations for atrial fibrillation in the placebo group vs. 335 (14.6%) in the dronedarone group. (HR 0.63, $p < 0.001$). There were no significant differences between the groups in number of hospitalizations for heart failure, syncope, or ventricular arrhythmias. There was a small decrease in the number of hospitalizations for acute coronary syndrome, with 62 (2.7%) in the dronedarone group and 89 (3.8%) in the placebo group (HR = 0.70; $p = 0.03$). Premature discontinuation of the study drug was observed in 30.2% of the patient receiving dronedarone compared to 30.8% of those receiving placebo. Presumed adverse events leading to discontinuation were seen in 12.7% of the patients in the dronedarone group vs. 8.1% in the placebo group. The most common significant adverse events observed with increased frequency in the dronedarone group were bradycardia, QT interval prolongation, gastrointestinal events, rash, and serum creatinine increase. There was no difference in the frequency of respiratory events, abnormal liver function tests, or thyroid dysfunction between the two groups. One case of polymorphic ventricular tachycardia with a long QT interval was observed in a 66-year-old woman on dronedarone during recovery from a previous out-of-hospital cardiac arrest. No other cases of torsades de pointes were documented.

Hohnloser et al concluded that dronedarone is associated with a significant reduction in the rate of hospitalization due to cardiovascular events or death, with a favorable side effect profile.

■ **COMMENTARY**

The criteria used to evaluate the efficacy of antiarrhythmic drugs in patients with atrial fibrillation need to be specific for the patient population studied. Among patients with frequent and highly symptomatic paroxysmal atrial fibrillation, changes in symptoms scores, the frequency and duration of episodes, and the need for hospitalizations are the primary useful measures. Among older patients with less frequent or less symptomatic episodes of atrial fibrillation, cardiovascular hospitalization, stroke, and death are more meaningful outcomes to measure. The ATHENA trial was the first really large study to use these new standards. In contrast to most prior antiarrhythmic drug studies, which have typically involved only several hundred patients, ATHENA included more than 4,600 subjects. The study did not really attempt to document recurrent atrial fibrillation, but rather focused on hospitalizations, many, but not all, of which were due to recurrent arrhythmia and death. Since dronedarone has effects to both prevent recurrent atrial fibrillation and also improve heart rate control during recurrent atrial fibrillation, this trial design highlights the benefits of a drug with more than one potentially beneficial activity.

It's important to note that patients with severe systolic heart failure were not included in ATHENA. Only a small number of patients had depressed left ventricular ejection fractions, and patients with recent or current decompensated heart failure were excluded. Another study of dronedarone, the ANDROMEDA trial, enrolled patients soon after a hospitalization for decompensated heart failure. In ADROMEDA, dronedarone was associated with increased mortality in the early phases, and the study was stopped by its Data Safety Monitoring Board. It has been hypothesized that some of this effect may have been due to reductions or discontinuation of ACE inhibitors or angiotensin receptor blockers in response to an early rise in serum creatinine after dronedarone was started. Investigators in ATHENA were aware that dronedarone can increase serum creatinine values without affecting the glomerular filtration rate and were instructed not to change therapy for minor creatinine elevations. However, the safety of dronedarone in patients with advanced heart failure with left-ventricular systolic dysfunction remains uncertain, and further data are needed before dronedarone can be recommended for use in such patients. ■

Microvolt T-wave Alternans: Useful in Predicting ICD Need?

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: Costantini O, et al. The ABCD (Alternans Before Cardioverter Defibrillator) trial. strategies using t-wave alternans to improve efficiency of sudden cardiac death . *J Am Coll Cardiol*. 2009;53:471-479.

The clinical utility of microvolt T-wave alternans (MWTA) testing to detect subtle beat-to-beat oscillations in the electrocardiogram's T-wave amplitude as a non-invasive method for predicting sudden cardiac death remains undetermined. In this study, Constantini et al report a multi-center trial in which patients being considered for ICD implantation underwent both MTWA testing and electrophysiologic studies (EPS) with programmed stimulation to compare the predictive accuracy of the two methods. Patients were eligible for enrollment if they had a left-ventricular ejection fraction ≤ 40% and non-sustained ventricular tachycardia documented by 24-hour ambulatory ECG recordings within six months of enrollment. All patients underwent both MTWA testing and EPS using a standard ventricular stimulation protocol. The results of MTWA tests were classified as positive, indeterminant, or negative. EPS was considered positive if sustained, monomorphic ventricular tachycardia was induced with any part of the protocol, or if ventricular fibrillation was induced with one or two extrastimuli. ICD insertion was mandated in all patients with either a positive MTWA or EPS results. In patients with MTWA indeterminate, or both tests negative, investigators could elect not to implant a device. ICD programming was standardized for detection of ventricular arrhythmias exceeding 171 bpm, with shock-only therapy at maximum outputs.

