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INSIDE

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Timing of Catheterization in NSTE-ACS

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Tricoci P, et al. Time to coronary angiography and outcomes among patients with high-risk non-ST-segment-elevation acute coronary syndromes: Results from the SYNERGY trial. *Circulation*. 2007;116:2669-2677.

An early invasive approach is preferred for higher risk non-ST elevation acute coronary syndromes (NSTE-ACS), but the optimal timing of cardiac catheterization is not clear. Thus, Tricoci and colleagues used data from the Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein 11b/111a Inhibitors (SYNERGY) trial to evaluate the relationships between the time from hospital admission to coronary angiography and ischemic and hemorrhagic events in over 6,000 patients with NSTE-ACS treated with an invasive strategy within 48 hours of hospital admission.

Patients enrolled in SYNERGY had ischemic symptoms within 24 hours, and two or more of the following high risk features: age > 60; biomarker elevations; ST depression; or transient ST elevation. The patients were randomized to unfractionated heparin or enoxaparin; all received antiplatelet therapy, and use of GP11b/111a agents were encouraged. Patients were grouped into 6-hour intervals from hospital admission to coronary angiography. The primary outcomes were: death or myocardial infarction (MI) in 30 days; major bleeding episodes; and need for blood transfusions. Sophisticated multivariate and landmark methods were employed to adjust for confounders. In general, patients who received an earlier catheterization were younger and had ST changes on the ECG. Adjusted estimates of 30-day death/MI increased as time to angiography increased. The adjusted odds ratio for death/MI in those receiving angiography in < 6 hours was 0.56 (95%; CI 0.41 to 0.74) as compared to .84 at > 30 hours. After 30 hours, the benefit on the primary end point plateaued through 48 hours. Major bleeding and transfusion requirements, not related to coronary bypass surgery, were not associated with time of catheterization. Tricoci et al concluded that shorter times from hospital admission to coronary angiography are associated with few deaths and MIs within 30 days, without any increase in bleeding complications.

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COMMENTARY

Most studies of NSTE-ACS have shown an advantage for an early interventional strategy, with regard to subsequent death and MI, but a few have not. Higher risk patients seem to benefit more from the early invasive strategy, but the definition of early in the reported studies has varied from an average of 22 hours after admission to four days. ISAR-COOL compared a < 6 hour invasive strategy to angiography after 3-5 days of cooling-off on maximal medical therapy. In that study, 30-day death or MI was less in the < 6 hour group, but no one had angiography between 6 hours and 3 days, when most cases are done outside of this trial. This timing issue is potentially important on several levels. If the problem is myocardial ischemia, then the earlier you restore adequate blood flow the better, and an early invasive strategy allows for early revascularization. If the results of a percutaneous coronary intervention (PCI) would be improved by 6 hours of preloading with clopridogrel and GP11b/111a agents, then this should be considered. There is also the issue of off-hours procedures, which cost the health care system more and may be conducted under less than ideal circumstances. Consequently, the results of this analysis of the SYNERGY trial is of interest, even though it is not a randomized trial of angiography delay times.

The results showed the best results were with angiography performed < 6 hours after admission (RR = 0.59). Between 6 and 29 hours, the RRs ranged from 0.67 to 0.76, but at 30-48 hours, they jumped to 0.84 to 0.87. Thus, < 6 hours was best, but if that isn't possible then < 30 hours is acceptable. Since this was not a randomized trial, some limitations need to be considered. Factors associated with being selected for an earlier catheterization included admission to a US hospital, younger age, white, positive biomarkers, and a weekday admission. Interestingly, higher risk patients with diabetes or heart failure received later catheterization on average. This may be due to the belief that it is better to control heart failure and diabetes before undertaking angiography. This may be true in some situations, but in ACS, where myocardial ischemia is the issue, it may not be. Clearly, this is a judgment call. I have seen patients thought to have NSTE-ACS with hypotension who, in the middle of a complicated catheterization, were found to have diabetic ketoacidosis when the admission labs came back. Also, I have seen cases thought to have NSTE-ACS with heart failure taken to the cath lab only to find there were no significant coronary lesions. Thus, sometimes in our haste to meet timing goals associated with ACS and PCI we end up putting some patients in more jeopardy. Although the weight of evidence now seems to say that earlier is better with regard to cardiac catheterization in high risk NSTE-ACS patients, this should not trump good clinical judgment and an appreciation of the resources available at a given time.

