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A monthly update of developments in cardiovascular disease

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INSIDE

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CRUSADE Study

ABSTRACT & COMMENTARY

By Jonathan Abrams, MD

Professor of Medicine, Division of Cardiology, University of New Mexico, Albuquerque

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

Source: Peterson ED, et al. Association Between Hospital Process Performance and Outcomes Among Patients with Acute Coronary Syndromes. *JAMA.* 2006;295:1912-1920.

CRUSADE (CAN RAPID RISK STRATIFICATION OF UNSTABLE Angina Patients Suppress Adverse Outcomes With Early Implementation Of The ACC/AHA Guidelines) is a large quality improvement initiative evaluating the performance of multiple hospitals with respect to current NSTEMI guidelines. This is an evaluation of 350 US hospitals, with a goal of determining variation of hospital performance for a large number of individual care processes; an additional goal is to identify hospital characteristics that are predictive of higher adherence to contemporary guidelines. CRUSADE is a voluntary observational data collection and quality improvement initiative that began in 2001. Enrolled hospitals collect and submit clinical information regarding the care and outcomes of NSTEMI with high risk clinical features. Extensive data extraction and statistical analyses are critical to the success of CRUSADE. Web-based collection tools were used and multiple procedures to monitor and improve data quality were employed. Complete data collection has been documented in audits of the CRUSADE sites.

The study population consists of 427 hospitals enrolling 78,000 patients with NSTEMI between January 2001 and September 2003. Participating hospitals in the analysis had to have at least 40 cases and 1 death during the study period. The final number of study patients was 65,000 at 350 CRUSADE hospitals. Nine ACC/AHA Class 1 guideline criteria for NSTEMI were utilized, including 4 process of care measures (aspirin, beta-blocker, heparin, and glycoprotein 2B-3A inhibitors within 24 hours). In addition, 5 discharge regimens were assessed (aspirin, beta-blocker, clopidogrel, ACEI, and lipid medication). Deaths within 24 hours were excluded from the analysis. Composite adherence scores were calculated at the patient and hospital level. Clinical characteristics, medications, pro-

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cedures, and mortality were compared among hospital and patients. Correlation of hospital adherence rates, mortality, procedures, medications, and patient clinical characteristics were assessed. Multiple markers were evaluated and many statistical analyses were carried out, including sensitivity analyses. Patients with or without elevated biomarkers and high risk elderly patients > 65 were also separately assessed.

The results indicate that 74% of all treatment care decisions were consistent with current guideline recommendations. Composite guideline adherence scores among the hospitals varied widely, with median composite adherence scores ranging between 82% in the highest performing hospitals to 63% in those in the lowest adherence quartile. Variability in use of recommended therapies were assessed, with the highest composite adherence hospitals having the highest average performance for acute, discharge, and secondary prevention metrics. Aspirin had the lowest degree of variance, while use of clopidogrel at discharge and in-hospital use of glycoprotein 2B-3A inhibitors showed considerable variance (up to 2-3 fold) among the hospitals. Secondary prevention measures were 20-30% higher in the highest performing quartile of hospitals versus the lowest. Predictors of outcomes were higher in institutions with cardiac revascularization facilities, as well as those with a higher proportion of patients treated primarily by a cardiologist. There was a significant inverse correlation between use of individual care processes and in-hospital mortality; the "highest associations between use and mortality were observed for acute intravenous glycoprotein 2B-3A inhibitors, discharge clopidogrel, and discharge lipid lowering agents."

Overall, adherence to the 9 ACC/AHA guidelines demonstrated a negative association in hospital mortality. Mortality rates in patients who had a documented MI were slightly higher than in the broader population of acute coronary syndromes (5.3% vs 4.9%). In-hospital combined death/MI rates decreased as a function of guideline adherence. After adjustment for mortality rates and adherence, there was a differential mortality for ACS of 6.3% in the lowest quartile compared to 4.1% in the highest quartile, $P = < 0.001$. The odds ratio for in-hospital mortality in the highest vs the lowest hospital adherence quartiles was 0.81. For every 10% increase in overall guideline adherence there was a corresponding 10% decrease in mortality.