The primary endpoint for the study was defined as either the first appropriate ICD discharge or sudden cardiac death during the first year of follow-up. Events were classified by an independent committee blinded to the results of the testing. The study was designed as a noninferiority comparison of the positive and negative predictive values of MTWA and EPS.

The study population included 566 patients who underwent both EPS and MTWA tests for risk stratification. For the entire group, the mean age was 65 years; 84% were male. Eighty-one percent of the patients were New York Heart Association functional class I or II. The mean left-ventricular ejection fraction was 28%. The group included 77 patients who had an ejection fraction between 0.36 and 0.40 and, therefore, would have a current indication for an ICD implant only if they were EPS positive. Patients were on stable medical therapy, including an ACE inhibitor or angiotensin receptor blocker in 89%, a beta

Table 1

12- and 24-Month Event Rates for MTWA and EPS

MTWA/EPS	Number	12-month event rate	24-month event rate
+/-	153	6.5%	12.0%
+/+	66	7.8%	15.3%
-/-	94	11.1%	10.1%
IND/+	62	14.8%	22.9%
IND/-	52	4.6%	11.0%
ALL	495	7.5%	14.0%

Adapted from: Constantini O, et al. *J Am Coll Cardiol*. 2009;53:471-479.

blocker in 86% and a statin in 81%. The MTWA test was positive, negative, and indeterminant in 46%, 29%, and 25% of the patients, respectively. The EPS was positive in 40%. Ninety-seven percent of patients who were either MTWA positive or EPS positive received ICDs. ICDs were implanted in 67% of patients with a negative or indeterminant MTWA result and a negative EPS and in 100% of those patients with a negative MWTA result and a positive EPS. During follow-up, the overall one- and two-year event rates were 7.5% and 14%, respectively. There were 55 appropriate ICD discharges and 10 sudden cardiac deaths.

As shown in *Table 1*, patients who were both MTWA- and EPS-negative had the lowest 12-month event rate (2.3%). Patients who were both MTWA-positive or indeterminant and EPS-positive had the highest one-year event rates (11.1% and 14.8%, respectively). At two years, however, both tests didn't perform as well. Even MTWA-negative and EPS-negative patients had a 24-month event rate of 10.1%. The two-year event rates in the four groups with one or another test positive or negative, ranged from 14%-22%. Overall, the event rate in patients with two normal tests at one year was three-fold lower than in patients with one abnormal test and six-fold lower than in patients with both tests abnormal. In a time-dependent analysis of hazard ratios, EPS was a significant predictor of events starting at nine months and continuing throughout the rest of the study. In contrast, MTWA was predictive in the early phase of follow-up but no longer predictive by 12 to 24 months.

Costantini et al concluded that a strategy involving MTWA and EPS might be used to identify low-risk patients who meet other criteria for ICD implant for primary prevention of sudden cardiac death.

■ COMMENTARY

The utility of MTWA as an effective risk stratifier for patients who are potential candidates for ICD implants remains controversial. Some studies have shown that MTWA can be used to identify low-risk patients, but in other recent studies, such as the MASTER trial (*J Am Coll Cardiol*. 2008;52:607-615) or the Sudden Cardiac Death Heart Failure Trial (*Circulation*. 2008;118:2022-2228), the predictive value of MWTA tests was less apparent. In patients with left ventricular systolic dysfunction, current pharmacologic therapy has resulted in most primary prevention groups being "low risk." Exactly how low the annual risk should be in order to justify ICD implants remains uncertain. The early primary prevention studies had two- or three-year event rates that ranged between 20% and 40%. However, more recent studies, including the ABCD trial reported here, have shown much lower early event rates, and a negative test result is less important.

