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Critical analysis of the latest clinical research in cardiovascular medicine

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ABSTRACT & COMMENTARY

Is It Time to Purge Full-Strength Aspirin from the Outpatient Armamentarium?

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

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

SOURCE: Xian Y, et al. The association of discharge aspirin dose with outcomes after acute myocardial infarction: Insights from the TRANSLATE-ACS Study. *Circulation* 2015. pii: CIRCULATIONAHA.114.014992. [Epub ahead of print].

Choosing an optimal maintenance dose of aspirin has been a matter of substantial debate for years. In the post-myocardial infarction (MI) setting, high-dose aspirin (325 mg/day) has been most commonly prescribed. This is despite data from observational and randomized trials suggesting a lack of benefit, the largest of which was the CURRENT-OASIS 7 trial, published in 2010. The American College of Cardiology/American Heart Association guidelines have changed in recent years to recommend low-dose rather than high-dose aspirin for maintenance therapy.

A recent analysis examined contemporary aspirin dosing in the TRANSLATE-ACS trial, which was a prospective, multicenter observational study of more than 12,000 ST segment elevation myocardial infarction or non-ST segment elevation myocardial infarction patients enrolled between 2010 and 2012 who were treated with PCI and ADP receptor inhibitors. Data, including discharge medications and outcomes, were tracked, and follow-up was performed at 6 weeks and at 6, 12, and 15 months post MI.

Of 10,213 patients eligible for analysis, 6387 (62.6%) received high-dose aspirin (325 mg) and 3826 (37.4%) received low-dose aspirin (81 mg) at discharge. Of those discharged on high-dose

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aspirin, nearly 35% were switched to low-dose by 6 months. In contrast, approximately 8% of patients discharged on low-dose aspirin were changed to high-dose by 6 months.

At 6 months post-discharge, the incidence of MACE was 8.2% in the high-dose aspirin group, compared with 9.2% in the low-dose group, which was not significantly different, even after multivariable adjustment. However, BARC-defined bleeding events, predominantly minor BARC type 1 or 2 bleeds not requiring hospitalization, were more frequent with high-dose aspirin. Results were unchanged after inverse probability-weighted propensity adjustment. MACE events generally were not different across subgroups defined by age, sex, home aspirin use, and type of ADP receptor antagonist used (clopidogrel vs prasugrel or ticagrelor) as part of the dual antiplatelet therapy regimen. However, the risk of bleeding associated with high-dose aspirin use was slightly increased in younger patients, men, those using aspirin before admission, and those prescribed higher-potency ADP receptor antagonists (prasugrel or ticagrelor, as opposed to clopidogrel) at discharge.

The authors concluded that high-dose aspirin is prescribed at discharge in a majority (nearly two-thirds) of U.S. MI patients treated with PCI, despite no apparent benefit in terms of MACE and a measurable increase in minor bleeding events by 6 months. They argue that their data support current guideline recommendations for low-dose as opposed to high-dose aspirin for maintenance therapy following MI.

■ COMMENTARY

Just a few short years ago, the dosing of aspirin for maintenance therapy in general, and after PCI specifically, was relatively complex. Official recommendations called for a higher dose of aspirin in the immediate post-PCI period, with conversion to a lower dose thereafter. Initial recommendations in the era of first-generation drug-eluting stents even called for differential periods of high-dose aspirin with sirolimus- vs paclitaxel-eluting stents. I can easily recall the discussion during our department cath conference after publication of the 2011 update to the ACCF/AHA/SCAI guidelines for percutaneous coronary intervention, which contained the following language as a IIa recommendation: "After PCI, it is reasonable to use aspirin 81 mg per day in preference to higher maintenance doses." Would we as a department choose to follow this new recommendation, or would we each make our own choices? A spirited debate ensued, with some arguing fervently for maintaining an initial period of high-dose aspirin.

What a long way we have come in only a few short years, at least on this one issue. The current study provides further evidence of a lack of benefit to high-dose maintenance aspirin, along with a suggestion of harm. The latest guidelines specifically recommend the use of low-dose aspirin for maintenance purposes, and for good reason. We should adopt low-dose aspirin for outpatient use in the United States, as much of the world has already done, and in doing so simplify treatment recommendations for ourselves and for our patients. ■

ABSTRACT & COMMENTARY

Antiplatelet Therapy After TAVR: Where are the Data?

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

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

SOURCE: Hassell ME, et al. Antiplatelet therapy following transcatheter aortic valve implantation. *Heart* 2015. pii: heartjnl-2014-307053. doi: 10.1136/heartjnl-2014-307053. [Epub ahead of print].