Multiple populations and situations were tested with sensitivity analyses and "the conclusions. . .were robust." For instance, NSTEMI mortality in the lowest quartile was 7.7% vs 4.3% in those in the highest hospital quartile. In patients > 65, the rate was 8.9% in lowest performing hospitals and 6.1% in the highest quartile; odds ratio of 0.83. Peterson and colleagues found that the outcomes were comparable, including or excluding the analysis to all 427 CRUSADE hospitals. Mortality rates were lower in matched pairs of patients treated at the leading adherence centers; 4.17% vs those in the "lagging quartile centers;" 5.47%, which reflected a 33% difference. Peterson et al conclude that in the overall population of the CRUSADE registry, "up to 25% of opportunities to provide guidelines recommended care were missed in current practice," confirming considerable variability among the centers. They state, "To our knowledge, our study is among the first to link variability in hospital process performance with patient outcomes." Guideline adherence was directly associated with mortality, supporting the use of guideline based process measures as a means assessing the quality of care at an individual institution.

Peterson et al point out that similar results have been suggested in other reports of under-utilization of evidence-based care measures in patients with ACS. They emphasize that multiple process metrics are needed to "fully characterize hospital care practices," as an individual measure does not necessarily predict outcomes. Only CABG availability and direct care by a cardiologist were significantly related to higher adherence rates. Of great importance, they state that there was a "strong dose-dependent association between hospital adherence to care guidelines and acute patient outcomes." Overall, the CRUSADE hospitals data

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demonstrated that the elderly, minorities, and patients with the most co-morbidities tend to be treated at hospitals with lower measures of adherence, in part because healthier patients are often transferred to high performing hospitals. Peterson et al suggest that adherence performance may be a surrogate marker for hospital culture and overall quality of care. Of interest, Peterson et al point out that use of statins, clopidogrel, and 2B-3A inhibitors may be closer and more accurate markers of hospital outcome than older and established treatments; the registry demonstrated significantly more variation with the newer therapies than in the older ones among the hospitals. They conclude that up to 25% of guideline-based care opportunities are missed in practice, emphasizing that quality assessment approaches are important. The strong association between hospital composite care performance and patient outcomes clearly "supports the central hypothesis of hospital quality improvement, namely, better adherence with evidence based care practices will result in better outcomes for patients who are treated."

COMMENTARY

This report, which is an extensive and detailed analysis of performance parameters for acute coronary syndromes measures in 350 hospitals. This enormous accomplishment demonstrated what could intuitively be predicted: the better a hospital's overall compliance and adherence to ACC/AHA guidelines, the better the outcomes. The fact that there is a substantial mortality difference between the highest and lowest quartiles of performance is important and disturbing. One would have assumed that mortality in ACS would be equal in almost all hospitals, but there was a significant difference between the highest and lowest level performers. The study emphasizes the use of multiple markers rather than a single variable to assess adherence and hospital performance, and this makes sense as well. Access to revascularization without transfer, and the participation of a cardiologist in the care of ACS patients, turned out to be independent predictors of high quality hospital adherence and performance, supporting the concept that patients do better at institutions that have multiple systems in place for appropriate care (and presumably have a high degree of cardiovascular business).

For the practicing physician, the CRUSADE registry appears to be an indicator of what the future holds. There are multiple, similar initiatives around the country looking at various aspects of cardiovascular care, with efforts to raise the bar for all hospitals, particularly low performers. The CRUSADE experience may or may not be surprising to physicians; it clearly indicates that guideline-driven therapy for acute coronary syndromes is valid and critical to producing the best outcomes. When there is a 20-30% variation in mortality among the 4 quartiles, the message is loud and clear: adherence to Class 1 guidelines is not simply rhetoric, but represents solid adherence to proven performance measures with the assurance that outcomes will be optimal. The era of close surveillance of practice measures is at hand. Peterson et al are to be congratulated for this pioneering report. ■

News About Clopidogrel

ABSTRACTS & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease.*

Sources: Bhatt DL, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. *N Engl J Med*. 2006;354:1706-1717; Wolfram RM, et al. Clopidogrel Loading Dose (300 versus 600 mg) Strategies for Patients with Stable Angina Pectoris Subjected to Percutaneous Coronary Intervention. *Am J Cardiol*. 2006; 97:984-989.