A large fraction of the costs and risks associated with ICD therapy occur at, or early after, implant. The average longevity of the most costly component, the ICD generator itself, should be at least five years. Therefore, studies that assess the value of risk stratification should probably use a longer follow-up duration than the 1-2 years seen in this study. Perhaps, future data from the ABCD investigators will provide further insights into the value of MTWA testing. ■

Physician Experience vs. Hospital Volume in Primary PCI

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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

Source: Srinivas VS, et al. Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol*. 2009;53:574-579.

Efforts to decrease door-to-balloon time for primary percutaneous intervention (PCI) in an acute ST elevation myocardial infarction (STEMI), may include preferential triage to hospitals expert in primary PCI, partly because of evidence suggesting better outcomes. Others suggest increasing the number of hospitals capable of performing primary PCI, as more experienced cardiologists are available in community hospitals with high efficacy in primary PCI. This study assesses the interaction between hospital and physician volume for primary PCI in STEMI using the New York State PCI reporting system.

The database consists of all acute STEMI PCI patients in New York over a two-year period (January 2000 to December 2002). PCI was carried out within 12 hours of chest pain, without thrombolytic therapy, by 266

physicians in 7,321 patients with STEMI. The yearly volume of PCI was obtained for each hospital and cardiologist. The major outcome was in-hospital mortality. Hospitals were categorized as < 50 or > 50 cases/year. Physician PCI volumes were categorized by < 10, 10-20, and > 20 cases/yr. Risk-adjusted mortality was calculated and predicted for each patient as the ratio of observed mortality to predicted mortality multiplied by the statewide mortality rate of 3.7%. The independent effect of hospital and physician volume on mortality was tested.

Results: Mortality was lowest in high-volume hospitals and with high-volume physicians (OR .58 and .66, respectively). However, risk-adjusted mortality rates were not statistically different between high-volume physicians in high-volume hospitals vs. low-volume physicians in low-volume hospitals (3.8% vs. 8.4%, $p = 0.09$). Also, high-volume physicians in low-volume hospitals had a risk-adjusted mortality of 4.8% vs. low-volume physicians of 8.4%. Whereas, in a high-volume hospital, low-volume physicians' mortality rate was 6.5% vs. 3.8% for high-volume physicians. Srinivas et al concluded that physician experience significantly affects the hospital-volume mortality relationship.

■ COMMENTARY

This report validates the power of PCI procedure volume in determining PCI results in patients with acute STEMI taken to the cath lab for immediate PCI. The data are unique in that all cath labs in New York are obligated to supply information about their PCI results. While hospital procedure volume is important, hospital volume does not show a strict correlation with hospital mortality. For instance, in hospitals with > 75 per year volume, risk-adjusted hospital rate was 3.32%, compared to 4.24% in hospitals < 75 per year, p = NS. Also, they demonstrate a dynamic relationship among hospital volume, physician volume, and mortality rates, which suggests that operator experience is a major factor in determining outcomes of primary PCI.

The main problem with these interesting data regarding high-volume and low-volume physicians and hospitals is the time elapsed between the present and 2000-2002; the data, thus, reflect PCI practice of up to nine years ago. This observation is not mentioned by Srinivas et al; more up-to-date data are likely to be at least equivalent or more likely superior, given the enormous interest in activating STEMI hospitals en route, sending ECG data en route or "straight to lab," activation done by ER and/or cardiology personnel. Moving the patient from the ambulance directly to the ER (better yet, directly to the cath lab), and emphasizing door-to-balloon time rather than the gross club of hospital volume, are important advances. It is likely that current practices and equipment are important, but physician expertise remains the mainstay of PCI in STEMI and all other invasive procedures. ■

CME Questions

18. In patients with low EF, which combination of results best predicts sudden cardiac death or ICD discharge?
a. Positive microvolt T-wave alternans (MTWA), negative electrophysiologic study (EPS)
b. Indeterminate MTWA and negative EPS
c. Positive MTWA and positive EPS
d. Negative MTWA and positive EPS

19. Coronary bypass surgery is superior to PCI for patients with:
a. three-vessel disease.
b. left-main disease.
c. mild CAD.
d. A & B

20. Dronedarone for atrial fibrillation (AF) demonstrated:
a. reduced hospitalization for recurrent AF.
b. reduced mortality in AF patients.
c. a 30% discontinuation rate.
d. All of the above

21. Mortality in primary PCI of STEMI is determined by:
a. hospital PCI volume.
b. physician experience.
c. Neither
d. Both

22. Surgery for asymptomatic patients with severe mitral regurgitation should be considered if which of the following is present?
a. Pulmonary hypertension
b. Large regurgitant orifice
c. Flail leaflet
d. All of the above

23. Proton-pump inhibitors may be contraindicated in PCI patients:
a. with significant GI bleeding.
b. on clopidogrel plus aspirin.
c. on aspirin alone.
d. All of the above

Answers: 18. (c); 19. (d); 20. (d); 21. (d); 22. (d); 23. (b)

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. ■

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VapoRub Revisited

Source: Abanses JC, et al. Vicks VapoRub induces mucin secretion, decreases ciliary beat frequency, and increases tracheal mucus transport in the ferret trachea. *Chest* 2009;135:143-148.