Hopefully, < 6 hour angiography will not become some new quality improvement goal like door-to-balloon time has because these data are observational and not robust. Also, there are several problems with this type of study; adjusting for confounders has its limits. For example, PCI was more often done when the patients were cathed early, and less often when done later. Presumably, this was anatomically driven, which suggests that those with true myocardial ischemia were being selected for early intervention. Of course there may be other explanations such as medical therapy reduces the need for PCI. The end point of death or MI is standard in these types of studies, but MI is problematic since many patients with NSTE-ACS have biomarker positivity and presumably have an MI. When does the initial MI end and a new one begin? Of note, when Tricoci et al eliminated the biomarker positive patients, they got the same results. Also, the selection of 6-hour increments in this study was arbitrary. In addition, the timing started at hospital admission, not onset of symptoms. Perhaps the latter should be taken into account. Unfortunately, a true randomized time trial will probably never be done, so we are stuck with the available data. At this time, it would appear that an earlier intervention is better in high-risk NSTE-ACS patients, but good clinical judgment needs to be exercised to avoid unnecessary increases in risk to the patient. ■

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Long-Term Outcomes with Bare Metal Stents

ABSTRACT & COMMENTARY

By Andrew Boyle, MBBS, PhD

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

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

Source: Doyle B, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal stents. *Circulation*. 2007;116:2391-2398.

Recently, there has been considerable concern regarding the long-term safety of drug-eluting stents. Reports of late (> 30 days post implantation), and very late (> 1 year post implantation), stent thrombosis have raised concern over these devices, and there has been a corresponding resurgence in the use of bare metal stents. Bare metal stents (BMS) are known to have a low rate of subacute stent thrombosis (< 30 days post implantation), less than 1% on dual anti-platelet therapy, both in clinical trials and in years of clinical experience. In-stent restenosis (ISR) is the major Achilles' heel of BMS, and ISR has been considered "benign" compared to stent thrombosis. Therefore, despite scant long-term follow-up data, BMS have been considered a safe option in the long term.

Doyle and colleagues performed a retrospective study of a large cohort of patients undergoing PCI at the Mayo Clinic from 1994 to 2000, to determine the long-term outcomes of BMS, with a focus on stent thrombosis and ISR. The follow-up period was up to 10 years. They included all patients who had PCI with BMS, performed in the standard manner followed by 2-4 weeks of dual anti-platelet therapy. All patients received intra-procedural heparin via the same protocol, and the use of platelet glycoprotein IIb/IIIa inhibitors was at the operator's discretion. Exclusion criteria were: cardiogenic shock; intra-procedural complications; brachytherapy; inability to receive dual anti-platelet therapy for any reason; patient refusal to participate; and the use of investigational stents. During the study period, 4855 patients underwent PCI and 4503 were eligible for the study; 93% of these had follow-up data available. Baseline demographics of this cohort showed 71% were male, mean age of 65 years, and 21% were diabetic, which is similar to many large cohort studies of real-world patients. Of the study participants, 68% presented with unstable angina, 10% with acute myocardial infarction (MI), and 14% presented within a week of acute MI, representing a relatively high-risk population. The procedural characteristics of this cohort also showed they were not at low risk: 41% of patients had 2 or more stents placed; 45% of lesions were type C; 13% were bifurcation lesions; 31% had visible thrombus; and 8% were in saphenous vein grafts.

The cumulative incidence of stent thrombosis was 0.5% at 30 days, 0.8% at 1 year, and 2.0% at 10 years. Stent thrombosis at any time after implantation is associated with an increased mortality. Doyle et al used the Academic Research Consortium (ARC) definition of definite and probable stent thrombosis, but did not include possible stent thrombosis. Late, or very late, stent thrombosis presented with ST elevation MI in 44% and with non-ST elevation MI in 56%. Doyle et al subdivided the cohort based on "on-label" use, a single stent in a native coronary artery for a de novo lesion, versus "off-label" use, including all other cases. At 10-years post-implantation, the incidence of stent thrombosis was slightly higher in off-label uses (2.5% vs 1.4%, $P = 0.024$ vs on-label), but there was no significant difference at earlier time-points. However, when saphenous vein graft PCI were excluded, there was no difference in stent thrombosis between "on-label" and "off-label" uses at any time-point. The factors that correlated with increased risk of late, or very late, stent thrombosis were a mix of lesion- and patient-specific factors: ulcerated lesions; vein graft PCI; prior MI; prior stroke; prior bypass surgery; heart failure; and peripheral arterial disease. This suggests that a large burden of atherosclerotic disease in a patient may predispose them to late events. Doyle et al point out that this may reflect progression of disease, rather than the stent itself, but further studies are needed to confirm this.