CLOPIDOGREL PLUS ASPIRIN HAVE BEEN SHOWN TO reduce subsequent events in patients with unstable angina, myocardial infarction (MI), and post percutaneous interventions. Its role in long-term prophylaxis in high-risk patients without these acute events is unclear. Thus, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial was conducted in 15,603 patients with either clinically evident cardiovascular disease or multiple atherothrombotic risk factors. They were randomized in a double-blind fashion to clopidogrel (75mg/d) plus aspirin or aspirin (75-160 mg/d) alone (plus placebo). The primary efficacy end point was death, stoke, or MI. The primary safety end point was severe bleeding. There were a variety of secondary end points and prespecified subgroup analyses. After a median follow-up of 28 months, the primary end point occurred in 6.8% of the clopidogrel group and 7.3% of the placebo group (P = .22). The primary safety end point occurred in 1.7% of the clopidogrel patients and 1.3% of the placebo group (P = .09). Bhatt and colleagues concluded that overall clopidogrel plus aspirin was no more effective than aspirin alone at preventing

subsequent events in patient with known cardiovascular disease or multiple risk factors for it.

Although clopidogrel is an important adjunct to aspirin therapy in patients undergoing percutaneous coronary interventions (PCI), there has been controversy over the appropriate loading dose. Thus, Wolfram and colleagues compared a 300 mg to a 600 mg loading dose immediately prior to PCI in 445 patients with stable angina. The primary end points were post procedure biomarkers of myocardial necrosis, bleeding, and vascular complications at 30 days. There was no difference in the primary end points between the 2 groups. Wolfram et al concluded that a 600 mg loading dose of clopidogrel pre-PCI is safe, but does not improve 30-day outcomes following PCI as compared to 300 mg.

COMMENTARY

Clopidogrel has become a staple of modern cardiovascular care, but higher doses and more widespread use do not seem to be indicated. With regard to pre-PCI use, a 300 mg load seems adequate. The lingering question is when clopidogrel is given many hours before PCI, what is the appropriate dose? Other trials have shown improved outcomes with a 600 mg load, but only when given hours before, which is not the usual practice in the United States. Also, higher doses may be warranted in patients with unstable syndromes. The patients described above had stable angina. One drawback to this study is that it is retrospective and the dose of clopidogrel was not randomized. Thus, there may have been individual selection biases that influenced the results. In fact, about two-thirds of the patients received 600 mg, suggesting that is/was the conventional wisdom at the Washington Hospital Center.

The idea that if clopidogrel plus aspirin is good for acute cardiovascular event patients that it must be good for all cardiovascular disease patients seems logical, but could not be proven in the CHARISMA trial. In some ways this is not surprising because cardiovascular events and procedures are associated with coronary endothelial damage and a greater risk for thrombotic complications, but stable patients probably have largely intact endothelium, and the risks of clopidogrel outweigh its benefit. There may be subgroups of stable patients who may have damaged endothelium and would benefit, but they may be difficult to identify. This study suggested that symptomatic patients may fall in this category, but such subgroup analyses are often inaccurate, and a prospective trial would be required to confirm this. For now it appears that aspirin alone is sufficient unless an acute coronary syndrome develops or PCI is required in stable cardiovascular disease patients or those with high likelihood of this disease. ■

Long-Term Fenofibrate and Ezetimibe

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *Long-term, 48-week co-administration of Fenofibrate plus Ezetimibe was well tolerated and more efficacious than Fenofibrate in patients with mixed hyperlipidemia.*

Source: McKenney JM, et al. Safety and Efficacy of Long-Term Co-Administration of Fenofibrate and Ezetimibe in Patients with Mixed Hyperlipidemia. *J Am Coll Cardiol*. 2006;47:1584-1587.

