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INSIDE

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Coronary CT Angiography to Rule Out Acute Coronary Syndromes in the Emergency Department

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

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

Source: Hoffmann U, et al. Coronary computed tomography angiography for early triage of patients with acute chest pain: The ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol*. 2009;53:1642-1650.

Patients presenting to the emergency department (ED) with acute chest pain are a significant portion of our health care budget. Current recommendations for the assessment and management of these patients involve extended periods of observation for repeated biomarkers and electrocardiograms (ECG). This often results in hospital admission to "rule out" myocardial infarction. Any advance in the speed or accuracy of diagnosis of the cause of chest pain, or to rule out myocardial ischemia as the cause, would be a significant clinical advance. Coronary computed tomography (CT) angiography (CCTA) has emerged as an accurate diagnostic imaging modality in suitable patients with stable coronary artery disease (CAD). However, its role in the triage of patients in the ED with acute chest pain has not been fully defined. Accordingly, Hoffman et al conducted a prospective, observational cohort study to assess the utility of CCTA in patients presenting with acute chest pain, who were being admitted and observed with low- to intermediate-risk for acute coronary syndromes (ACS).

Hoffman et al enrolled adult patients presenting to the ED with chest pain of at least five minutes duration, who were being admitted for observation for possible ACS, who were in sinus rhythm and were able to perform an adequate breath hold for the CCTA. They excluded patients with known coronary artery disease, elevated biomarkers, or ECG changes. Patients who were not suitable for CCTA also were excluded — those with renal impairment, contrast allergy,

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thyroid disorders, hemodynamic instability, or taking metformin. Patients underwent CCTA prior to admission, and the treating physicians were not informed of the results. The diagnosis of ACS was made by standard practice, without knowledge of the CCTA findings. Hoffman et al screened 1,869 patients and enrolled 368 in the study, mean age 53 ± 12 years; 61% were male. Mean BMI was 29 6 kg/m^2, 11% were diabetic, 39% had hypertension, 49% current or former smokers, and 37% had measured dyslipidemia. CCTA was performed in standard fashion, with two blinded reviewers reporting the results as normal, presence of plaque, or presence of > 50% stenosis. When there was discrepancy, a third reviewer was consulted.

ACS was diagnosed in 31 of 368 patients (8.4% of the cohort; unstable angina in 23, myocardial infarction [MI] in 8). All patients with ACS had coronary plaque (100% sensitivity and 100% negative predictive value), whereas 24 of 31 also had coronary stenosis > 50% (77% sensitivity and 98% negative predictive value). In the subgroup of patients with myocardial infarction, plaque was present in all (100% sensitivity and 100% negative predictive value) and stenosis > 50% was present in five of eight patients (63% sensitivity and 99% negative predictive value). No patient without coronary plaque developed ACS during that hospitalization or over the ensuing six months. Despite the excellent sensitivity and negative predictive value of coronary plaque for ACS, the specificity and positive predictive value were low to moderate because many patients had plaque but did not have ACS (specificity 54% and positive predictive value 17%). Importantly, in patients who did not have ACS, there were no major adverse cardiac events (MACE) at six months.

Among the 185 subjects with any coronary plaque detected, those who were diagnosed with ACS had a greater burden of coronary plaque, with more coronary artery segments involved (7.2 vs. 4.2 segments; $p < 0.0001$), they had more calcified plaque (6.5 vs. 3.6 segments; $p < 0.0001$) and more non-calcified plaque (3.6 vs. 1.8 segments; $p < 0.0001$) than patients who were not diagnosed with ACS. The type of plaque detected by CCTA did not influence the likelihood of ACS.

The presence of coronary stenosis > 50% was not as sensitive for detecting ACS as the presence of any coronary plaque. Sensitivity was 77% and negative predictive value was 98%, because there were seven patients without stenosis on CCTA who were actually found to have ACS. The specificity of coronary stenosis >50% for detecting ACS was lower in those over 65 (58% vs. 91%; $p < 0.0001$), and these patients had a higher prevalence of coronary calcium (84% vs. 39%; $p < 0.0001$). In logistic regression analysis, after adjustment for age sex, and TIMI risk score, each additional segment of plaque was associated with a 28% increase in having ACS ($p < 0.0001$), and the presence of stenosis >50% increased the odds ratio of having ACS by over eleven-fold (OR 11.69; $p < 0.0001$). The authors conclude that both plaque and stenosis detected by CCTA predict ACS independent of risk factors or TIMI risk score. Fifty percent of patients with chest pain and low to intermediate risk are free of CAD and have no ACS. Given the large number of such patients, early CCTA may significantly improve patient management in the ED.

■ COMMENTARY

Patients presenting with ACS and high-risk features are treated with aggressive medical therapy and often with an early invasive strategy. But patients presenting with low- or intermediate-risk ACS represent a more heterogeneous group and the optimal management strategy is less clear. Inappropriate discharges after missed ACS can result in MI or death. Thus, clinicians err on the side of caution and often admit low- to intermediate-risk patients for observation and serial ECG and biomarkers. CCTA in the ED holds promise to add incremental value to our current risk stratification protocols. This study by Hoffmann et al confirms the potential of CCTA to aid in decision-making in patients with low to intermediate risk of ACS. In their study, 50% of patients had no coronary disease by CCTA: none of

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Questions & Comments

Leslie Hamlin,
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these patients were found to have ACS on admission and none had MACE in the six-month follow-up period. This may have important implications for improving work-flow in the ED, reducing inappropriate admissions and reducing health care expenditure. However, the results presented herein, although exciting and provocative, require confirmation in other centers before becoming part of the standard of care.