ISR was found in at least one stent in 9.6% of patients at 1 year, 13.9% at 5 years, and 18.1% at 10 years. Interestingly, although ISR is often considered benign, the presentation of ISR over 10 years with stable angina in 9%, unstable angina in 7.4%, MI in 2.1%, and other unstable presentations like decompensated heart failure or ventricular arrhythmias in 0.4%. Doyle et al focused on the 2.1% of patients whose ISR presented with MI. These patients had increased mortality, with a hazard ratio of 2.4, compared to those whose ISR did not present with MI. Patients with ISR who did not present with MI had the same mortality as those with no ISR at all. Doyle et al caution that BMS are associated with a 2.1% rate of ISR presenting with MI over 10 years, and that this is associated with an increased mortality. Therefore, choosing a BMS because restenosis is considered "benign", compared to the risk of stent thrombosis caused by drug-eluting stents, may not necessarily be appropriate. Furthermore, although BMS have lower rates of stent thrombosis than drug-eluting stents, the rates of death and MI appear similar.

Doyle et al suggest that the 2.1% rate of MI presentation of ISR, and the corresponding increase in mortality, may explain this discrepancy.

COMMENTARY

This study is limited by its retrospective design and the small numbers of events. Also, no data regarding duration of, or compliance with, dual anti-platelet therapy are presented. Another limitation is that the BMS used during the study period may not reflect the outcomes of newer BMS technologies that have reached the market since then. Finally, no comparisons can be drawn with other methods of treating coronary disease, such as medical therapy, drug-eluting stents, or bypass surgery. Notably, most of the patients in this study presented with acute coronary syndromes, so patients with stable coronary artery disease treated with BMS may not have the same outcomes. However, this study provides excellent long-term follow-up in a large cohort of patients reflecting current real-world clinical practice. Furthermore, using contemporary definitions of stent thrombosis, rather than old trial definitions, provides important new information that may help guide clinicians in decision-making in the cardiac catheterization lab.

In summary, use of BMS is associated with a significant risk of both stent thrombosis (2.0%) and ISR presenting with acute MI (2.1%) over a 10-year follow-up associated with increased mortality. The current tendency to use BMS over drug-eluting stents, for reasons of safety, may not be justified. Clinical decision-making should weigh the relative risks of restenosis and thrombosis on the basis of lesion- and patient-specific variables. ■

VT Ablation to Reduce ICD Shocks

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Professor of Medicine, Division of Cardiology, University of Virginia, Charlottesville

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

Source: Reddy VY, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. *N Engl J Med*. 2007; 357:2657-2665.

THIS PAPER GIVES THE RESULTS OF THE SUBSTRATE Mapping and Ablation in Sinus Rhythm to Halt Ventricular Tachycardia (SMASH-VT) study. This study was designed to test the hypothesis that early prophylactic catheter ablation in patients with implantable cardioverter defibrillators (ICD) would decrease the frequency of ICD shocks during follow-up. Reddy and colleagues recruited patients with prior myocardial infarction who had either a planned or recent ICD implantation for spontaneous or electrically-induced ventricular tachycardia or a prior ICD implantation for primary prophylaxis, and subsequently received appropriate ICD therapy for a single event. Patients were excluded if they were receiving class I or class III antiarrhythmic drugs. Most patients were on beta blockers and ACE inhibitors. Smaller proportions were on statins and aspirin. Ventricular tachycardia ablation was performed using a 3-step protocol. First, programmed electrical stimulation was used to induce ventricular tachycardia, and the ECG morphology of all the ventricular tachycardias induced was recorded. Substrate 3 dimensional mapping then was used to define the localization and extent of any myocardial scar. Finally, pace mapping was used to locate probable exit sites for ventricular tachycardia from the areas of the scar. Mapping was performed using an electrical anatomical 3-dimensional mapping system (CARTO) using either a retrograde or combined retrograde transseptal approach.

The study group included 128 patients who were randomly assigned to VT ablation or no further therapy. The mean age was 67 years, and a large majority were men. Approximately 80% were New York Heart Association functional class I or II. The mean left ventricular ejection fraction was 31%. Two patients assigned to the ablation group did not undergo the procedure, and in three patients, no endocardial scar was visualized and no ablation lesions were placed. The number of VTs induced per patient, and the success of the ablation procedure in suppressing VT induction, was not reported. There were three significant complications related to the ablation procedure: one patient developed a pericardial effusion without tamponade; a second patient had an exacerbation of congestive heart failure, which required a prolonged hospitalization; and one patient developed a deep venous thrombosis.