In patients with mixed hyperlipidemia, the role of ezetimibe added to fenofibrate is not clear. Based upon favorable short-term benefits, this long-term trial was conducted. Mixed hyperlipidemia was defined as LDL cholesterol of 130 to 220 mg/dL, or 100 to 180 if diabetic, and a triglyceride level of 200 to 500 mg/dL. Ezetimibe 10 mg, fenofibrate 160 mg, both, or placebo were the groups for the initial 12-week study. This was followed by a 48-week extension comparing fenofibrate alone to fenofibrate plus ezetimibe. Safety and efficacy were the objectives of this double-blind study. The primary safety variables were adverse experiences, liver function tests, and creatinine kinase levels. The primary efficacy end point was percent change in LDL cholesterol. Secondary end points included other lipoprotein components and high-sensitivity C-reactive protein. Of the 587 patients who entered the study, 576 continued into the 48-week extension. The risk-adjusted LDL cholesterol targets were achieved less frequently with fenofibrate alone (48%) than with fenofibrate plus ezetimibe (76%). HDL cholesterol increased more with the combination (21 vs 18%, $P = .002$) and triglyceride levels decreased more (46 vs 42%; $P = .002$). Also, apolipoprotein B decreased more (25 vs 16%; $P < .001$), but there was no difference in high-sensitivity C-reactive protein reductions. About 15% of the subjects experienced adverse events, of which 1% were serious, but there was no difference between groups. Liver function test abnormalities occurred in

about 1% of both groups, and no one had marked elevation in creatinine kinase. McKenney and colleagues concluded that the long-term co-administration of fenofibrate and ezetimibe was well-tolerated and was more efficacious than fenofibrate alone in patients with mixed hyperlipidemia.

COMMENTARY

Fenofibrate has been traditionally used to decrease triglycerides and this was the biggest change in lipids noted on fenofibrate alone (> 40% reduction). In patients with mixed hyperlipidemia, LDL cholesterol is also elevated and often HDL is decreased. One approach has been to add niacin to fenofibrate, as was done in the CLAS study with good outcomes. However, niacin remains a tough sell for many patients. Thus, ezetimibe emerges as a viable alternative. In this study, adding it further reduced triglycerides and increased HDL by small amounts. The major change was a marked augmentation of LDL lowering by adding ezetimibe (-22% vs -7%; $P < .001$). Since the average baseline LDL was abou 160 mg/dL, this is a major beneficial effect and should correlate with reduced vascular events.

Although adverse events were uncommon, few were serious and only about 5% discontinued treatment because of them. There were no cases of myopathy and a very low incidence of significant liver dysfunction. Creatinine elevations have been described with fenofibrate and, in this study, levels > 1.5 mg/dL occurred in about 10%. Fenofibrate can also increase the incidence of gallstones, which was seen in 0.5 to 1.0% of the subjects. No adverse event was significantly greater after the addition of ezetimibe, suggesting that it has few side effects and that there was no adverse event synergy between the 2 drugs.

There are several caveats to this study. The patient population was relatively young: mean age in the early 50s and only 15% > age 65 years. Over half the patients had metabolic syndrome, but only about 15% had diabetes. However, it was a high-risk group based upon a mean high-sensitivity C-reactive protein of 2.5-3.0 mg/dL. These are the type of patients that could benefit greatly from effective lipid changes. Unfortunately, there is no outcome data in the study and it was not powered for cardiovascular events. Regardless, the combination of fenofibrate plus ezetimibe in mixed hyperlipidemia patients appears to be a reasonable choice for first-line therapy or for those in whom fenofibrate is insufficient to meet treatment goals. ■

Status of ECG Q-Waves

ABSTRACT & COMMENTARY

By Michael H. Crawford, MD

Synopsis: *The new Q-wave criteria may be too nonspecific, resulting in an inappropriately high number of false-positive results.*

Source: Jensen JK, et al. Redefinition of the Q Wave—Is There a Clinical Problem? *Am J Cardiol*. 2006:97:974-976.

In 2000, the joint European Society of Cardiology (ESC) and American College of Cardiology (ACC) task force redefined ECG Q-waves indicative of myocardial infarction (MI). Thus, Jensen and colleagues from Denmark evaluated the diagnostic value of the old criteria vs the new criteria as compared to radionuclide myocardial perfusion scanning. From patients referred for coronary artery disease, 79 met the World Health Organization criteria for MI after reviewing their medical record (pain, biomarkers, ECG). Also, 77 control patients were selected who had not had an MI clinically or by perfusion scanning. Abnormal Q-waves were classically defined as ≥ 40 ms or ≥ 25% of the R-wave in 2 contiguous [limb] leads. The new definition is any Q-wave ≥ 30 ms in V1-V3 or any Q-wave ≥ 1 mm in 2 contiguous limb leads or V4-V6. As would be expected, there were several differences between the baseline characteristics of those with and without prior MI. Specifically, the percent with no significant coronary lesions was 17% vs 68%, $P < .001$. By design none of the controls had a perfusion defect.