This study design allows for unbiased assessment of the performance of the CCTA, because the results were not communicated to the clinicians and, therefore, were not used as part of the clinical decision-making process. Thus standard diagnostic measures could be compared to the CCTA results, rather than using the CCTA results as part of the diagnosis. The absence of MACE during the six-month follow-up for patients without coronary artery disease is reassuring and lends weight to the use of CCTA as a decision-making tool in the ED. However, there are some limitations to the study. Firstly, many patients were excluded, including those who presented outside business hours, those with known coronary artery disease, and those with renal impairment. Secondly, elderly patients were under-represented in this cohort. These patient groups make up a large percentage of those presenting with chest pain. Thirdly, this was a single-center study with physicians highly experienced in CCTA. Many centers are not so experienced in interpreting this evolving technology. These factors may mean the results of this study are not generalizable to all centers. Finally, only 92% of patients were evaluable at 6-month follow-up, and therefore it is possible that some clinical events were missed. Prior to changing standard practice, these results should be confirmed in multi-center randomized studies, with rigorous follow-up, that are powered to detect clinical end-points. ■

Continuous ECG Monitoring for Detection of Ischemia After ACS

ABSTRACT & COMMENTARY

By Andrew J. Boyle, MBBS, PhD

Source: Scirica BM, et al. Ischemia detected on continuous electrocardiography after acute coronary syndrome: Observations from the MERLIN-TIMI 36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction 36) trial. *J Am Coll Cardiol*. 2009;53: 1411-1421.

After acute coronary syndromes (ACS), recurrence of ischemia is a harbinger of worse prognosis. Previous studies have suggested that continuous electrocardiograph (cECG) monitoring can detect ischemia, but that this method is associated with poor cardiovascular outcomes. However, recent advances in medical therapy and percutaneous coronary intervention (PCI) for ACS have changed clinical practice significantly. The role of cECG in detecting recurrent ischemia and determining prognosis in the current era of PCI and intensive pharmacotherapy has not been defined. Accordingly, Scirica et al present data from 6,355 patients undergoing cECG monitoring for seven days after ACS as part of the MERLIN-TIMI 36 study.

The MERLIN-TIMI 36 study was a randomized, placebo-controlled study investigating the efficacy of ranolazine in patients with ACS. They enrolled 6,560 patients, of whom 6,355 had cECG performed using two bipolar leads at 128-Hz sampling rate for seven days. The primary endpoint was ischemia determined by 1 mm ST-segment depression lasting at least one minute during a heart rate of < 100 beats/min. Secondary endpoints included ischemia with 0.5 mm ST depression lasting one minute and the incidence of ischemia occurring in the first 72 hours of randomization. cECG endpoints were analyzed by cardiologists blinded to clinical details. Analyses comparing ischemia detected by cECG excluded events that occurred during the time of cECG monitoring.

Twenty percent of the patients (n = 1,271) had at least one episode of ischemia on cECG. The majority of patients had their first episode of ischemia within 48 hours; the median number of ischemic episodes was three per patient. Patients with ischemia detected, compared to those with none detected, were older (mean age 66.6 vs. 62.7 years; $p < 0.001$), more likely to be female (38.6% vs. 34.2%; $p = 0.003$), and had lower body mass index (27.6 vs. 28.4; $p < 0.001$). They had higher prevalence of hypertension, prior angina, prior heart failure, and renal impairment (77.1% vs. 72.9%, $p = 0.002$; 66.4% vs. 53.0%, $p < 0.001$; 20.7% vs. 15.9%, $p < 0.001$; 29.8% vs. 19.4%, $p < 0.001$, respectively). The presentation and treatment strategy during hospitalization for ACS influenced the likelihood of ischemia detected with cECG. Patients with detectable ischemia were more likely to have presented with ST-segment depression, elevated troponin, elevated BNP, and a higher TIMI risk score (all $p < 0.001$). Fewer patients with detectable ischemia had been treated with an initial plan for an early invasive strat-

egy (36.4% vs. 41.4%, $p < 0.001$), but more had actually undergone revascularization (42.3% vs. 38.6%, $p = 0.015$). Medication use patterns were different between groups, with those having detectable ischemia being less likely to take thienopyridines (48.5% vs. 53.7%, $p = 0.001$), statins (74.2% vs. 78.0%, $p = 0.004$), and calcium channel blockers (28.7% vs. 35.4%, $p = 0.015$), but more likely to be taking nitrates (38.6% vs. 28.3%, $p < 0.001$) at discharge. Beta-blocker use was not different between groups.

Patients with detectable ischemia on cECG had higher rates of adverse clinical outcomes. The primary endpoint of the trial was a combined endpoint of cardiovascular death, MI, and recurrent ischemia, which was higher in those with ischemia on cECG (28.5% vs. 17.8%, unadjusted HR 1.75; $p < 0.001$). The individual components of the composite endpoint were also higher in the group with demonstrated ischemia (cardiovascular death: 7.7% vs. 2.7%, HR 2.94, $p < 0.001$; MI: 9.4% vs. 5.0%, HR 2.0, $p < 0.001$; recurrent ischemia: 17.5% vs. 12.3%, HR 1.43, $p < 0.001$). Scirica et al performed a multivariable analysis, including clinical and biomarker data, and ischemia on cECG remained a strong predictor of events (adjusted HR 2.46 $p < 0.001$ for cardiovascular death, adjusted HR 1.57, $p < 0.001$ for primary composite endpoint). The relationship between ischemia and increased clinical event rate was consistent whether the events occurred early (within 48 hours) or late, whether the patients received revascularization or not, whether the ischemia was detected before or after revascularization, and even in the presence of no or minimal coronary artery disease on coronary angiography.