Patients were followed for a mean duration of 22.5 ± 5.5 months. During follow-up, 8 patients in the ablation group (12%) and 21 patients in the control group (33%) received appropriate ICD therapy at least once. In 6 of the 8 ablation patients, and in 20 of the 21 control patients, at least one appropriate ICD shock was delivered. Mortality was 9% in the ablation group, compared to 17% with the control group; this difference was not statistically significant. Episodes of multiple ICD shocks ("VT storms") were noted in 4 patients assigned to the ablation group and in 12 control patients. In both groups,

there was no change in the overall New York Heart Association functional class.

Reddy et al concluded that substrate-based catheter ablation reduces the incidence of ICD therapy in patients with a prior history of arrhythmias.

COMMENTARY

The results of the SMASH-VT study confirm that catheter ablation of ventricular tachycardia can be a useful adjunct in patients with implantable defibrillators. Most electrophysiologists use drug therapy as the initial approach to decrease VT shock frequency in ICD patients. In SMASH-VT, the control group was not treated with antiarrhythmic drugs, and catheter ablation did prove to be better than no therapy. The most relevant randomized trial to compare to SMASH-VT is the OPTIC trial (*JAMA*. 2006; 295:165-171). In that study, ICD patients were randomized to treatment with either beta blockers, sotalol alone, or beta blockers plus amiodarone. Sotalol resulted in a 30% reduction in ICD therapy, and amiodarone resulted in a greater than 70% reduction in ICD therapy. Therefore, it appears that the results of catheter ablation are similar to drug therapy, but it is likely that catheter ablation is more expensive and may have more early complications.

It is also interesting that most of the catheter ablations were apparently carried out in the single non-US site. The reason for this is unexplained in the paper, but is probably due to pre-enrollment bias at the two US sites.

I don't think that SMASH-VT will change the approach of most electrophysiologists to the use of catheter ablation. Catheter ablation will remain an effective and useful tool, but most patients will receive a course of drug therapy before being referred for the procedure. ■

Stroke and Infective Endocarditis

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Dickerman SA, et al The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: An analysis from the ICE prospective cohort study (ICE-PCS). *Am Heart J*. 2007;154: 1086-1094.

THE APPROPRIATE TREATMENT OF INFECTIVE ENDOcarditis (IE), to avoid embolic stroke, is unclear. Thus, Dickerman and colleagues explored the International Collaboration on Endocarditis Prospective Cohort Study (ICE-CPS) database to define the temporal occurrence of stroke in relation to antibiotic therapy. The study population included 1437 patients with left-sided IE who met modified Duke criteria for the diagnosis of IE. The case report forms from 61 centers in 28 countries included 275 variables, including indications for surgery. However, information on vegetation size and mobility was not collected. Most of the patients were male (67%), elderly (mean age 62), and had native valve IE (74%). The numbers with IV drug use or AIDS were small (6 and 2%).

In this cohort, 219 (15%) had a stroke, but incomplete data about the stroke reduced the analyzed population to 185 stroke patients. One half had a stroke prior to antibiotic administration. The daily rate of stroke fell dramatically the second day of antimicrobial therapy. This observation is influenced by the fact that stroke was often the reason for seeking medical attention. If day one is eliminated, the rate of stroke still fell 65% in the second week of therapy (4.82/1000 patient days to 1.7, $P < .001$). Correction for patients going to surgery did not change the results significantly. After one week of therapy, only 3% of the entire cohort (44/1437) experienced a stroke. Multivariate analysis showed mitral vegetation ($P < .0001$), *S. aureus* ($P = .01$), and intracardiac abscess ($P = .02$) were significantly associated with stroke. Viridans strep was associated with a lower risk of stroke ($P = .04$). Overall, 40% of the patients had valvular surgery on the index admission, but only 3.5% had the indication of large mobile vegetations alone. All the rest met standard criteria for surgery. Patients who had surgery had a lower incidence of stroke. There was no subgroup in which antibiotic therapy did not reduce the risk of stroke. Dickerman et al concluded that the risk of stroke falls dramatically after initiation of effective antibiotic therapy and precludes stroke prevention as a sole indicator for valve surgery after one week of therapy.

COMMENTARY

The decision regarding when to operate in patients with IE is difficult because of a lack of randomized, controlled data, as well as the small numbers of patients in observational series. The ICE-PCS gets around the latter problem and, since a randomized, controlled trial of surgery vs medical therapy will never be done, is worth considering. The purpose of this analysis was to determine the relationship between antibiotic therapy and subsequent stroke. The finding that stroke risk decreases rapidly after antibiotic therapy is started confirms the results of older, smaller, often single-center experiences. Also, the results extend to those with any organism and

any valve involvement. After one week of effective therapy, stroke risk from that point forward is 1-3%, depending on the valve and the organism. Stroke risk is higher with S. aureus and mitral valve involvement.