Results: As expected, the sensitivity of the new criteria for MI was 71% vs 33% for the old criteria, but specificity decreased to 60% new vs 97% old. Thus, the positive predictive value of a Q-wave by the new criteria was only 64% vs 93% by the old. Negative predictive value was a little better by the new criteria 67% vs 59%. Jensen et al concluded that the new Q-wave criteria are nonspecific and will result in frequent false positive diagnoses.

COMMENTARY

This joint decision by the ESC and ACC is laudable for uniting world opinion and for clarifying the variable applications of the older Minnesota code. However, it may leave us with more false positive diagnoses to evaluate at some increased cost to the

health care system. In this study, false positives went from 7% to 36%. This seems to be part of some recent movement toward more sensitive tests that has been spearheaded by radiologists and emergency department physicians. These specialties prefer high sensitivity and very low false negative rates to reduce missed diagnoses and potential liability. False positives are not their problem, as these patients are passed on to other physicians to sort out. Hence, the unbridled enthusiasm for troponin and BNP. Such tests leave those of us who take care of patients after the presumptive diagnosis is made with a lot of extra nonproductive work, anxious patients, and clogged systems. Also, if cardiac catheterization is done, the patient is subjected to unnecessary risks.

Some might argue what's wrong with very sensitive tests for prior MI since this is an important diagnosis? Why not use the most sensitive tests? Missing an MI is worse than a false-positive diagnosis. The clinical scenario assessed in this study was chest pain patients. Currently, < 15% of patients presenting to the hospital with chest pain have acute coronary syndromes; so more specific criteria seem appropriate. Also, modern non-cardiac surgery carries a very low risk of acute cardiovascular events, and extensive diagnostic testing has not been shown to reduce these low event rates. Anything that increases the perceived need for more tests is not going to help the situation. In addition, it is naïve to think that the snapshot of any one test is all there is to diagnosis. Many other factors come into play, and the progress of time often clarifies diagnostic dilemmas. Long-term patient management physicians have always been comfortable with test sensitivities and specificities in the 80% range. We don't always need a 99% sensitivity and a 60% specificity. Perhaps the new Q-wave criteria would make sense if you are evaluating an airline pilot, but in everyday practice I see trouble.

There are some limitations to this study. It is small, retrospective, and biased toward chest pain patients likely to have coronary artery disease. However, I cannot imagine less false-positives in a more unselected population. Also, myocardial perfusion imaging as the MI gold standard is problematic since there are false-positives and negatives with imaging. Clearly, more data are needed, but I don't think the basic outcome will change. The new criteria are more sensitive by design and, consequently, will be less specific. Use them at your own risk. ■

Complications Associated With ICD Replacement

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.

Synopsis: *ICD generator replacement in patients with device advisories is associated with a substantial rate of complications, including death.*

Source: Gould PA, et al. Complications Associated with Implantable Cardioverter-Defibrillator Replacement in Response to Device Advisories. *JAMA*. 2006;295:1907-1911.

In this study, Gould and colleagues from the Canadian Heart Rhythm Society tracked complications associated with implantable cardioverter-defibrillator (ICD) generator replacements that were performed in response to recent device manufacturers' advisories or recall notices. The objective of the study was to document the frequency of and the reasons for replacements and of any complications associated with the replacements. Participants in the survey included 17 of the 21 ICD implant centers in Canada. These centers represent a catchment area that includes almost 93% of Canada's population. Questionnaires were completed by each center describing the number of patients they followed with devices covered by advisories or recalls in 2004 and 2005. The reason for any device replacement was recorded and complications of device replacement documented. Devices replaced for indications (upgrades, normal battery depletion, infection, etc.) other than the advisory were not included.