Scirica et al also analyzed the outcomes of patients with lesser degrees of ST-segment depression (0.5-1 mm), which occurred in only 3.9% of patients, and those with ST-segment elevation, which occurred in 3.2% of patients. Neither of these findings were associated with an increase in clinical events in these small subgroups. Furthermore, whether patients were randomized to ranolazine or placebo had no influence on the prevalence of ischemia on cECG monitoring. They concluded that detection of ischemia by cECG provides incremental prognostic information with which to assess the risk of recurrent major cardiovascular events in patients after NSTE ACS.

■ COMMENTARY

Each year, 1.3 million Americans are hospitalized with non ST-elevation ACS. Scirica et al demonstrate that, in contemporary practice, the addition of cECG monitoring for seven days after ACS adds additional prognostic information. With 20% of their cohort demonstrating ischemia, and this group having worse clinical outcomes, this has the potential to have a significant impact on the risk stratification of large numbers of patients. The strengths of the study include the large number of patients enrolled and the fact that the events that occurred during monitoring were censored, allowing it to be used as a prognostic tool only. However, several limitations must be acknowledged. Firstly, this study is an observational substudy, and no treatment effect has been studied here. Therefore, the results are hypothesis-generating, and one cannot recommend that we should be using cECG monitoring clinically based on these results. Secondly, there were a number of exclusion criteria in the MERLIN-TIMI 36 study, such as baseline ECG abnormalities, so that the results cannot necessarily be extrapolated to all patients. Thirdly, there were significant differences in the medical management between the groups with and without ischemia. Thus, the effects of the ischemia on outcomes may have been related to the differences in treatment. Despite multivariable adjustments, these differences cannot be disregarded, and may have some clinically meaningful effect on the outcomes. Despite these limitations, this is a valuable study, confirming that, in the era of contemporary PCI and optimal medical management, continued ischemia remains an indicator of poor prognosis. Whether cECG will guide more effective treatment strategies remains to be tested in prospective, randomized, controlled clinical trials. ■

CRP in Pulmonary Hypertension

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

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

Source: Quarck R, et al. C-reactive protein. A new predictor of adverse outcome in pulmonary arterial hypertension. *J Am Coll Cardiol*. 2009;53:1211-1218.

New markers for a variety of diseases have recently received considerable attention, specifically B-type natriuretic peptide (BNP), N-terminal-pro-BNP, C-reactive protein, or CRP, and CRP-hs (high sensitivity). Levels of these compounds are useful guides in assessing the severity of important medical conditions,

such as congestive heart failure and acute myocardial infarction chest pain. CRP-hs is not disease-specific and, generally, increased levels reflect inflammation or infection. CRP elevations are found in a variety of diseases/conditions. A new study assesses the value of measuring CRP levels in severe pulmonary hypertension (PH) subjects. The results are encouraging, demonstrating that CRP levels are useful predictors of mortality in several types of PH.

Two types of PH were evaluated: consecutive patents with classic pulmonary artery hypertension (PAH), characterized by distal pulmonary arterial arteriopathy; chronic thromboembolic pulmonary hypertension (CTEPH) with "occasional" proximal vessel occlusions and distal vessel remodeling; and normal controls. An inflammatory substrate has been suggested by some in PAH; recent data have reported increased interleukin-1, interleukin-6, and CX chemokine macrophage inflammatory-chalk protein-1 alpha. CTEPH with "dysregulated thrombus" may contribute to the pathophysiology of PH. CCL2 chemokine monocyte chemoattractive protein is unregulated in large pulmonary arteries in CTEPH subjects. Thus, significant inflammation in PH patients is not certain, but is probable, with CRP serving as a marker for inflammation.

This study seeks to see if CRP levels could be predictive of PAH severity and subsequent outcomes. The protocol employed was a prospective study of consecutive PAH and CTEPH subjects, all of whom underwent right heart catheterization (University of Leuven) between 2004-2008. Parameters studied included functional class, a 6-min walking test (6 MWD), medications, and right heart hemodynamic data (right-sided catheterization); survival rates were documented. C-reactive protein blood samples were analyzed. Specific levels of CRP were expressed in log mg per liter and will not be reported in this narrative, as they are not commonly used in U.S. labs' reporting of CRP levels.

Baseline survival and event-free Kaplan-Meier survival curves were generated, contrasting subjects with CRP above and below the upper limit of normal. Sensitivity and specificity of CRP to predict survival was assessed via ROC operating characteristics. Cox regression was utilized, and multiple variables were included.

Results: Two pulmonary hypertension patient populations were examined, 104 with PAH, 79 with CTEPH, and a control group of 95 healthy subjects. Half of the PAH patients had idiopathic PAH and half had associated diseases. In the CTEPH cohort, 75% had a history of acute venous pulmonary thromboembolism, with 66% having at least one thrombophilic disorder. Overall, 35 patients died, 44 CETPH had a pulmonary endarterectomy, five PAH had a living transplant, and 11 were started on prostacyclin analogs.

CRP was higher than controls but not different between CTEPH and PAH subjects. In PAH patients, CRP levels correlated with NYHA functional class, RA pressure and, inversely, with the 6-min walk test. CRP levels were higher in NYHA III-IV patients and non-survivors, who had lower functional class, higher RAP, and poorer six-min walk outcomes. Kaplan-Meier curve showed that all PAH, idiopathic PAH, and treatment-naive patients had a lower two-year survival (65% vs. 82%, $p = 0.02$) with high CRP levels. Subjects with CRP above the upper limits of normal had a lower event-free survival (two years 57% vs. 75%). Lower levels of CRP were associated with better event-free survival at two years. NYHA class, CRP, 6 MWD, etiology, and RAP predicted increased mortality in PAH. Disease-specific medication in PAH subjects was associated with a significant decrease in PVR. Patients with disease-specific treatments had better outcomes overall. Patients who normalized CRP (responders) had higher survival rate at three years.