The practical implications of this information are that antibiotic therapy should be started early in IE and that stroke prevention alone may not be an indication for surgery. The classical indications for surgery were present in 96.5% of the patients who had surgery (heart failure, significant valve regurgitation, and persistent bacteremia). However, 40% of the patients had surgery, and surgery was associated with a lower risk of stroke. Although large mobile vegetations have been touted as a surgical indication in some studies, not all have found this. In this study, only 3.5% underwent surgery for this indication alone, but we don't know how many patients had this finding and were not operated upon because detailed echo data are not currently in their database. Also, there is no data on prior stroke or embolus (repeated emboli) as an indication for surgery. These issues will have to be the subject of future studies. ■

Patent Foramen Ovale and Cryptogenic Stroke

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Source: Handke M, et al. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med*. 2007;357: 2262-2268.

PATENT FORAMEN OVALE (PFO) HAS BEEN ASSOCIATED with cryptogenic stroke in young individuals, but the association is less clear in older individuals where other causes of stroke predominate. Thus, this study from Germany is of interest. Out of 596 patients admitted to their stroke center, 503 were able to undergo transesophageal echocardiography (TEE), and thus formed the study population. They also had head CT, MRI, or both and carotid artery duplex sonography. Cerebral angiography by MRI or contrast, before transarterial thrombolysis, was done in 231 (46%). In addition, transthoracic echo and ECG were done, and those suspected of having atrial fibrillation had 24-hour Holter monitoring. Before TEE, the TOAST criteria were applied to classify the patients into one of the 4 known-causes of strokes or cryptogenic stroke. TEE was done a median of 2 days after the stroke with contrast and Valsalva.

Results: Of the 503 patients, 26% were younger than 55 years of age. A cause of stroke could be identified before TEE in 55% of the patients. The rest were classified as cryptogenic (63% younger and 39% of the older patients). The prevalence of PFO was significantly greater in patients with cryptogenic stroke vs known cause stroke in the younger (44% vs 14%, OR 4.7, $P < .001$) and older patients (28% vs. 12%, OR 2.9, $P < .001$), as was the prevalence of PFO with atrial septal aneurysm (13 vs 2%, OR 7.4 younger and 15 vs 4% or 3.9 in the older). Multivariate analysis showed that PFO was independently associated with cryptogenic stroke in both groups (OR 3.7 young and 3.0 older). Handke and colleagues concluded that PFO with paradoxical embolism is a cause of cryptogenic stroke at all ages.

■ COMMENTARY

Previous studies of the association between PFO and cryptogenic stroke have focused on younger patients because they have few confounding diseases that also are associated with stroke. Thus, when PFO is found in younger cryptogenic stroke patients, especially if atrial septal aneurysm is present as well, the decision to close it is easy to make. Older individuals present a challenge because of their higher frequency of alternative causes of stroke, as well as the paucity of data in older patients. This study solves the latter problem by doing TEE in a large group of older patients with stroke, and finding an association with PFO in those classified as cryptogenic. Also, the stronger association of PFO plus atrial septal aneurysm was also observed in the older patients. In addition, the older patients with cryptogenic stroke and PFO were observed to have less thick aortic atherosclerotic plaques. Although the incidence of PFO decreases with age (34% < 30 years vs 20% > 80 years), the incidence of venous thromboembolism, right atrial pressure elevation, and larger PFOs increased with age. Thus, it is not surprising that PFO is associated with cryptogenic stroke in older patients.

The issue is what to do with this information therapeutically? Despite the issue that cryptogenic stroke prevalence was probably inflated in this study, since cerebral angiography was done in only half the patients, the incidence of PFO was < 50% in this group. So, there are many patients with some other unknown cause of stroke. Also, some patients with known cause stroke also had PFOs (12-14%). Just because you have a PFO, does this absolutely mean it is the cause of the cryptogenic stroke? Certainly not. Perhaps in those with PFO plus atrial septal aneurysm and cryptogenic stroke, causality is a better bet, since few with known cause stroke had this finding (2-4%). Until we know the

results of the device vs medical therapy trials in cryptogenic stroke currently underway, what do we do? It seems reasonable, if cryptogenic stroke is diagnosed after a full evaluation including MR angiography, and TEE shows PFO plus atrial septal aneurysm, to close it. With a PFO alone, the decision becomes more difficult. Clearly, if there is any history of deep venous thrombosis, or evidence of it on peripheral Doppler examination, then closure seems reasonable; although you could reasonably offer lifelong warfarin as an alternative. With PFO alone, you and the patient will have to decide between aspirin, warfarin, or closure. How to close the defect is also not entirely clear, and I don't know of any trials of minimally-invasive surgical closure vs percutaneous device closure. A recent young patient of mine opted for minimally-invasive surgery over a device whose long-term history is unknown. Surgical closure in the absence of pulmonary hypertension in a young person should have a mortality of zero. Although this study contributes important new information on the topic, the management of PFO in patients with cryptogenic stroke at all ages is still a challenge. ■

