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ABSTRACT & COMMENTARY

Thienopyridine Pretreatment in Patients with Non-ST Elevation Acute Coronary Syndromes: Where's the Evidence?

By Jeffrey Zimmet, MD, PhD

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

SOURCE: Bellemain-Appaix A, et al. Reappraisal of thienopyridine pretreatment in patients with non-ST elevation acute coronary syndrome: A systematic review and meta-analysis. *BMJ* 2014;349:g6269 (Published 24 October 2014).

Each year when I lecture the incoming cardiology fellows on the management of non-ST elevation acute coronary syndromes (NSTE-ACS), we embark on a discussion of optimal guideline-driven treatment vs real-world practicalities. Current ACC/AHA guidelines assign a class I recommendation to the administration of dual antiplatelet therapy to unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) patients at the time of presentation. This applies whether an initial invasive or conservative strategy is planned, and it emerged more than a decade ago based primarily on the results of the 2001 Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. In our hospital system, however, the reality is that such pretreatment — giving thienopyridine before coronary angiography — may adversely affect the subset of patients who are later found to have surgical anatomy. I say good luck finding a surgeon willing to operate on your clopidogrel-loaded patient. Cardiothoracic surgeons generally prefer that thienopyridines be withheld until after cardiac catheterization.

Now, it seems the surgeons have more support for their point of view. In their recent meta-analysis, Bellemain-Appaix and colleagues looked at thienopyridine (P2Y12 inhibitor) pretreatment in seven studies that included primarily NSTEACS patients, including four

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randomized, controlled trials and three registries. In the overall cohort, pretreatment did not reduce the risk of all-cause mortality or cardiovascular death. Major adverse cardiovascular events were reduced in the pretreatment group (odds ratio [OR], 0.84; 95% confidence interval [CI] 0.72 to 0.98; $P = 0.02$), but individual endpoints, such as myocardial infarction, were not significantly affected. Among the subset of patients who underwent percutaneous coronary intervention (PCI), which represented a minority of the total cohort, there was likewise no reduction in death or cardiovascular death, but pretreatment with P2Y12 inhibitors was associated only with a non-significant trend toward a reduction of major adverse cardiac events (MACE). Within the PCI group, pretreatment was associated with a reduction of urgent revascularization (OR, 0.72; 95% CI, 0.52 to 1.00); however, this result was driven primarily by the results of the PCI subset of the CURE, in which the delay from admission to revascularization averaged a relatively long 10 days.

By contrast, pretreatment with thienopyridine showed a consistent and significant effect on the primary safety endpoints in this study. Major bleeding was increased in the overall cohort (odds ratio 1.32 [1.16 to 1.49], $P < 0.0001$), as well as in the subset undergoing PCI (odds ratio 1.23 [1.00 to 1.50], $P = 0.048$). Minor bleeding was increased significantly only in the unselected group of patients with NSTEACS. The authors concluded that the risk-benefit ratio of thienopyridine pretreatment is not favorable in unselected patients with NSTEACS.

■ COMMENTARY

In the patients studied as part of this meta-analysis, pretreatment with thienopyridine had a relatively modest effect on MACE in the overall cohort, with no effect on mortality, but a consistent hazard with regard to bleeding. The authors' conclusion, that the risk-benefit ratio of thienopyridine pretreatment is not favorable in unselected patients with NSTEACS, seems to be a reasonable one. That is not to say that pretreatment is never beneficial or warranted in these patients. For a more nuanced conclusion, we should look more closely at the studies included in this analysis.

Only the ACCOAST (a comparison of prasugrel at PCI or time of diagnosis of non-ST elevation myocardial infarction) trial, which was the sole dataset in the analysis to use prasugrel, looked specifically at the question of pretreatment prior to coronary angiography in NSTEMI patients. In ACCOAST, treating patients upfront with antithrombotic therapy and aspirin, but delaying prasugrel administration until the time of coronary angiography, did not alter ischemic outcomes, but reduced by one-half the incidence of major bleeding compared with early administration of prasugrel. It is worth noting that even before ACCOAST, prasugrel was the only P2Y12 inhibitor specifically not recommended for administration prior to coronary angiography, based on its specific bleeding profile.