The authors conclude, "…CRP levels were higher in patients with pulmonary hypertension compared to those with control subjects. Severe pulmonary hypertension was associated with increased circulatory CRP levels. . . CRP predicted mortality and clinical worsening." The key observation: "The novelty of the present study is a potential role of CRP as a predictor of adverse responses to therapy in PAH."

■ COMMENTARY

Quarck et al propose that CRP is an independent predictor of outcomes in PAH, as suggested in prior studies of COPD patients. They suggest adding CRP to NT-proBNP as a biomarker in the evaluation of pulmonary hypertension. They conclude that CRP can help predict outcomes and response to therapy in PAH. Subjects who had normalization of CRP concentrations "had a significantly better survival with a decrease in NYHA functional class and an increase in cardiac index." The data suggest that the beneficial effects of prostacyclin analogues can be suggested by a fall in CRP into the normal range. CRP levels were noted to improve after pulmonary artery endarterectomy, suggesting another role for CRP. The low-cost, low-risk measurement of CRP should be considered in the evaluation of patients with pulmonary hypertension and in the selection of therapeutic options.

C-reactive protein or CRP is a marker of inflammation which has been valuable in assessing outcomes in various settings. The recent JUPITER trial suggests that

elevated CRP-hs in subjects without overt vascular disease and normal LDL cholesterol identifies patients who may benefit from statin therapy. This report deals with a very different population — severe pulmonary hypertension of various causation. Evidence of inflammation as an important player in PAH patients is suggested by this report, with elevated inflammation markers and compounds. These data are consistent with evidence that CRP can play a role in determining severity and, perhaps, outcomes of PAH of various causation.

The number of subjects in each category or etiology of pulmonary artery hypertension is relatively small; 104 with typical pulmonary arterial hypertension (PAH); 79 with CTEPH or chronic thromboembolic hypertension; and 95 control subjects. Also, therapy was not standardized or adjusted based upon the CRP levels, so the role of CRP in selecting and adjusting therapy is speculative. The data support the view that a CRP higher than "normal" is associated with an increased risk of death, no matter the cause of PAH. However, increased mortality is seen in patients with poor LV function, high NYHA class, high right-atrial pressure and a poor 6-min walk test.

NT-pro-PNP has also been used as a marker of outcomes in PAH. Quarck et al emphasize that, in addition, CRP has prognostic value and is low cost. I agree that it may be worthwhile to obtain serial CRP measurements, and the data in this study suggest it can guide potential treatment with various new approaches during follow-up. Much more data are needed, particularly regarding the use of CRP cut-off points to predict outcomes, which seem somewhat of a blunt instrument. ■

Syncope and Hypertrophic Cardiomyopathy

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

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

Source: Spirito P, et al. Syncope and risk of sudden death in hypertrophic cardiomyopathy. *Circulation*. 2009;119: 1703-1710.

Syncope is commonly accepted to be a danger sign in patients with hypertrophic cardiomyopathy (HCM). In this paper, Spirito et al report data from a registry of 1,511 patients with HCM who have been followed longitudinally at four institutions. The diagnosis of HCM was based on standard echocardiographic criteria. The data available in the registry included: age, gender, family history of sudden death, NYHA functional class, degree of left ventricular (LV) outflow tract obstruction, LV wall thickness, left atrial dimension, and treatment. Syncope was defined as a sudden and brief loss of consciousness associated with loss of postural tone with spontaneous recovery. Based on clinical data, episodes of syncope were classed as either "neurally mediated" or "unexplained."

At the time of their initial evaluation, 207 patients had a prior history of syncope. In 153 patients, the syncope was classified as "unexplained," with 118 in this group reporting syncope at rest and 35 during intense exertion. Fifty-two patients reported syncope with features suggesting a neurally mediated origin. The remaining 1,306 patients did not have a history of syncope when they initially presented. There were few clinically significant differences between the groups. Overall, the mean age was 46 ± 20 years. The entire group was 61% male. A family history of sudden death was reported by 19% of the patients, and 11% of the patients were New York Heart Association functional class III or IV. Only 7% had left ventricular wall thickness greater than 30 mm. At the time of the initial evaluation, 41% of the patients were receiving beta blockers, 25% calcium antagonists, 6% amiodarone, and 12% diuretics. During a follow-up period of 5.6 ± 5.2 years, there were 240 deaths (14% of the entire group). Of these deaths, 74 were classified as sudden and presumed cardiac, 54 were caused by heart failure, 26 were stroke-related, and 60 were due to noncardiac causes. For those patients who died suddenly, the mean age was 42 ± 18 years. Among the 1,511 study patients, there were 98 (6%) who received an ICD after initial evaluation. Of these 98 ICD recipients, five patients received one or more appropriate ICD therapies. Prior syncope, if unexplained, could be related to risk for sudden death. For the 153 patients with a history of unexplained syncope, the relative risk for sudden death was 1.78. There was, however, no relationship between neurally mediated syncope and sudden death (relative risk 0.91). Recurrent episodes of syncope, reported by 63 patients, did not increase the risk for sudden death. For these patients, the relative risk was 1.26. Unexplained syncope was more ominous in patients under 18 years of age. In this age group, the hazard ratio was 8.0. The time interval between unexplained syncope and the risk of sudden death was also examined. Patients with a recent (within six months) episode

of unexplained syncope had a five-fold increased risk for sudden death compared to patients without recent syncope. Patients with only remote episodes of syncope (greater than five years previously) had no increased risk of sudden death (hazard ratio 0.38). Finally, Spirito et al examined the interaction between age, syncope, and sudden death. There were 147 patients who were under 18 years of age at study entry. During 6.5 ± 5.7 years of follow-up, 15 (10%) of these patients died suddenly. The sudden death incidence in this group was 15.7 per 1,000 person years.