During the period of the survey the centers reported there were 2915 patients with devices under advisory. Of these, 533 patients (18%) underwent elective replacement, a mean of 26.5 months after the initial implant. The mean age of the patients was 64 years and 77% were male. Sixty-six percent had received their ICD for secondary prevention, 45% had previously received an appropriate shock, and 21% were pacer dependent. Replacement rates, however, varied widely between centers. Four of 17 centers replaced less than 10% of the devices they followed that were covered by an advisory notice, whereas, 5 of 17 replaced more than 30%.

Complications associated with device replacement were noted in 43 patients. Twelve of these, however,

were classified as minor, including 9 medically-managed incisional infections. Major complications were noted in 31 patients (5.8%). Ten patients developed pocket infections that required system extraction, and 2 patients died as a result of either persistent infection or as a result of the extraction attempt. Re-operation after generator change was required in 21 patients (3.9%). The reason for re-operation was either a large hematoma requiring drainage, system malfunction, or site pain.

During the period of the study, only 3 spontaneous device malfunctions covered by the advisory notices were detected. These were not associated with clinical injury.

Gould et al conclude that complication rates after device replacement may have been underestimated in the past. There is a substantial morbidity and detectable mortality associated with elective device replacement, even in high volume ICD implant centers. They urge consideration of these data when guidelines concerning device replacement in a recall or advisory situation are formulated.

COMMENTARY

ICD and, to a lesser extent, pacemaker malfunction were top medical news stories in 2005. The trigger for the increased media interest was the death of a young man with hypertrophic obstructive cardiomyopathy whose death was associated with an electrical short in his defibrillator circuitry. The device's manufacturer came in for considerable criticism when it was revealed that similar events had been reported earlier and were being tracked by the company. Although these malfunctions had been reported to the FDA, no direct public notification had been made. One of the companies' rationales for not issuing a public advisory was that their projection that the risk of replacement for patients in general would probably be higher than the overall risk of failure. This argument has been largely rejected by the physician community who feel that physicians and patients should make any decision about replacing an ICD or pacemaker based on individual patient characteristics rather than leaving the decision to the device manufacturer.

Recent proposed guidelines from the Heart Rhythm Society are that the decision to replace a device with a systematic malfunction should be made on an individual basis, with the final decision made by the patient and his doctor. The data reported here should be helpful to both patients and physicians when they consider any possible replacement. In this study, the risk of replacement was considerably higher than the risk of patient injury associated with device failure. A similar observation was made 10 years ago when a large number of patient injuries and deaths occurred during attempts to remove Telectronics ACCU-FIX atrial leads.

Decisions about whether or not to replace a device under a recall or advisory remain quite difficult. This paper gives us a better estimate of the real risk of replacement. Physicians will also be dependent upon manufacturers and regulatory agencies to provide accurate predictions of the real failure rates during use, and an accurate clinical assessment of the consequences should the device fail. Only with full access to and understanding of the necessary information, can physicians and patients make informed decisions. ■

Clinical Features of Arrhythmogenic Right Ventricular Dysplasia

ABSTRACT & COMMENTARY

By John P. DiMarco, MD, PhD

Synopsis: *The various identified defects in cell adhesion proteins in ARVD/C lead to the same clinical consequences.*

Source: Dalal D, et al. Clinical Features of Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Associated with Mutations in Plakophilin-2. *Circulation*. 2006;113: 1641-1649.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a clinical syndrome characterized by right ventricular dysfunction and ventricular arrhythmias. It has been recognized that this disorder may be associated with a number of different genetic mutations. In this paper, Dalal and colleagues report on the clinical features of patients with one of the more common mutations associated with ARVD/C—those involving plakophilin-2.

Dalal et al identified 58 unrelated ARVD/C patients from the Johns Hopkins registry. Their medical histories were tabulated, as were results of noninvasive testing, including electrocardiography, signal averaged electrocardiography, Holter monitoring, and imaging studies. Most patients underwent electrophysiologic study, and 48 of the patients eventually received an implantable cardioverter defibrillator during chronic follow-up. Relevant data from these patients were also analyzed.