Childhood Obesity — A Looming Disaster

ABSTRACT & COMMENTARY

Sources: Baker, et al. Childhood body-mass index and the risk of coronary heart disease in adulthood. *N Engl J Med*. 357:2007; Ludwig, David S. Childhood obesity — The shape of things to come. *N Engl J Med*. 357:2007.

THIS REMARKABLE STUDY IS A POPULATION ANALYSIS of a huge cohort of children in Denmark who were followed, since 1930 or later, for the presence of coronary heart disease (CHD), and had all mandatory annual examinations at schools in Copenhagen. The study analyzed data from 277,000 children, aged 7-13. During a 46-year period, over 10,000 CHD events occurred among men and 4,300 among women; there were 5 million person-years of follow-up! BMI was identified for each child from years 1955-1960; the BMI score was calculated by subtracting the child's BMI from the mean BMI in this fixed-reference population and dividing the result by the standard deviation of the reference population. The investigators employed the National Death Registry in Denmark, as well as the ICD-8 and ICD-10 curves (International Classification of Diseases). Late follow-up of subjects began at age of 28, or in 1977 (when the Hospital Discharge Registry was established). Almost 281,000 subjects were eligible for analysis. Cox proportional-hazards regression data were used to assist in the analysis of data to determine the probability of adult CHD events. Probabilities for children were calculated separately at ages 7 and 13.

Results: During the 46 years of surveillance, over 14,000 CHD events were recorded. When the data was assessed for the effect of childhood BMI on the effect of any CHD event, it was found that the risk for events in adulthood increased significantly for each one unit increase for BMI score. The risk of adult CHD was highest for boys who had the highest BMI values and lowest for boys with the lowest BMI levels. The risk of an adult event increased as the children's age increased for both boys and girls; risk for girls was lower for all events. The risk of non-fatal events was associated with childhood BMI, and increased with the age of the child; the association between childhood BMI and adult non-fatal events was linear. Fatal events occurred in 32,000 women with risk, and were associated with increasing age in those with a high childhood BMI. Probabilities of CHD events during adulthood was not high in either group of children, but were elevated when compared to non-obese subjects. For instance, an average-sized boy of 13 had a 33% higher risk of a CHD event in adulthood if he was obese in childhood.

The authors conclude that "higher childhood BMI values elevated the risk of having a CHD event in adulthood, with risk increasing linearly in boys and girls." Birth weight was not shown to have an interaction with subsequent obesity or with an increase in events. "Childhood BMI, even after the effects of birth weight have been taken into account, is associated with CHD in adulthood."

■ COMMENTARY

Many studies and publications emphasize risk factors for CHD, which are essentially the same in childhood as in adults. These include hypertension, abnormal glucose, and dyslipidemia. Body weight in childhood is associated with the presence of these risk factors in children, linking high childhood BMI with an increase risk of adult CHD. Identifying at-risk boys and girls is important, in that subsequent CHD events can be ameliorated. The authors note that the BMI relationship to coronary events began before the "emergence of the obesity epidemic," and all birth cohorts showed the same relationships to adult CHD. The investigators believe that "the associations. . .observed are based on the biologic effects of the children's BMI," as childhood obesity is already associated with distinct biologic risk factors. They note

that contemporary children are heaver than their counterparts from the past, with no evidence of a slow down in childhood overweight and obesity; this situation occurs in Denmark and presumably many other countries. The authors calculated the probability of a child having a future CHD event, with the example of a 13-year-old boy who weighs 11 kilos more than average and who has a 33% increase in probability of a CHD event before age 60. Between 7 and 13 years old, there is a substantial increase in risk, which suggests "the possibility of intervention during this period of childhood can reduce the risk of future CHD.