With the exception of ACUITY (acute catheterization and urgent intervention triage strategy), most of the included clopidogrel trials were older and were performed in a clinical environment that had important differences from today. Compared with that time period, contemporary practice has seen more widespread adoption of an early invasive strategy, the use of a higher loading dose for clopidogrel (600 vs 300 mg), and the availability of newer and more potent P2Y12 receptor antagonists. In CURE, the clopidogrel group showed ischemic benefit within hours, and the event curves for clopidogrel- and placebo-treated patients continued to separate throughout the study. Patients who fit the CURE paradigm of longer waiting times to angiography would seem to be appropriate beneficiaries of early thienopyridine treatment.

What, then, should we do with this information? As always, the right course of action will depend heavily on individual patient- and environment-specific factors. In intermediate-risk patients with a short expected interval from admission to cardiac catheterization, pretreatment has little recommendation and should be avoided. However, for higher-risk patients in whom there is an expected delay to angiography of longer than 24 to 48 hours, pretreatment with either clopidogrel or ticagrelor should be considered on a case-by-case basis. ■

ABSTRACT & COMMENTARY

FFR in Coronary Lesion Assessment: When is Negative Truly Negative?

By Jeffrey Zimmet, MD, PhD

SOURCE: Depta JP, et al. Risk model for estimating the 1-year risk of deferred lesion intervention following deferred revascularization after fractional flow reserve assessment. *Eur Heart J* 2014 Oct 21. pii: ehu412. [Epub ahead of print].

Fractional flow reserve (FFR) is an invasive technique for determination of the physiologic significance of an intermediate coronary lesion. Multiple studies have demonstrated the ability of FFR to guide revascularization decisions. For the most part, a negative FFR predicts the ability to safely defer interventional treatment of an intermediate lesion, with a relatively low risk of downstream events. The commonly used cutoff values of 0.75 and 0.80, although derived rather inelegantly thorough comparisons with non-invasive stress testing, have been validated empirically and overall performed well in clinical studies. However, not all lesions assessed as "negative" by FFR will remain quiescent. Among lesions for which intervention was deferred based on FFR, rates of future revascularization have ranged from 2.5-11% in the first year. The determinants of such delayed lesion intervention (DLI) have not been described previously.

Depta and colleagues from the Washington University School of Medicine retrospectively analyzed 720 patients with 881 intermediate-severity coronary stenoses who had a percutaneous coronary intervention (PCI) deferred based on FFR results performed between 2002 and 2010. Unlike some prior studies, which primarily looked at patients in the stable setting, approximately one-half of the subjects in this study underwent FFR assessment during an acute coronary syndrome (ACS), of which a majority were unstable angina (39%) and a lesser fraction were acute myocardial infarction (MI) (12%). The mean FFR value among deferred lesions was 0.85, and only 7% of deferred lesions had FFR values below the FAME study-inspired cutoff of 0.80.

After the index procedure, 5% of all PCI-deferred lesions underwent subsequent revascularization in the first year, while 18% (n = 155) underwent deferred lesion intervention (DLI) (74% by PCI and 26% via coronary artery bypass grafting) during a mean follow up of 4 years. Of the DLI lesions, 65% were treated in the ACS setting, while the remaining 35% were treated primarily for stable angina. Within the study population, 79 acute MIs occurred during the study period; the culprit lesion was identified as the lesion that had previously been deferred based on the index FFR in 38% of the acute MIs (n = 30).

A prediction model for DLI was developed using stepwise Cox regression. In the final model, multivariable predictors of DLI at 1 year included lower FFR value, younger age, current or former smoking, history of coronary artery disease (CAD) or prior PCI, multi-vessel CAD, and increased serum creatinine. The predicted risk of DLI at 1 year in the cohort varied from 1%-40%. The authors concluded that "Knowledge of a patient's risk for future revascularization of a lesion deferred based on FFR may provide clinicians and patients with useful information when considering potential strategies to prevent later adverse events leading to revascularization."