Spirito et al concluded that unexplained syncope, particularly if it is recent and if it occurs before age 18, is a major risk factor for sudden death in patients with HCM.

■ **COMMENTARY**

Sudden death is the most dreaded complication of HCM. Prior reports have described risk factors for sudden death in these patients. Commonly cited risk factors include a history of syncope, spontaneous non-sustained ventricular arrhythmias, hypotension with exercise, a positive family history of sudden death at a young age, and massive left ventricular hypertrophy. Any one of these risk factors is considered a possible indication for ICD implantation for primary prevent of sudden death. This paper further clarifies the prognostic significance of syncope. Syncope with the classic features of a neurally mediated event is not associated with increased risk. A remote episode of syncope with no recurrence for several years also should not be considered a risk factor. Recent "unexplained" syncope, however, is more worrisome and, particularly in younger patients, may be the deciding factors toward proceeding with an ICD. ■

Valsartan for Atrial Fibrillation?

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Source: The GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. *N Engl J Med*. 2009;360: 1606-1617.

It has been postulated that angiotensin-converting enzyme (ACE) inhibitors and angiotensin II-receptor blockers (ARBs) decrease the risk of developing atrial fibrillation both indirectly by better control of hypertension and heart failure and directly by effects on fibrosis, inflammation, and atrial remodeling. In this study, the GISSI-AF investigators report a controlled, randomized trial using the ARB valsartan in patients with atrial fibrillation. Patients were eligible for inclusion in the study if they had two or more episodes of symptomatic atrial fibrillation in the previous six months or had been successfully cardioverted from atrial fibrillation within the previous fourteen days. Patients were required to have a risk factor for stroke including at least one of the following conditions: heart failure or left ventricular dysfunction, hypertension with or without left ventricular hypertrophy, diabetes, prior stroke or peripheral artery disease, coronary artery disease, or left atrial dilatation. Patients were maintained on a stable regimen for the treatment of atrial fibrillation and other cardiac disorders for a minimum of one month before enrollment. Patients were permitted to continue other cardiac medications that had been started earlier, including ACE inhibitors, antiarrhythmic drugs, and beta adrenergic blockers. Patients enrolled were randomly assigned to receive either valsartan or matching placebo. The initial dose of active study drug was 80 mg daily for two weeks. The dose was then increased to 160 mg daily for two weeks and, finally, increased to 320 mg daily. Patients who could not tolerate a daily dose of 160 mg or more had their study drug discontinued. Follow-up was obtained by office visits periodically during the year of the study. All patients also were provided with a transtelephonic monitoring device, which they could use to transmit a 30-second electrocardiogram either with the occurrence of symptoms or routinely at least once per week.

The study had two primary endpoints: time to recurrence of atrial fibrillation and the proportion of patients who had more than one episode of atrial fibrillation during one year follow-up. Secondary endpoints included: total number of episodes of atrial fibrillation, hospitalization for any reason, hospitalization for a cardiovascular event, death, and thromboembolic events.

The study enrolled 1,442 patients at 114 centers over a 2.5-year period. The valsartan and placebo groups were similar in terms of their baseline characteristics. Hypertension was present in 85.4%, diabetes in 14.6%, and heart failure in 7.9%. At the time of randomization, 35% of the patients were receiving amiodarone, 57% were receiving ACE inhibitors, 34% were on a beta blocker, and 57% were on a vitamin K antagonist. The target dose of 320 mg of valsartan or matching placebo was achieved in 84% of the patients, with no difference between the two groups. Only five patients in each group

could not tolerate a daily dose of 160 mg.

Valsartan had no significant effect on atrial fibrillation. At one year, there was no difference in the recurrence of atrial fibrillation between the two groups (51.4% valsartan vs. 52.1% placebo). After adjustment for baseline variables, the adjusted hazard ratio was 0.97 (96% confidence interval, 0.83 to 1.14; $p = 0.73$). The median time from randomization to the first occurrence of atrial fibrillation was 295 days in the valsartan group and 271 days in the placebo group. Recurrent episodes of atrial fibrillation were noted in 27% of the valsartan patients and 28% of the placebo group. There was also no difference between the groups in the frequency or duration of atrial fibrillation events. There were no significant differences between all-cause hospitalizations, cardiovascular hospitalizations, or deaths. The authors did note a slight excess in the number of thromboembolic events in the valsartan group (10 vs. 2), but considered this due to chance. Subgroup analyses showed that the hazard ratios for the first occurrence of atrial fibrillation were similar in all predefined subgroups. The study drug was well tolerated. One patient in the valsartan group had severe hypotension and one had renal dysfunction plus hyperkalemia.

The authors conclude that daily valsartan added to standard therapy in patients with a history of atrial fibrillation does not reduce the incidence of recurrent atrial fibrillation compared to placebo therapy.