THOSE OF US IN THE BABY-BOOMER generation may recall in the 1940s-50s the application of a generous quantity of some Vicks® VapoRub-type salve (VvR) to the chest wall as a time-honored remedy that grandma suggested for the common cold. Toxicity of VvR, rather than efficacy, was the subject of this publication.

As with essentially any therapeutic agent, there is always the potential for adverse effects. Based upon a single case report of a toddler who developed respiratory distress subsequent to peri-nasal application of VvR, Abanses et al investigated potential adverse physiologic effects of VvR by experiments in ferrets.

VvR resulted in increased mucin secretion and decreased ciliary beat frequency (as observed by video microscopy), the combination of which could lead to small-airway obstruction. The authors report upon studies of menthol (an ingredient of VvR) in adults, in which, despite a decrease in nasal airflow, subjects universally report improved nasal symptoms; this change is attributed to the cooling effect of menthol in the nasal passages, which the brain interprets as increased airflow across the nostrils.

VvR appears to be a generally safe remedy, but case reports suggest caution in young children. The case presented here was initially treated as asthma; clinicians might consider asking about VvR use in children who present with new, otherwise unexplained symptoms of respiratory distress. ■

Prostate Cancer Risk with Testosterone Replacement

Source: Shabsigh R, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: A systematic review. *Int J Impot Res* 2009;21:9-23.

GROWTH AND DEVELOPMENT OF THE prostate is recognized to be testosterone (TST)-dependent. Clinicians have long held concerns that TST therapy might not only worsen symptoms of benign prostatic hyperplasia (BPH), but also stimulate the development, growth, proliferation, or aggressiveness of prostate cancer (PCa). Some of this concern stems logically from the observation that TST deprivation has salutary effects on prostate cancer growth.

This systematic review of 44 articles using FDA-approved agents was unable to directly provide a definitive answer to the question of whether TST replacement increases risk of PCa, but provides other interesting insights. First, trials of hypogonadal men treated with TST have not evidenced an increased risk for PCa; if anything, a protective effect may occur. Second, TST-treated men with a history of PCa did not experience more recurrences or metastases. Third, TST did not appear to influence Gleason scores when PCa was detected.

The authors conclude, "There is no evidence that TST increases risk of prostate cancer in hypogonadal men." Of some concern, however, are the case reports of aggressive PCa in recipients of a non-FDA-approved supplement containing TST, estradiol, chrysin, and elk velvet antler. ■

The Suicidal Process: Time to Intervene?

Source: Deisenhammer EA, et al. The duration of the suicidal process. *J Clin Psychiatry* 2009;70:19-24.

SUICIDE HAS BEEN IN THE TOP CAUSES of death in the United States for more than 20 years, usually ranking among the top 10. Clinicians would like to play a useful role in suicide prevention, yet data are sparse to inform about the interval between first suicidal ideation and a suicide attempt. Deisenhammer et al attempted to bridge this knowledge gap with a study of persons with failed suicide attempts, all of whom (n = 82) were interviewed within 72 hours of attempted suicide.

Most (83%) subjects were alone at the time of suicide conceptualization, and almost half reported the time from first suicide conception to attempt was 10 min or less. Nonetheless, during this brief interval, most (77%) had some contact (usually by telephone) with friends or family, and the majority indicated their wish to die or (according to their subjective reports) hinted at their death wish.

Interviews with subjects did not provide any insight as to what might have deterred the suicide attempt. Nonetheless, the fact that most suicidal subjects did make contact with others leaves open the possibility that some component of interpersonal communication has the potential to change the course of suicide attempts. ■

BNP to Guide Treatment of Heart Failure

Source: Pfisterer M, et al. BNP-guided vs symptom-guided heart failure therapy. *JAMA* 2009;301:383-392.