■ COMMENTARY

We all like simple tools to aid in clinical decision-making. FFR has grown in use based in large part on a purely binary treatment algorithm: Intervene on lesions with values below a certain cutoff and defer those with values above. This study drives home an important point that although a lesion has been assessed as non-significant by FFR, there is considerable risk that the same lesion may require revascularization at a later point in time. At 1 year in this real-world study, 1 in 20 initially deferred lesions had been revascularized, while at 4 years this approached 1 in 5. Keep in mind that there may very well be a different rate of DLI among patients referred for elective cardiac catheterization vs those presenting with ACS.

Of all the variables that fell out of the prediction model, it is the FFR value itself that is likely the most significant, if not also the most obvious. It should be unsurprising that a lesion for which PCI was deferred based on an FFR value barely above the cutoff, at 0.81 for example, would have a higher risk of requiring future intervention compared with a lesion with a much higher FFR value of 0.95.

Can such a prediction model actually inform medical practice? We all strive to prescribe optimal medical therapy to every patient with confirmed coronary atherosclerosis. The idea that some ill-defined additional preventive measures could be directed specifically toward those higher-risk patients with FFR-deferred lesions is likely not very realistic. Nonetheless, closer follow up, as well as maintaining a high index of suspicion for worsening symptoms or changing clinical conditions in these patients, could ultimately prove to be beneficial. ■

ABSTRACT & COMMENTARY

The Value of Family History in CAD

By Michael H. Crawford, MD, Editor

SOURCE: Cohen R, et al. Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the Multi-Ethnic Study of Atherosclerosis). *Am J Cardiol* 2014;114:1210-1214.

Although a routine part of the patient's medical history, little is known about the value of family history in predicting coronary artery disease (CAD) events in otherwise low-risk patients. Thus, these investigators from the Multi-Ethnic Study of Atherosclerosis (MESA) assessed the risk of a cardiovascular (CV) event in subjects with a coronary artery calcium score by computed tomography (CT) of zero, separating the subjects by whether they had a family history of CAD. A positive family history was one of a myocardial infarction in a parent, sibling, or child. Age of the family member was not considered. Of the 6814 men and women (50-50 distribution) without known CVD, 3185 had a baseline calcium score of zero and complete data. Their mean age was 58 years and 37% were men. The subjects were followed for a median of 10 years with yearly telephone follow-up. All CV events included: myocardial infarction, cardiac death, cardiac arrest, angina pectoris, stroke, stroke, death, and other CV deaths. CAD events (myocardial infarction, CAD death, cardiac arrest, and angina) were analyzed separately. A history of a first-degree relative with CAD was self-reported in 1185 subjects (37%). Baseline hypertension, statin use, and aspirin use were more common in those with a family history of CAD.

Overall, 3.2% of subjects with zero calcium score had a CV event and 1.8% had a CAD event. Among those with a positive family history, more events were noted (4.3% vs 2.5% for CV events and 2.4% vs 1.4% for CAD events, $P = 0.007$ and $P = 0.056$, respectively). After adjustments for age, sex, ethnicity, Framingham risk score, and baseline aspirin and statin use, a family history of CAD was only significantly associated with CV events (hazard ratio, 1.72; 95% confidence interval, 1.01-2.91), but not CAD events. Adjustments for anti-hypertensive medications, and the new CV risk score did not effect the risk of events. The authors concluded that subjects without known CV disease and a zero calcium score, who had a family history of CAD in a first-degree relative, were at increased risk for CV events, but the absolute event rates were <5% over 10 years.

■ COMMENTARY

Clearly, the subjects selected for this study were low risk with no clinical evidence of CVD and a CT calcium score of zero. Previous studies have suggested that such patients have a 10-year CAD event rate of around 1%. In this study, the CAD event rate was 1.8% for the whole group and 3.2% if all CV events were included. A family history of CAD in a first-degree relative raised the CAD events to 2.4% and all CV events to 4.3%. Only the increase in all CV events was statistically significant. The results remained the same if adjustments were made for the Framingham risk score and the new CV risk score, neither of which includes family history as a variable. Thus, as clinicians have suspected, family history is a predictor of the risk of CV events in a low-risk population and it would be reasonable to include these data in decisions about the aggressiveness of risk reduction strategies.