An accompanying editorial stresses the history of weight gain over the past 40 years, "with average weight increasing progressively among children from all social and economic levels, racial and ethnic groups, and regions of the country." The author, David Ludwig, suggests that one in three children in adolescence are overweight (BMI in to the 85th-95th percentile for age and sex) or obese (BMI above the 95th percentile), with risk ratio close to one in two in minority groups. Phase one of the obesity revolution was the last 40-50 years, and phase two is now characterized by serious weight-related problems in children, including diabetes, fatty liver, orthopedic problems, sleep apnea, psychological problems, including social isolation, eating disorders, and often an adverse socio-economic background. Other data confirm these statements. Ludwig states that "pediatric obesity may shorten life expectancy in the United States by 2-5 years by mid century, an effect equal to that of all cancers combined." A true epidemic will become possible through acceleration of the obesity rates through multiple mechanisms over many years. "Obese children tend to be heavy in adulthood, in part because obesity-promoting habits persist." In addition to metabolic problems, many abnormalities are related to childhood obesity and subsequent adverse events. He calls for a comprehensive national strategy, involving junk food meals and advertising, adequate funding for healthy lunches, regular physical activity, and the restructuring of the foreign subsidy program to favor nutrient-dense rather than calorie-dense foods that are of high quality.

The data from this very large study speaks for itself. This elegant analysis of many decades, with remarkably complete follow-up, and confirmation that CHD risks have been accelerating over decades, calls for immediate and major public action. The overall prevalence of obesity in adults has been steadily increasing. Enormous effort and literally billions of dollars have been spent on adult obesity in the past decade or more, and there has been some suggestion of a slowing of the atherogenic conditions in our adult population. How much better it would be to link childhood, early adulthood, and full adulthood together in educational programs, emphasizing changing our dietary patterns, emphasizing healthy nutrients, including vegetables and fruits, demanding healthy lunches in our schools, and providing our children and adults with regular exercise programs. The Danish study should be a clarion call for national policy makers, industry, and health care workers of all types, resulting in an increase expenditure of funds for fighting obesity in children. ■

CME Question

5. Optimal 30-day benefits of an invasive strategy selected as high risk NSTE-ACS are obtained when catheterization is performed:
a. < 6 hours after admission.
b. 6-12 hours after admission.
c. 12-24 hours after admission.
d. > 24 hours after admission.

6. The best way to prevent stroke in infective endocarditis is:
a. surgery.
b. warfarin.
c. prompt antibiotic therapy.
d. A and C

7. There is a 2% in 10-year risk of:
a. stent thrombosis with drug eluting stents.
b. stent thrombosis with bare metal stents.
c. in-stent restenosis MI with bare metal stents.
d. A and C

8. PFO is associated with stroke in patients:
a. < 16 years old.
b. 16-55 years old.
c. > 55 years old.
d. all ages.

Answers: 5. (a); 6. (d); 7. (d); 8. (d)

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. ■

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.

Another Study Implicates Avandia

In this issue: *Rosiglitazone (Avandia) implicated in yet another study; Prilosec and Nexium not associated with cardiac events; Anastrozole (Arimidex) shown more effective than tamoxifen for treatment of early-stage breast cancer; antibiotics show no effect on sinusitis; FDA actions.*

THE HANDWRITING MAY BE ON THE WALL FOR GlaxoSmithKline's rosiglitazone (Avandia) with yet another study implicating the drug with an increased risk of heart failure, cardiovascular events and mortality when compared to other oral hypoglycemic agents. The study was a nested case-control analysis of a retrospective cohort study using health care databases in Ontario. The patient population was nearly 160,000 older (>65 years of age) type 2 diabetics on at least one oral agent. The primary outcome was emergency visit or hospitalization for congestive heart failure, while secondary outcomes were AMI and all-cause mortality. After a mean follow-up of 3.8 years, monotherapy with rosiglitazone was associated with an increased risk of CHF (RR 1.60; 95% CI 2.10; *P*<.001), AMI (RR 1.40; 95% CI, 1.05-1.86; *P*=.02), and death (RR 1.29; 95% CI, 1.02-1.62; *P*=.03). Thiazolidinediones in general were evaluated in the study, but the adverse effects were limited to rosiglitazone. Adverse effects were found in patients who took the drug as a single agent or in combination with other hypoglycemic drugs (*JAMA*. 2007;298:2634-2643). Meanwhile, two large pharmacy benefit managers, Prime Therapeutics and HealthTrans, have dropped rosiglitzone from their formularies and the Department of Veterans Affairs is severely limiting the drug's use. Sales of the drug dropped 27% in the second quarter of 2007 and 39% in the third quarter.