Among the 58 patients, Dalal et al identified 25 with the mutation in PKP-2, the gene encoding Plakophilin-2. Thirteen different mutations were identified among the 25 individuals. Among the 13 mutations identified, 6 were insertion-deletion mutations, 3 altered a critically conserved nucleotide that formed the intron/exon splice site, 2

were nonsense mutations, and 2 were missense mutations. Patients with the PKP2 mutations tended to be younger than the ARVD/C patients without the mutation, 28 ± 11 years vs 36 ± 16 years. There was a slight male predominance in both groups. Palpitations and syncope were the most common presenting symptom in both groups, and there was no difference in clinical presentation between those with and without the PKP2 mutation. Clinical characteristics and noninvasive testing also were not statistically different between the 2 groups. There were a similar proportion of patients with severe right ventricular dilatation and local ventricular aneurysms between the 2 groups. ECG abnormalities, including the prolongation of the QRS in V1 through V3, the presence of delta waves, and the T-wave inversions in V1 through V3 were similarly distributed. The signal-averaged ECG was abnormal in 60% of those without a PKP2 mutation vs 17 of 23 (74%) patients with the PKP2 mutation. Fifty-six percent of the patients without a PKP2 mutation vs 48% of those with a PKP2 mutation had experienced an ICD discharge after insertion. It was interesting to note that among the patients with PKP2 mutation and inducible ventricular arrhythmias at electrophysiologic study, the presence of severe right ventricular dysfunction and the presence of spontaneous VT on Holter were not predictors of ICD intervention, whereas these risk factors appear to be valid predictors of ICD intervention in patients without the PKP2 mutation.

Dalal et al conclude that mutations in Plakophilin-2 are common and are associated with the clinical syndrome of ARVD/C. Although there was little difference in the clinical pattern between those patients with and without PKP2 mutations, they proposed that genetic testing for PKP2 mutations would be useful criteria for establishing the diagnosis.

COMMENTARY

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is a genetic cardiomyopathy that has been linked to defects in cell adhesion proteins, including plakoglobin, desmoplakin, plakophilin-2, and desmoglobin-2. This paper shows that PKP2 mutations are perhaps the most common genetic cause for ARVD/C. Previously, the diagnosis of ARVD/C was made on the basis of major and minor diagnostic criteria. These criteria might include the family history, the presence of ECG conduction or repolarization abnormalities, a clinical history of arrhythmias, regional dysfunction, most prominent in the right ventricle, and fibrofatty replacement of right ventricular myocardium seen at autopsy or in biopsy specimens. As ARVD/C has become better recognized and several registries have been established, more specific diagnostic criteria are beginning to emerge. Unfortunately, the limited data presented in these 2 reports don't show much difference between patients with and without one of the more commonly identified mutations. The natural history of the disease in both groups seems to be fairly similar. Perhaps as more insights into the mechanisms underlying ARVD/C are identified, more specific treatment approaches based on specific genetic profiles may be developed. However, at the present time, it appears that all of the identified defects in cell adhesion proteins lead to similar clinical consequences. For now, management recommendations will be similar for all patients with ARVD/C. ■

CME Questions

30. In mixed hyperlipidemia, fenofibrate plus ezetimibe further:
a. lowers triglycerides.
b. lowers LDL cholesterol.
c. raises HDL cholesterol.
d. All of the above

31. New criteria for significant ECG Q-waves are:
a. more sensitive.
b. more specific.
c. less specific.
d. A and C

32. Clopidogrel plus aspirin is indicated for:
a. stable CVD patients.
b. unstable coronary syndromes.
c. post PCI.
d. B and C

33. Prior to PCI for stable angina, the dose of clopidogrel should be:
a. 75 mg.
b. 300.
c. 600.
d. 1200.

34. Arrhythmogenic RV dysplasia has been linked to:
a. myosin mutations.
b. cell adhesion protein defects.
c. Neither
d. Both

Answers: 30. (d); 31. (d); 32. (d); 33. (b); 34. (b)

CME Objectives

The objectives of *Clinical Cardiology Alert* are:

• To present the latest information regarding diagnosis and treatment of cardiac disease;

• To discuss the pros and cons of these interventions, as well as possible complications;

• To discuss the pros, cons, and cost-effectiveness of new and traditional diagnostic tests; and

• To present 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.

Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

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In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■