Perhaps the results would have been more robust if only premature CAD events were labelled a positive family history. The authors performed a sensitivity analysis of those in whom this information was available and it did raise the risk further, but not significantly ($P = 0.09$). However, this analysis was underpowered. On the other hand, why would someone middle aged with a CT calcium score of

zero ever have an event? Other studies using CT angiography have shown non-calcified soft plaque in 5-25% of subjects with a zero or < 10 calcium score and no overt disease. Perhaps family history helps identify these individuals. Also, a family history may be associated with more risk factors. For example, more of the subjects in this study with a family history were hypertensive (38 v 33%, p=0.003) and were on statin (12% v 9%, p=0.005). So a family history may shorten the warranty on a zero calcium score.

The authors estimated the potential impact of family history in this low risk group. It would raise the CV event rate from 0.33% a year to 0.44% and the CAD event rate from 0.18% to 0.24% per year. The number needed to treat (NNT) to prevent one CV event over 5 years for statins would be 197 with a family history and 327 without. For aspirin the NNT would be 312 with a family history and 605 without. It should be pointed out that family history in this study was defined as a history of a "heart attack", which is fraught with misinterpretation. Perhaps a more robust analysis of family history would have strengthened its predictive value. I believe a more nuanced family history is valuable information and despite its limitations, this study lends strength to that belief. ■

ABSTRACT & COMMENTARY

Clinical Value of Handheld Echocardiography

By Michael H. Crawford, MD, Editor

SOURCE: Mehta M, et al. Handheld ultrasound versus physical examination in patients referred for transthoracic echocardiography for a suspected cardiac condition. *JACC Cardiovasc Imaging* 2014;7:983-990.

Small handheld ultrasound units are being deployed in emergency departments and other sites to aide in point-of-care cardiac diagnosis. However, little is known about the clinical value of handheld echocardiography (HHE). Thus, this group of investigators from the University of Oregon compared conventional echocardiography (CE) to HHE and physical examination findings in 250 patients referred to the echo lab for the possible diagnosis of left ventricular (LV) dysfunction, valve disease, cardiac source of embolism, and possible structural heart disease in arrhythmia patients. The physical examination was performed by an attending cardiologist, who was only told the reason for the echo request. Another cardiologist blinded to the other clinical findings performed the HHE. HHE did not include saline or contrast injections, and it does not have spectral Doppler. A cost analysis of further tests needed to make the diagnosis after physical examination or HHE was done. Of the 250 patients, 142 had a significant abnormal finding on CE. HHE correctly identified 82% of these abnormal findings and physical examination identified 47%. When broken down by abnormality, HHE was superior at identifying abnormal LV and right ventricular function and moderate or severe valve disease, with the exception of aortic stenosis. However, physical examination rivalled HHE for detecting pulmonary hypertension and excluding significant valve disease. Further testing was recommended in the patients with abnormalities detected by CE (90% after physical exam and 91% after HHE). In those with no abnormalities on CE, further testing was recommended after HHE in 56% and after physical examination in 82% ($P < 0.001$). Costs were not appreciably altered by the addition of HHE. The authors concluded that when used by cardiologists, HHE was superior to physical examination for identifying most cardiac abnormalities, and a negative HHE results in less additional testing vs physical examination alone.

■ COMMENTARY

As small handheld portable echo machines have gotten smaller and included color Doppler, their use has increased. They are frequently used in emergency departments and critical care units to rapidly diagnose severe LV systolic dysfunction, pericardial effusion, and pulseless electrical activity. Some, like the authors of this paper, are recommending its routine use to supplement or replace the cardiac physical examination. In

fact, some medical schools are now issuing these machines to incoming first-year students. Using CE as the gold standard, this study compared the results of physical examination vs HHE for diagnosing common cardiac conditions. In many ways, this is an apples to oranges comparison, and the results are predictable. One wouldn't expect physical exam to be terribly good at detecting mild LV systolic dysfunction or moderate tricuspid regurgitation, and it wasn't. On the other hand, physical exam was highly accurate at detecting severe aortic stenosis vs an HHE machine with no spectral Doppler.