■ COMMENTARY

A number of studies on the use of both ACE inhibitors and ARBs in patients with heart failure have reported a decreased incidence of AF as a secondary endpoint. A recent meta-analysis by Healey et al (*J Am Coll Cardiol*. 2005;45:1832-1839), reported that therapy with ACE inhibitors and ARBs resulted in relative risks for developing atrial fibrillation of 0.72 and 0.71, respectively. In a retrospective analysis from the AFFIRM trial, ACE inhibitor or ARB use associated with less atrial fibrillation recurrence in patients with heart failure or decreased ventricular function. Only an insignificant trend was seen in the whole AFFIRM population. (*Heart Rhythm*. 2004;1:669-675.). Blockade of the renin-angiotensin-aldosterone system in experimental models of heart failure has had favorable effects on atrial electrical and structural remodeling. In this randomized trial, adding an ARB to standard therapy in patients with atrial fibrillation did not decrease the risk of recurrence. The current study results should be a significant disappointment to clinicians caring for patients with atrial fibrillation. The ARB, when added to other therapy, did not change the risk for recurrent atrial fibrillation or diminish the number or recurrent episodes, but the follow-up was only a year. There remains the strong possibility that use of ACE inhibitors or ARBs in patients with hypertension or heart failure, if started early in the course of their disease before they develop atrial fibrillation, may still prove to be a correct strategy. ■

CME Questions

27. CRP-hs is of prognostic value in:
a. coronary artery disease.
b. pulmonary hypertension.
c. mitral valve prolapse.
d. A & B

28. Which finding on continuous ECG monitoring post-NSTEMI is of prognostic value?
a. ST elevation
b. ST depression
c. T-wave inversion
d. All of the above

29. The ED use of CT angiography for chest pain patients can diagnose ACS with:
a. 100% sensitivity and negative predictive value.
b. 54% specificity.
c. 17% positive predictive value.
d. All of the above

30. Valsartan is useful for the prevention of:
a. hypertension.
b. heart failure.
c. atrial fibrillation.
d. A & B

31. In hypertrophic cardiomyopathy, syncope is a particularly bad prognostic sign if it:
a. is unexplained.
b. is recurrent.
c. occurs before age 18 years.
d. All of the above

Answers: 27. (d); 28. (b); 29. (d); 30. (d); 31. (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. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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ACCORD-MIND: Memory in Diabetes

Source: Cukierman-Yaffe T, et al. Relationship between baseline glycemic control and cognitive function in individuals with type 2 diabetes and other cardiovascular risk factors: The action to control cardiovascular risk in diabetes-memory in diabetes (ACCORD-MIND) trial. *Diabetes Care* 2009;32:221-226.

THE ACCORD TRIAL HAS BEEN NEWSworthy in the last several months primarily due to the early results of increased cardiovascular events associated with very tight glucose control. The ACCORD trial also has BP and lipid control arms, and includes a substudy on cognitive function called ACCORD-MIND: Memory in Diabetes. This cross-sectional study used a variety of cognitive tests to evaluate the relationship between glucose control and cognitive function.

In MIND (n = 2977), there was a linear relationship between baseline A1c and cognitive scores. For instance, on the Digital Symbol Substitution Test (DSST), for every 1% increase in A1c, there was a 1.75 point decreased DSST score; for comparison, in this age group each 1 year increase in age is associated with a 0.7 point DSST score decrease (and the aforementioned decrease had already been age-adjusted). Essentially, each 1% increase in A1c correlated to the same decline in cognitive function that would be seen (on average) with 2 years of aging.

Diabetes predisposes to cognitive decline, some of which is attributable to the increase risk of stroke in diabetics. Because subjects with stroke-related cognitive decline were excluded from this trial, the results suggest that hyperglycemia is negatively (inversely) related to cognitive function. Whether control of hyperglycemia has a favorable impact upon cognitive function remains to be determined. ■

Pulmonary embolism in acute COPD exacerbations

Source: Rizkallah J, et al. Prevalence of pulmonary embolism in acute exacerbations of COPD. *Chest* 2009;135:786-793.

IN CONTRAST TO MOST OF THE TOP 10 causes of death in the United States, the COPD mortality rate (the 4th most common cause of death) is rising. The majority of COPD deaths happen during an acute COPD exacerbation, usually attributed to an infectious agent. Still, as many as 30% of exacerbations are of uncertain etiology.

The symptoms of acute pulmonary embolism and exacerbations of COPD have some overlap. Indeed, it is easy to explain away new dyspnea, cough, and worsening of pulmonary status by simply attributing symptoms to COPD exacerbation, which is, after all, the most common explanation. Recent studies have suggested, however, that pulmonary embolus may be an overlooked etiology for symptoms that are misattributed to COPD exacerbations.

Rizkallah et al performed a meta-analysis of trials in patients (n = 550) with apparent exacerbations of COPD who underwent CT scanning, pulmonary angiography, or both. They found that in patients who were hospitalized, as many as 25% were ultimately determined to have suffered pulmonary embolus; the prevalence in studies incorporating data from both inpatients and outpatients showed only a slightly lower prevalence (24%).

Although it is tempting to accept that new onset of dyspnea and cough in a patient with COPD is most likely due to an acute exacerbation, these data suggest a higher level of vigilance for pulmonary embolism in this population. ■

PLCO supports USPSTF recommendations

Source: Andriole GL, et al. Mortality results from a randomized prostate-cancer screening trial. *N Engl J Med* 2009;360:1310-1319.

THE PROSTATE, LUNG, COLORECTAL, and Ovarian Cancer Screening Trial (PLCO) enrolled 76,693 men between 1993 and 2001, half of whom were assigned to receive annual PSA and DRE, and the other half of whom received usual care (USU). One of the endpoints of the trial was the mortality rate comparison between screened and USU men over 7-10 years of follow-up.

As might be intuitively obvious, the incidence of prostate cancer in the PSA/DRE group was somewhat higher (22% higher) than the USU group (116 vs 95 per 10,000), since men with an elevated screening PSA were referred for biopsy. Additionally, since PSA screening has become progressively more common as a component of usual care, one would not be surprised to learn that in this trial, 52% of men in the USU group had also received PSA screening.