Current guidelines both in the United States and in Europe recommend that patients post-transcatheter aortic valve replacement (TAVR) be treated with 3 to 6 months of dual antiplatelet therapy (DAPT), including low-dose aspirin and a thienopyridine, such as clopidogrel. The use of antiplatelet and antithrombotic medications following TAVR is currently based more on empiricism and experience than on hard data and is at least in part taken from the experience with coronary stenting. Dual antiplatelet therapy is associated with higher rates of bleeding compared with aspirin alone, but evidence supporting its efficacy post-TAVR is sparse.

Hassell et al pooled data from two randomized controlled trials (RCT) and two registry studies, collecting information on a total of 672 TAVR patients who were treated with either DAPT (n = 257) or aspirin alone (n = 415). Patients who were treated with warfarin and those who were treated with clopidogrel alone were excluded. After propensity matching, the final analysis comprised 434 patients, including 235 patients from the matched cohorts and 199 patients from the RCTs.

Net adverse ischemic and thrombotic events, including stroke, were no different between the DAPT and the aspirin monotherapy groups at 30 days. With regard to individual endpoints, no significant difference was observed between all-cause mortality (pooled odds ratio [OR] 0.91; 95% confidence interval [CI], 0.36-2.27; $P = 0.83$), acute coronary syndrome (pooled OR, 0.5; 95% CI, 0.05-5.51; $P = 0.57$), and stroke (pooled OR, 1.21; 95% CI 0.36-4.03; $P = 0.75$). However, there was a trend toward less life-threatening or major bleeding with aspirin alone. Clinical outcomes were further assessed separately for the included studies. All-cause mortality and acute coronary events were not increased for the aspirin treatment group in both the RCTs and the matched cohorts.

The authors conclude the value of adding a thienopyridine (clopidogrel) to aspirin for post-TAVR patients is in question, and potentially places patients at increased hazard of bleeding without corresponding benefit.

■ COMMENTARY

Optimal antiplatelet and antithrombotic therapy following TAVR is an area that clearly warrants further study. The hazard for stroke post-procedure is greatest in the first 24 hours, when approximately 50% of events occur. These early events most likely occur as a result of embolic phenomena from the procedure, and are unlikely to be affected by oral antiplatelet therapy. Subsequently the risk of stroke remains elevated for up to 2 months. The current study suggests that DAPT does not have a significant beneficial effect on the risk of stroke during this period, and likely comes at a cost of increased bleeding.

The landscape for antithrombotics in TAVR has become more complicated recently, with multiple reports showing a small but significant incidence of valve thrombosis detectable by CT imaging, with a subset of these showing clinically significant hindrance of valve function. These cases seem to occur despite dual antiplatelet therapy and tend to be responsive to vitamin K antagonists.

Although the study by Hassell et al is not sufficient to change guidelines, it clearly calls attention to the low level of evidence supporting current recommendations and highlights the need for randomized studies to refine treatment. For now, there is room to individually tailor therapy for these patients. For example, DAPT is not absolutely required for patients with thrombocytopenia and high risk of bleeding, and TAVR patients with atrial fibrillation may do better with warfarin, either alone or in combination with a single antiplatelet agent. Meanwhile, there are no data at all on use of the novel oral anticoagulants in TAVR patients Randomized trials are ongoing and will ultimately provide much-needed evidence for treatment of this population. ■

ABSTRACT & COMMENTARY

New Insight into Anthracycline Cardiotoxicity

By Van Selby, MD

Assistant Professor of Medicine, UCSF Cardiology Division, Advanced Heart Failure Section, San Francisco, CA

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

SOURCE: Cardinale D, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation* 2015;131:1981-1988.

Anthracyclines are used to treat a broad range of malignancies. Cardiotoxicity is a well-known complication that leads to substantial morbidity and often limits the utility of these agents. Current understanding of anthracycline cardiotoxicity is primarily based on retrospective studies, with wide variation in reported incidence and prognosis. As a result, evidence-based consensus recommendations for the identification and treatment of anthracycline cardiotoxicity are lacking.

Cardinale et al prospectively measured left ventricular ejection fraction (LVEF) at baseline and at regular intervals before, during, and after treatment in 2625 adult patients receiving an anthracycline-containing regimen. Patients were followed for a median of 5.2 years. Cardiotoxicity was defined as a decrease in LVEF > 10 points and to < 50%. All patients with cardiotoxicity were started on heart failure therapy with enalapril and beta-blockers titrated to maximal tolerated doses.

["...this study provides valuable insights into anthracycline cardiotoxicity and may ultimately change the current classification system and understanding of the underlying pathophysiology..."]