The most important issue in the adoption of this technology for routine practice is cost. This paper hypothesized that by making better diagnoses at the bedside, downstream testing costs would decrease and the health system overall would see reduced cost. The results could not conclusively confirm this hypothesis, partly because the study wasn't designed as a proper cost analysis study. On the other hand, there are clear costs associated with employment of this approach that were barely touched upon. First, the device costs several thousand dollars and the service is not billable. Also, in the authors' hands, HHE took an additional 8 minutes to perform. Once cardiologists have seen three patients and used HHE, they have decreased their patient throughput by one patient (24 minutes for 3 HHE exams). A full clinic day's patient volume would be reduced by 25%, with no additional billing to compensate. That just isn't economically feasible today.

A strength of this study was that the physical exam and HHE were done by staff cardiologists. Since echocardiography is part of every cardiologist's training and is tested at a basic level on the Board exam, presumably HHE was well done. Physical examination is known to be a declining skill. It would have been useful to know if a particular protocol was used by all. Since the average cardiac physical exam took 5 minutes in this study, it sounds comprehensive, but I would like more details. Also, what stethoscopes were used. In cardiac auscultation unlike lung auscultation, equipment does matter. Not a week goes by when I don't hand a resident my $300 stethoscope so they can hear the murmur that they missed with the free stethoscope they got in medical school.

So the debate goes on. At this point HHE has a clear role in specific hospital settings and is superior to physical examination for many subtle diagnoses. However, for routine clinical use, the benefits don't yet outweigh the costs. As these machines become part of your phone in the future, acceptance will grow, but it won't take off until the economics of their use improves. ■

ABSTRACT & COMMENTARY

Value of ECG LVH in Aortic Stenosis

By Michael H. Crawford, MD, Editor

SOURCE: Chin CW, et al. Left ventricular hypertrophy with strain and aortic stenosis. *Circulation* 2014;130:1607-1616.

Progressive, compensatory left ventricular hypertrophy (LVH) in aortic stenosis (AS) ultimately leads to myocardial injury, fibrosis, and LV dysfunction. These investigators from the United Kingdom hypothesized that the LV strain pattern on electrocardiogram (ECG) is a marker for this degenerative process and may be useful to select asymptomatic patients with severe AS for valve replacement. Three groups of patients were studied. First, patients with any severity of AS were evaluated by cardiac MRI and plasma troponin to determine the pathophysiology of the LVH strain pattern (n = 102). The findings were validated in a similar population from another UK center (n = 64). The third group was recruited from an AS lipid-lowering trial population to determine outcomes related to the ECG strain pattern (n = 140). Confounders such as bundle branch block, cardiomyopathy, AV replacement, reduced LV systolic function, and digoxin use excluded patients from these groups. In the first group, 50% of the patients had LVH on ECG, and 40% of these patients had the strain pattern. Using magnetic resonance imaging (MRI) as the gold standard, ECG had a 96% positive predictive value for LVH and an 89% negative predictive value. Those with the LVH strain pattern had the highest LV mass indices on MRI and the

most severe AS ($P < 0.001$). Despite similar LV ejection fractions, the patients with LVH strain pattern had reduced longitudinal and midwall shortening. Also, they had higher troponin values, MRI extracellular volume, and all of them had MRI late gadolinium enhancement. MRI showed localization of fibrosis in the mid ventricular area. LVH strain was not associated with the presence of coronary artery disease (CAD). Findings in the validation group were similar. In the outcome group, 14% had LVH strain pattern, which was associated with reduced 10-year event-free adjusted survival (hazard ratio, 2.67; 98% confidence interval, 1.35-5.27; $P < 0.01$). The authors concluded that the ECG LVH strain pattern in patients with AS is a marker for LV midwall fibrosis and predicts a lower 10-year event-free survival.