The incidence of prostate cancer-related death per 10,000 subjects was very similar: 2 in the screening group vs 1.7 (USU). This slightly higher (but not statistically significantly different) prostate cancer-related mortality in the screened group suggests that PSA screening does not improve mortality over an interval as long as 10 years, giving credence to the recent USPSTF suggestion recommending against PSA screening in men older than age 75. ■

Balloon kyphoplasty for vertebral fractures

Source: Wardlaw D, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): A randomised controlled trial. *Lancet* 2009; 373:1016-1024.

VERTEBRAL FRACTURE (VFX) IS THE most common complication of osteoporosis. Although often asymptomatic, VFX can cause pain, deformity, and loss of function. Until recently, treatment for VFX was generally conservative, consisting of pain medication, prevention of further osteoporosis, and physical therapy. Balloon kyphoplasty (BKY) is a minimally invasive technique that has been shown to restore function and relieve pain. The procedure is brief (typically < 1 hour), can be done on an inpatient or outpatient basis, and requires minimum down time post-intervention (often ≤ 48 hours).

Wardlaw et al performed a controlled trial comparing BKY with conservative care for patients with VFX (n = 266). The primary outcome was the physical function component of the SF-36 quality of life scale over a 1-month interval from the time of intervention.

In the BKY group, the SF-36 score improved by 7.2 points vs 2.0 points in the conservative care group. There was no difference in adverse events between the groups.

Kyphoplasty is a minimally invasive procedure that provides prompt relief of pain, restoration of structural integrity, and improvements in function, with very favorable tolerability. Clinicians should consider BKY as a viable option in patients with acute osteoporotic VFX. ■

Exercise improves QOL in CHF patients

Source: Flynn KE, et al. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;301:1451-1459.

PATIENTS WITH CHRONIC HEART FAILure (CHF) report progressively worse dyspnea with exercise, ranging from Class I NYHA (symptoms only present with strenuous exercise) to Class IV NYHA (symptoms present with any activity, even at rest). Such exertional dyspnea provides disincentive for exercise, and often leads to deconditioning, thereby worsening ability to participate fully in activities of daily living. In the past, there has been some concern that exercise for CHF patients might lead to increased adverse events.

Flynn et al randomized patients with systolic CHF (n = 2331), all of whom had an ejection fraction < 35%, to an intensive supervised exercise training program (EXE) vs usual care (USU). The intensive intervention consisted of supervised aerobic exercise training for 36 sessions, at 60-70% of heart rate reserve, three times weekly; subjects then underwent home-based training 5 times per week. The primary outcome was the score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), a validated, heart failure-specific metric. KCCQ scores were obtained quarterly for 1 year, and then annually for an additional 3 years.

KCCQ scores were statistically superior in the EXE group as early as 3 months, and stayed that way through the remainder of the trial. Aerobic exercise training improves the quality of life and activity scores for persons with CHF. ■

CBT for anxiety in older adults

Source: Stanley MA, et al. Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care: A randomized clinical trial. *JAMA* 2009;301:1460-1467.

THE PREVALENCE OF GENERALIZED anxiety disorder (GAD) in older adults is as high as 11% in primary care settings. GAD can often be successfully treated with antidepressants and or benzodiazepines, but such interventions can also be associated with adverse effects and cost. The efficacy of cognitive behavior therapy (CBT) for late-life GAD has not been well established.

Stanley et al enrolled 134 adults (mean, age 70) with GAD in a randomized trial comparing CBT with usual care (USU) in a population of patients attending University of Texas Clinics in the greater Houston area. The primary outcomes of the study were intensity of worry and overall GAD severity.

The CBT intervention was administered in 10-12 sessions over 3 months. CBT intervention included multiple components: motivational interviewing, relaxation training, cognitive therapy, problem-solving skills, and sleep management. The USU group received biweekly phone calls to provide support, and offer consultation if symptoms worsened. At baseline, similar numbers of persons in both groups were receiving antidepressants (31-34%) and/or anxiolytics (17%).

For both primary and secondary outcomes, CBT was superior to USU. Benefits of CBT were seen as early as 3 months, and persisted at 15-month follow-up. CBT has been shown to provide outcomes improvement in older adults with GAD. ■

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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*.

Guidance on the Appropriate Use of NSAIDs

In this issue: NSAIDs in the elderly; managing GI and CVD risk with NSAIDs; low-dose naltrexone and fibromyalgia; treating glucocorticoid-induced bone loss; FDA Actions.

NSAIDs and dementia

Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) in the elderly may increase the risk of dementia and Alzheimer's disease according to a new study. This is in contrast to previous studies that suggested that NSAIDs may actually be neuroprotective. The current study from Seattle looked at members of Group Health who were age ≥ 65 years (median, 74.8 years) and free of dementia. Patients were followed for up to 12 years to identify dementia and Alzheimer's disease. Of the 2736 patients studied, 351 (12.8%) were heavy users of NSAIDs at enrollment and another 107 became heavy users during follow-up. Over the course of the study 476 individuals developed dementia including 356 who developed Alzheimer's disease. Those defined as heavy NSAID users showed an increased incidence of dementia (hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.24-2.24) and Alzheimer's disease (HR, 1.57; 95% CI, 1.10-2.23). The authors suggest that this study looked at an older cohort than previous studies. Decreased rates of dementia seen in the previous studies may have reflected a delay in onset of dementia, which may explain the increased incidence seen in the older patients in this study (*Neurology* 2009 April 22; epub ahead of print). ■