The overall incidence of cardiotoxicity was 9%. The median time elapsed between the completion of chemotherapy and development of cardiotoxicity was 3.5 months, and 98% of all cardiotoxicity occurred within the first year after chemotherapy was completed. Key predictors of cardiotoxicity were LVEF at the end of chemotherapy and cumulative anthracycline dose. With medical therapy for heart failure, 11% of patients had full recovery and 71% had partial recovery (defined as an increase in LVEF of at least 5 points and > 50% with no heart failure symptoms). Severity of LV dysfunction and NYHA functional class were the strongest predictors of recovery. The authors conclude that cardiotoxicity is a relatively common complication of anthracycline-based chemotherapy in adults, almost always occurs within the first year after chemotherapy is completed, and usually recovers with prompt initiation of heart failure therapies.

■ COMMENTARY

With improvements in the detection and treatment of malignancies, cancer patients are living longer and side effects of chemotherapy, such as anthracycline cardiotoxicity, are gaining importance. This study marks a major advancement in our understanding of the incidence, risk factors, and time course of anthracycline cardiotoxicity, as well as the response to treatment. Chronic anthracycline cardiotoxicity traditionally has been divided into early-onset and late-onset progressive disease. The findings of Cardinale suggest the vast majority of cardiotoxicity actually occurs early on, within the first year after treatment. Most patients were asymptomatic (NYHA class I or II) at the time of diagnosis. Rather than separate disease entities, anthracycline cardiotoxicity may represent a continuum, with most "late" cardiotoxicity actually developing much earlier. Patients are often only diagnosed with cardiotoxicity once they become symptomatic from their LV dysfunction. In fact, all of the five patients who developed late-onset LV dysfunction (more than 1 year after finishing chemotherapy) in this study had other risk factors for heart failure. It is possible the prior anthracycline exposure was not the only cause of cardiotoxicity in these patients.

The response to heart failure therapy observed in this cohort is impressive and highlights the importance of early detection. Anthracycline cardiotoxicity is traditionally thought of as a type I cardiotoxicity, characterized by irreversible cardiomyocyte death. Cardinale et al challenge this notion and prove, at least in the early stages, that anthracycline-mediated LV dysfunction does not appear to be an irreversible process.

There are several important limitations to this study. All patients were treated with heart failure therapy once cardiotoxicity was identified, so we cannot make definite conclusions regarding the natural history of this early, often asymptomatic LV dysfunction. It is possible that many of the patients who were treated with beta-blockers and ACE inhibitors never would have gone on to develop clinically significant heart failure. The study also doesn't discuss what adjustments were made to the chemotherapy regimen after cardiotoxicity was identified nor what impact any changes may have had on their oncologic outcome.

Current guidelines from the AHA/ACC recommend echocardiography at baseline and for re-evaluation

to monitor patients exposed to anthracyclines. The guidelines do not specify how frequently monitoring should be done, which echocardiographic parameter to use, or how treating physicians should respond to a decrease in LV systolic function. The FDA recommends discontinuing doxorubicin in all patients with a 10% decrease in LVEF or to < 55%.

Although more research is still needed in the emerging field of cardio-oncology, this study provides valuable insights into anthracycline cardiotoxicity and may ultimately change the current classification system and understanding of the underlying pathophysiology. The key lessons are that cardiotoxicity occurs early on, and with prompt initiation of standard medical therapy for systolic heart failure, most patients can usually recover LV function. Surveillance based solely on symptoms may miss this early window during which patients are responsive to treatment. ■

ABSTRACT & COMMENTARY

Long-Term Weight Loss Rivals Medications and Ablation for AF Rhythm Control

By Cara Pellegrini, MD

Assistant Professor of Medicine, UCSF; Cardiology Division, Electrophysiology Section, San Francisco VA Medical Center

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

SOURCE: Pathak RK, et al. Long-term effect of goal-directed weight management in an atrial fibrillation cohort: A long-term follow-up study (LEGACY). *J Am Coll Cardiol* 2015;65:2159-2169.

Atrial fibrillation (AF) — a condition affecting millions of people — currently has no cure. Symptoms are managed via medications, ablation, and, in selected cases, with pacemaker implantation and ablation of the AV node. The rhythm control strategy often leads to disappointing results, with meta-analysis data suggesting only slightly better than half the patients undergoing AF ablation are "free of AF" at just over a year mean follow-up. Antiarrhythmic drug results are generally worse. Further, the risks of procedural complications, drug side effects, and toxicities must be recognized. Recently, there have been several publications from Dr. Sanders and colleagues in Australia examining the effects of weight loss and risk factor management (including blood pressure control, diabetic control, and treatment of sleep apnea) on symptomatic AF burden that have been promising, but follow-up has been short. Their latest effort looks at longer-term follow-up of weight loss and effects of weight fluctuation on AF rhythm control.