For Americans aged 65 or older, congestive heart failure (CHF) remains the most common diagnosis for hospital admission. Despite advances in therapy, the outcome of CHF remains daunting, with 5-year mortality rates as high as many malignancies. Because brain natriuretic peptide (BNP) reflects left ventricular wall stress, it can be useful to assist in diagnosis of CHF. Additionally, some, but not all, clinical trials have suggested that intensification of therapy to achieve optimization of BNP is associated with improved outcomes. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) was devised to provide a more definitive comparison between the success of treatment intensification based upon symptoms vs level of BNP.

Patients with CHF (n = 499) were randomized to BNP-directed management (titrate treatment until BNP < 400 ng/mL) vs symptomatic management (intensify treatment until NYHA class II symptoms or better). Follow-up for the primary endpoint—hospitalization-free survival—was 18 months.

The BNP group experienced more aldosterone antagonists use, as well as more frequent increases in dose and utilization of ACE inhibitors and ARBs. However, there was no difference in the primary endpoint. In subjects age < 75 years, there was a reduction in mortality favoring BNP-directed management; however, because this was a secondary endpoint and the primary endpoint did not achieve statistical significance, it must be considered exploratory, not established. BNP-guided intensification of treatment is no more effective than standard symptom-directed methods. ■

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Clopidogrel and CV Events: One Size Does NOT Fit All

Source: Simon T, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-375.

Utilization of clopidogrel (CPG) in patients with acute coronary syndromes (ACS is well established. Similarly, long-term prophylaxis with CPG for secondary prevention of CV events is evidence-based: The CAPRIE trial indicated that CPG is marginally superior to aspirin for endpoint reduction, and the PROFESS trial demonstrated that ER-dipyridamole/aspirin (Aggrenox®) failed to meet the non-inferiority threshold when compared to CPG for stroke prevention.

Residual risk in persons receiving CPG remains substantial, suggesting that perhaps the efficacy of CPG is not universal; i.e., some subjects might metabolize CPG differently than others, leading to different levels of efficacy (or adverse effects).

The French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) study enrolled ACS patients on CPG, and studied the relationship of genetic variants that result in variations in absorption, activation, and biologic activity of CPG. Next, the relationship between these genetic variants and adverse outcomes (death, stroke, MI) were studied.

The most important genetic variant appeared to be at the P450 2C19 gene. Those with 2 loss-of-function 2C19 genes were almost 4 times as likely to have a CV event over the next year as those without. The P450 2C19 gene is utilized for metabolism of CPG to its active metabolite; lesser antiplatelet activity would be anticipated in persons with impaired P450 2C19 activity. These results support the findings of another trial in the same issue of *The New England Journal of Medicine* that identified increased CV risk in persons with reduced 2C19 P450 functionality. ■

Estrogen + Progesterone and Breast Cancer

Source: Chlebowski RT, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573-587.

The Women's Health Initiative (WHI) provided convincing evidence that the use of estrogen + progesterone (E+P) in postmenopausal women is associated with an increased risk of breast cancer (BrCa). The outcomes of this clinical trial motivated large numbers of women and their clinicians to rethink the risk-benefit balance of hormone therapy (HT), evoking a sea-change in prescribing habits.

Despite the acknowledged association between E+P and BrCa in WHI, a concomitant decline in use of mammography following the WHI news invited the possibility that post-WHI, less BrCa screening might have influenced the observed BrCa decline rather than simply less E+P use. To study this issue, WHI investigators evaluated two data sets: the original WHI population (n = 16,608 women without BrCa at baseline) and a second observational study population (n = 41,449 without BrCa at baseline). The observational study group did not receive advice about whether to use E+P, but were informed about the results of the interventional WHI when it became available. In the observational WHI population, more than 16,000 women were taking E+P at baseline.

Long-term follow-up of the observational WHI population showed an increased incidence of BrCa in women who had used E+P. BrCa incidence in this population declined subsequent to HT discontinuation. This suggests the possibility that some early breast cancers may regress or disappear if HT is stopped. The data did not, however, provide a meaningful association between lesser use of mammography and reduced BrCa. ■

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert*, *Clinical Oncology Alert*, *Critical Care Alert*, *Infectious Disease Alert*, *Internal Medicine Alert*, *Neurology Alert*, *OB/GYN Clinical Alert*, *Primary Care Reports*, *Travel Medicine Advisor*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■