Prilosec and Nexium Cleared

Omeprazole (Prilosec) and esomeprazole (Nexium) are not associated with increased rates of cardiac events, according to statements on the FDA web site. Concern was raised after AstraZeneca submitted data from two long-term studies in patients with severe gastroesophageal reflux to assess treatment with either drug vs surgery. Evaluation of secondary outcomes raised the question of whether long-term use of these drugs increased risk of cardiovascular events including sudden death. In a statement published on the FDA web site (www.fda.gov) on December 10, the agency states that it has completed a comprehensive scientific review of known safety data for both drugs. Based on review of the two studies presented by AstraZeneca and analysis of 14 comparative studies of omeprazole, no evidence of increased rate of cardiac events was seen. "Therefore, FDA continues to conclude that long-term use of these drugs is not likely to be associated with an increased risk of heart problems. The FDA recommends that health-care providers continue to prescribe, and patient's continue to use, these products as described in the labeling for the two drugs."

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Anastrozole over Tamoxifen for Breast Cancer

Anastrozole (Arimidex) is more effective than tamoxifen as adjuvant treatment for early-stage breast cancer according to a study published online as an early release in the *Lancet Oncology*. The study looked at 6241 women with locally invasive breast cancer who were randomized to anastrozole or tamoxifen and followed for a median of 100 months. Primary endpoints were disease-free survival, and secondary endpoints were time to recurrence, incidence of new contralateral breast cancer, time to distant recurrence, overall survival, and death after recurrence. Endpoints were evaluated in the total population and in the hormone-receptor-positive subpopulation. The primary endpoint and all secondary endpoints favored anastrozole except for deaths after recurrence and overall survival for which there is no significant difference. Fracture rates were higher in patients receiving anastrozole compared to tamoxifen. There was no difference in cardiovascular morbidity or mortality between the two treatment groups. The authors conclude that the study "establishes long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with hormone sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after five years of adjuvant treatment with anastrozole." (*Lancet Oncology* early online publication, 50 December 2007).

Antibiotics and Steroids Not for Sinusitis

Antibiotics and topical nasal steroids are of no benefit for patients with acute maxillary sinusitis according to a new randomized controlled trial of 240 adults. Patients with acute non-recurrent sinusitis were randomized to treatment with antibiotics and nasal steroids, placebo antibiotic and nasal steroid, antibiotic and placebo nasal steroids, or placebo antibiotic and placebo nasal steroid. Amoxicillin 500 mg three times a day for seven days and budesonide spray once daily were the active drug use in the study. The main outcome was proportion of clinically cured at 10 days and the duration of symptoms. Antibiotics made no difference in the proportion of patients with symptoms lasting 10 days or more (29% with antibiotics, 33.6% with no antibiotics). Use of nasal steroid also made no difference for the same measure (31.4% with budesonide, 31.4% with no budesonide). The authors conclude that neither an antibiotic nor topical steroid alone or in combination was effective as the treatment for acute sinusitis in the primary care setting (*JAMA*. 2007;298:2487-2496).

FDA Actions

An expert advisory panel of the FDA has recommended against approving Merck's petition to take lovastatin (Mevacor) over-the-counter. This was the third request in 7 years for OTC status for the cholesterol-lowering drug. The advisers voted 10-2 against approval citing concerns whether patients were capable of determining if they are appropriate candidates for the medication. The FDA generally follows the advice of its advisory panels.

The FDA has approved yet another beta-blocker for the treatment of hypertension. MylanBertek's nebivolol (Bystolic) is a selective beta-1-adrenoreceptor blocker with vasodilating effects. The drug is the 19th beta-blocker approved in the United States.

Wyeth has received an approvable letter for bazedoxifene, a new selective estrogen receptor modulator (SERM) for the prevention of osteoporosis in postmenopausal women. In issuing the letter, the agency asked for more data on the risk of blood clots and stroke, problems that have plagued the other marketed SERM for this indication (raloxifene-Evista). The agency did not ask for new studies however. Wyeth is also seeking the indication for treatment of osteoporosis in postmenopausal women. When approved, bazedoxifene will be marketed as Viviant.

The FDA has issued a safety warning on fentanyl skin patches after several reports of deaths and life-threatening side effects associated with inappropriate use. The warning stresses that the patches are only for patients who are opioid-tolerant and have poorly controlled pain on other narcotic pain medications. The patches are not for postoperative pain or sudden or occasional pain. Patients who used the patch should be aware of the signs of fentanyl overdose. Patients and physicians should be aware of potential drug interactions and physicians and pharmacists need to instruct patients on appropriate use of the patch. Patients also need to be aware that heat sources such as heating pads, electric blankets, saunas, heated waterbeds, hot baths, sunbathing and even fever may result in sudden increases in blood levels of fentanyl.

The FDA has approved a new volume expander for the treatment of volume loss during surgery. German drugmaker Fresenius Kabi's Voluven utilizes a new synthetic starch that is insoluble in water. In clinical trials the product was found to be as safe and effective as Hespan, a currently approved starch solution volume expander. ■