The LEGACY study reports on the four-year mean follow-up of 825 obese patients with AF who were offered weight management. Patients were grouped according to degree of weight loss success: group 1 (≥ 10%), group 2 (3-9%), group 3 (< 3%). AF outcomes were measured by 7-day ambulatory monitors. Symptoms were assessed with the well-validated AF severity scale; in addition to weight, blood pressure, metabolic, and inflammatory markers, echocardiographic parameters were followed. Weight loss ≥ 10% was associated with a six-fold greater probability of arrhythmia-free survival compared to the other two groups. At final follow-up, 45.5% of group 1 were free of AF without the aid of ablation or antiarrhythmic medications. Almost double that (86.2%) were AF free with the addition of ablation(s) ± antiarrhythmic drugs (only 10% of patients in group 1 were on an antiarrhythmic at follow-up). Weight loss was associated with a dose response benefit in metabolic and inflammatory markers, blood pressure control, and need for anti-hypertensive medications, and even echocardiographic parameters. For example, left atrial volume fell from 37.6 mL/m^2 to 30.9 mL/m^2 in group 1. Notably, weight fluctuation of > 5% partially offset the benefit of weight loss, with a two-fold increased risk of arrhythmia recurrence compared to those with < 2% weight fluctuation. The authors conclude that long-term sustained weight loss was possible and was associated with a significant reduction in AF burden.

■ COMMENTARY

Although obesity has not been proven causative of AF, increasing BMI values have been associated with incrementally higher AF risk. Whether obesity (and weight loss) modulates AF risk directly or via its impact on other cardiovascular risk factors

is also unclear. The results of this study and others make clear that weight loss does result in reversal of negative cardiac remodeling, metabolic derangements, and symptomatic AF progression. The magnitude of the impact of weight loss is striking. Although the true AF burden was likely underestimated in this study due to the intermittent nature of the monitoring performed (across all groups), this was not different than many past studies of ablation and antiarrhythmic drug effect. Given the long follow-up duration in this study, weight loss alone compares quite favorably with other strategies for AF rhythm control.

It is important to recognize that participation in a weight management clinic greatly enhanced the likelihood of sustained weight loss in this study. Eighty-four percent of those in the ≥ 10% weight loss group chose to attend this clinic as opposed to 57% in the 3-9% weight loss group and 30% in the < 3% weight loss group. Similar trends were seen for weight fluctuation, with smaller numbers of patients who participated in the clinic showing > 5% weight fluctuation. Thus, the recommendation our patients hear from us should not be only an admonishment to lose weight, but a referral to a program to maximize the patient's success in this long-term endeavor.

Obviously, weight loss and risk factor modification generally at any point is beneficial. Previous results have shown that weight loss concurrent with AF ablation enhances the results of the ablation. The superiority of the ≥ 10% weight loss group in the "total AF freedom," which included effect of ablation (performed in similar numbers across groups), meds, and weight loss, echoed that. The tantalizing prospect is the idea that weight loss and general risk factor modification can be a practical long-term strategy alone. In our clinic, we are pushing patients to have their sleep apnea treated and blood pressure controlled prior to consideration of ablation. Perhaps we should be giving more attention to a well-resourced weight loss effort early on as well. ■

ABSTRACT & COMMENTARY

Folate Supplements and Primary Stroke Prevention

By Seema Gupta, MD, MSPH

Primary Care Physician, Charleston, WV

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

SYNOPSIS: In a Chinese study of hypertensive adults without history of stroke or myocardial infarction, the combined use of enalapril and folic acid, compared with enalapril alone, significantly reduced the risk of first stroke.

SOURCE: Huo Y, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China. The CSPPT randomized clinical trial. *JAMA* 2015;313:1325-1335.

Stroke is the fifth leading cause of death in the United States and a major cause of disability.[1,2] Worldwide, stroke is the second-most common cause of mortality and the third-most common cause of disability. About 800,000 Americans have a stroke each year, more than 600,000 of whom have had first attacks. On average, one person dies from a stroke every 4 minutes in the United States. With 6.8 million stroke survivors > 19 years of age, it remains a leading cause of functional impairment. Primary prevention is key, since more than three-fourths of strokes are first time events. An international case-control study of 6000 individuals found that 10 potentially modifiable risk factors could explain 90% of the risk of stroke occurrence.[3] This illustrates that targeted interventions can potentially be implemented to prevent stroke at individual and population levels. From a prevention perspective, the effect of folic acid supplementation on cardiovascular disease, including stroke, has been studied in many observational settings and randomized trials, and results have been mixed.