■ COMMENTARY

The timing of aortic valve replacement in AS is a challenge. In the new AHA/ACC Valve Disease Guidelines (2014) class I recommendations for valve replacement in severe AS include: symptoms and a LV ejection fraction (EF) < 50% or when undergoing other cardiac surgery. The problem with symptoms is that they are subjective and hard to determine in sedentary elderly patients. LVEF < 50%, in my experience, is a late manifestation of severe AS. Clearly, earlier objective indicators are needed. Two have made it to class IIa indicators for surgery in severe AS: a heavily calcified valve and the development of hypotension during exercise testing. The former has no quantitative criteria and the latter represents some risk to the patient and is not always feasible in older sedentary individuals. Thus, the search continues.

This interesting study shed considerable new light on the subject and proposes some new criteria for valve replacement in asymptomatic severe AS patients. The simple ECG LVH with strain pattern is associated with midwall fibrosis, myocardial injury, and reduced myocardial shortening. Also, it predicts reduced event-free survival over 10 years. Although the association of ECG LVH strain and poor outcomes has been observed in prior studies, this is the longest follow-up of such patients in the literature. Previous studies have hypothesized that the LVH strain pattern may be due to myocardial ischemia, which is due to increasing LVH or CAD, or both. This study does not address coronary blood flow per se, but does show the LVH strain pattern is associated with increased fibrosis on MRI, which could be the result of ischemia or the stimulation of fibrous cell growth along with myocardial cell growth. Interestingly, LVH strain was not associated with the presence or absence of coronary artery disease in this study.

USING MRI AS THE GOLD STANDARD, ECG HAD A 96% POSITIVE PREDICTIVE VALUE FOR LVH AND A 98% NEGATIVE PREDICTIVE VALUE.

One limitation to this study is that all the subjects were Caucasians. Equatorial Africans are known to have a higher frequency of high ECG QRS voltage and other unusual ECG patterns that could alter the reliability of the LV strain pattern in such individuals. In addition, the study employed three different patient populations that could introduce other biases that may have affected the results.

So would the LVH with strain pattern be a good early indication for valve replacement? Although highly specific for myocardial fibrosis (100%), it is not very sensitive (< 70%). In the multivariate analysis done in this study, only MRI fibrosis and the severity of AS were independent predictors of ECG LVH strain. MRI may be a sophisticated and expensive tool to decide in asymptomatic severe AS patients, whom to replace their valve. On the other hand, just replacing the valve in everyone with severe AS may also make sense. Unfortunately, it is a tough sell in asymptomatic patients. As transcutaneous atrioventricular valve replacement becomes more successful, this sell may be easier. ■

QUESTIONS & COMMENTS:
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CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
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CME QUESTIONS

1. Current handheld echo imaging is superior to physical examination for detecting:

A. pulmonary hypertension.

B. significant aortic stenosis.

C. mild-to-moderate LV dysfunction.

D. All of the above

2. Patients with a coronary lesion with normal fractional flow reserve have what percent chance of needing subsequent revascularization in 1 year?

A. 5%

B. 10%

C. 20%

D. 30%

3. Thienopyridine pretreatment in non-ST elevation acute coronary syndromes (NSTE-ACS) patients undergoing percutaneous coronary intervention (PCI) should be withheld:

A. if PCI will be delayed > 48 hours.

B. if PCI is done in < 24 hours.

C. in high-risk younger patients.

D. All of the above

4. In aortic stenosis patients, the electrocardiogram left ventricular hypertrophy (ECG LVH) with strain pattern is associated with:

A. midwall myocardial fibrosis.

B. severe AS.

C. poor long-term outcomes.

D. All of the above

5. After adjustment for other risk factors, a family history of coronary artery disease (CAD) increases the risk of:

A. all cardiovascular events.

B. only CAD events.

C. only non-cardiac events.

D. all-cause mortality.

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.