GI and CVD risk with NSAIDs

In a related story, the Canadian Association of Gastroenterology Consensus Group has published guidelines on use of long-term NSAIDs in patients at risk for GI bleeding and cardiovascular disease. The guideline includes the recommendation that NSAIDs should always be used at the lowest effective dose for the shortest possible duration of treatment and that patients should be evaluated for the need for gastroprotective strategies and cardiovascular risk. For patients at low GI risk but high cardiovascular risk, the group recommends naproxen because of potentially lower cardiovascular risk than other NSAIDs or COX-2 inhibitors. For patients at high risk for GI side effects and low cardiovascular risk, a COX-2 inhibitor alone or traditional NSAIDs with a PPI offers similar protection. For patients at very high risk for GI bleeding, a COX-2 inhibitor plus a PPI is the safest option. In patients with both GI and cardiovascular risks, NSAIDs should be avoided if possible, but if anti-inflammatories are needed, and the patient is already on aspirin, the recommendations included naproxen plus a PPI if cardiovascular risk is the main concern or a COX-2 plus a PPI if GI side effects are the primary concern (*Aliment Pharmacol Ther* 2009;29:481-496). ■

Low-dose naltrexone and fibromyalgia

Perform a Google search of "low-dose naltrexone"

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5468. E-mail: paula.cousins@ahcmedia.com.

and you will find a myriad of anecdotal testimonies to the benefits of the drug in a wide range of diseases including fibromyalgia. Now a small study suggests that naltrexone may be of some benefit in this difficult condition. Naltrexone (not to be confused with naloxone) is an opioid receptor antagonist used primarily for treatment of alcohol dependence and opioid dependence. Because of multiple internet reports of benefit in patients with fibromyalgia, researchers from Stanford performed a single-blind, placebo-controlled crossover study of 10 patients with moderately severe fibromyalgia who were not on opioids. The dose of naltrexone used was 4.5 mg per day, which is less than 10 times lower than the dose used for addiction (50 mg per day). Patients on active treatment reported a 32.5% reduction in fibromyalgia symptoms compared to baseline vs a 2.3% reduction for placebo (P = 0.003 vs placebo). Side effects, which included insomnia and vivid dreams, were rare. Interestingly, patients with higher sedimentation rates had the greatest reduction in symptoms and best response to low-dose naltrexone. The authors hypothesize that low-dose naltrexone may inhibit the activity of microglia and reverse central or peripheral inflammation, thus reducing symptoms of fibromyalgia, although more studies are needed. They also suggest that naltrexone can be used in addition to other medications commonly used for fibromyalgia (*Pain Med* 2009 April 22; epub ahead of print). ■

Treating glucocorticoid-induced osteoporosis

For patients with glucocorticoid-induced osteoporosis, a once-yearly infusion of zoledronic acid is as effective as daily risedronate for the prevention and treatment of bone loss according to a new study from *Lancet*. In a 1-year, international, randomized, double-blind, placebo-controlled, non-inferiority study, 833 patients with glucocorticoid-induced osteoporosis were randomized to receive zoledronic acid 5 mg as a 100 mL IV infusion over 15-20 minutes on day 1 plus oral placebo or 5 mg of risedronate daily and 100 mL IV placebo infusion on day 1. Patients were allocated to a prevention or treatment subgroup depending on the duration of glucocorticoid use preceding study. Zoledronic acid infusion was non-inferior and superior to risedronate for increase of lumbar spine bone mineral density in both the treatment (P = 0.001) and prevention groups (P < 0.0001), respectively. Adverse events were more frequent in patients given zoledronic acid primarily because of increased flu-like symptoms within the first 3 days after the infusion. The authors conclude that a single 5 mg intravenous infusion of zoledronic acid is non-inferior and possibly more effective and more acceptable to patients than 5 mg of oral risedronate daily for prevention and treatment of bone loss associated with glucocorticoid use (*Lancet* 2009;373:1253-1263). An accompanying editorial suggests that once-yearly zoledronic acid seems to have obvious advantages over an oral regimen but the long-term safety is still unknown and also raises the question of whether anabolic drugs, such as teriparatide, which stimulate bone formation by acting on osteoblasts and osteocytes, might eventually be a better option (*Lancet* 2009;373:1225-1226). ■

FDA Actions

Plan B, the so-called "morning after pill" will soon be available to women age 17 and older without a prescription. Previously the FDA and the Bush administration had limited the access of the drug to women 18 and older but a U.S. district judge ruled in March that the older age limit was "arbitrary and capricious." The judge also directed the agency to evaluate clinical data to determine whether there should be any age restrictions on use of the drug. The FDA has no plans to appeal the court's decision. Duramed Pharmaceuticals must file paper work with the FDA, a process that is expected to take 30 days. Plan B is levonorgestrel in a 2-pill pack, the first to be taken within 72 hours of unprotected intercourse and the second pill 12 hours later.

The FDA has approved a new TNF-alpha blocker monoclonal antibody for the treatment of rheumatoid arthritis, active psoriatic arthritis, and active ankylosing spondylitis. Golimunab is given once a month as a subcutaneous injection in combination with methotrexate for rheumatoid arthritis. It may be used with or without methotrexate for psoriatic arthritis and as monotherapy for ankylosing spondylitis. As with all TNF-alpha blockers, the FDA is requiring a risk evaluation mitigation strategy (REMS), which includes a medication guide for patients and a communication plan for physicians regarding potential side effects. Also similar to other drugs in this class, golimumab will carry a boxed warning regarding the risk of tuberculosis and invasive fungal infections. Golimumab was developed by Centocor Ortho Biotech, a division of Johnson & Johnson. The drug will be marketed under the trade name Simponi™. ■