In their study, Huo and colleagues conducted a randomized, double-blind clinical trial of 20,702 adults in China with hypertension who had never had a stroke or myocardial infarction (MI). The randomly assigned participants received double-blind daily treatment with a single-pill combination containing 10 mg enalapril and 0.8 mg folic acid

(n = 10,348) or a tablet containing 10 mg enalapril alone (n = 10,354). Methylenetetrahydrofolate reductase (MTHFR) is the main regulatory enzyme for folate metabolism. Polymorphism of the MTHFR gene C677T leads to a reduction in enzyme activity, resulting in decreased folate levels. Study participants were also stratified by MTHFR C677T genotypes (CC, CT, and TT). The primary outcome studied was first stroke.

The trial was terminated early, after 4.5 years, per the recommendations by the data and safety monitoring board. The researchers found that the enalapril/folic acid group had a significant risk reduction in the incidence of first stroke, the primary endpoint, of 2.7% (282 events) vs 3.4% (355 events) in the enalapril-alone group (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.68-0.93). Analyses of secondary outcomes showed that the enalapril/folic acid group had a significant risk reduction in the incidence of ischemic stroke of 2.2% vs 2.8% in the enalapril alone (HR, 0.76; 95% CI, 0.64-0.91). Similar benefits were also found for composite cardiovascular events (3.1% in the enalapril/folic acid group vs 3.9% in the enalapril alone group; HR, 0.80; 95% CI, 0.69-0.92). However, no significant difference between groups was found for risk of hemorrhagic stroke or all-cause deaths. In stratified analysis performed, no significant interactions in any of the subgroups were found, including MTHFR C677T genotype. However, the beneficial effect appeared to be more pronounced in participants with lower baseline folate levels.

■ COMMENTARY

Folate occurs naturally in many animal products, green leafy vegetables, beans, and citrus fruits. In the United States, folic acid fortification of flour is mandated, which has led to the declining prevalence of folate deficiency. However, the most common cause of folate deficiency remains nutritional, due to poor diet and/or alcoholism. Certain conditions can also lead to increased requirements such as pregnancy, lactation, chronic hemolytic anemias, and drug-induced interference with folate metabolism (e.g., trimethoprim, methotrexate, phenytoin). Huo et al found a statistically significant reduction in risk of first stroke by 21% among adults with hypertension in China without a history of stroke or MI, with enalapril/folic acid therapy, compared with enalapril alone. In earlier studies,

["The combined use of enalapril and folic acid compared with enalapril alone significantly reduced the risk of first stroke."]

the possible benefits of folic acid supplementation in cardiovascular disease have been controversial. Prior studies have suggested that the greatest benefit from folate might be for stroke; however, most of the previous trials had been conducted among individuals with prior cardiovascular disease, unlike this study.[4,5] Although all the current study participants had hypertension, it is likely that the results would apply to normotensive persons, though the absolute effect may not be as robust.

Therefore, the current study has significant implications for stroke prevention across the globe by utilizing a safe and inexpensive folate supplementation or fortification strategy. In the United States, this approach should be individualized to target those with the TT genotype and/or those with low or moderate folate levels. ■

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CME QUESTIONS

1. A recent study shows that folate supplementation in hypertensive patients reduced the incidence of:

a. first stroke.

b. all-cause mortality.

c. hemorrhagic stroke.

d. acute myocardial infarction.

2. High-dose aspirin (325 mg/day) after primary PCI for acute MI, results in which of the following vs low-dose aspirin (81 mg/day)?

a. Fewer strokes

b. Fewer recurrent MIs

c. More minor bleeding episodes

d. More major bleeding

3. What percent weight loss is associated with a significant prolongation of time free from atrial fibrillation in AF patients?

a. < 3%

b. 3-6%

c. 6-10%

d. > 10%

4. Which of the following is most correct concerning anthracycline chemotherapy toxicity to the heart?

a. It completely recovers after cessation of chemotherapy.

b. It occurs in > 50% of patients treated.

c. It almost always occurs in the first year after therapy.

d. It is unrelated to anthracycline dose.

5. Post TAVR dual antiplatelet therapy is associated with:

a. fewer strokes.

b. fewer acute coronary events.

c. lower mortality.

d. a trend toward more major bleeding when compared to aspirin alone group.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.