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Clinical Cardiology [ALERT]

A monthly update of developments in cardiovascular disease

ABSTRACT & COMMENTARY

FFR-Guided PCI vs Medical Therapy in Stable Coronary Artery Disease

By Andrew J. Boyle, MBBS, PhD
Assistant Professor of Medicine, Interventional Cardiology, University of California, San Francisco

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

SOURCE: De Bruyne B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. *N Engl J Med* 2012;367:991-1001.

In patients with stable coronary artery disease (CAD), medical therapy is the mainstay of treatment. Percutaneous coronary intervention (PCI) guided by angiographic stenosis is more effective than medical therapy at reducing angina, but does not change the rate of death or myocardial infarction (MI). The potential benefit of PCI appears to depend on the extent of myocardial ischemia that is relieved by that revascularization. Fractional flow reserve (FFR), using a pressure-sensing guidewire in the cardiac catheterization laboratory, can determine the physiologic significance of a coronary artery stenosis in producing ischemia. Recent studies have shown that FFR-guided PCI is safer and more effective in guiding PCI than angiography alone. Whether FFR-guided PCI can improve clinical outcomes over medical therapy alone is not known. In the Fractional Flow Reserve vs Angiography for Multivessel Evaluation 2 (FAME 2) trial, De Bruyne and colleagues tested the hypothesis that FFR-guided PCI in stable CAD would improve outcomes over medical therapy alone.

They enrolled patients with stable CAD who were being considered for PCI, and performed FFR on all coronary stenoses. If there were one or more significant coronary stenoses (FFR ≤ 0.80), the patients were randomized to FFR-guided PCI of the significant lesions plus the best available

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Clinical Cardiology [ALERT]

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medical therapy (PCI group) or to the best available medical therapy alone (medical therapy group). Patients with no significant stenoses (FFR > 0.80 in all vessels) were enrolled in a registry and received the best available medical therapy. All patients were prescribed aspirin, metoprolol, ACE inhibitors (or angiotensin receptor blocker if intolerant), and a high potency statin ± ezetimibe aiming for an LDL of < 70 mg/dL. Those who underwent PCI received a loading dose of clopidogrel 600 mg and then 75 mg daily for 12 months, and all received second-generation drug-eluting stents (DES). The primary endpoint was a composite of death, MI, or urgent admission for revascularization.

The baseline characteristics were well matched between groups. The mean age was 64 years, three-quarters were male, and 27% had diabetes. Approximately 11% were asymptomatic and 18%, 45%, 18%, and 6% had angina in Canadian cardiovascular society (CCS) classes I, II, III, and IV, respectively. The study was halted prematurely by the data safety and monitoring board after enrollment of 1220 patients (n = 447 randomized to PCI, n = 441 randomized to medical therapy, and n = 332 patients enrolled in the registry) because of a highly significant difference between groups with respect to the primary endpoint (4.3% in the PCI group vs 12.7% in the medical group; $P < 0.001$). There was no difference in the rate of death or MI between the PCI and medical therapy groups. The difference in the composite primary endpoint was driven by a lower rate of urgent revascularization in the PCI group (1.6% vs 11.1%; hazard ratio [HR] 0.13, $P < 0.001$). Interestingly, the rates of death from MI and urgent revascularization were similar between the PCI group and those in the registry who had no significant stenoses at all. The authors conclude that in patients with stable CAD and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization. In patients without ischemia, the outcome appeared to be favorable with the best available medical therapy alone.

■ COMMENTARY

This study tested a strategy of treating ischemia-producing lesions with PCI plus medical therapy vs medical therapy alone and showed that PCI results in fewer urgent hospital admissions requiring revascularization. Previous studies have tested PCI vs medical therapy based on angiographic guidance, which may overestimate the functional significance of coronary lesions. This study adds to the growing body of literature that treating ischemia, rather than angiographic stenoses, should be our goal because it results in better outcomes. In addition, this trial used second-generation DES in all patients, whereas prior studies, such as the COURAGE trial, used predominantly bare-metal stents. These differences in trial design may contribute to the benefits of PCI over medical therapy alone.

Several limitations of the study should be noted. First, the data safety and monitoring board stopped the trial prematurely because the primary endpoint was reached in favor of PCI over medical therapy. The study was therefore effectively underpowered to determine any difference in MI or death; there was only a difference in the rate of urgent revascularization, and the follow-up period was very short (mean 7 months). Unfortunately, this leaves us with an incomplete dataset. How much importance should we place on the endpoint of urgent revascularization? The patients who had urgent revascularization were all admitted to the hospital and nearly half of these had elevated biomarkers, ECG changes, or both. Considering that there were eight times more of these in the medical therapy group than the PCI group, I think this is an endpoint worth taking into account. Second, clopidogrel was given to all patients in the PCI group, but was left to the physicians' discretion in the medical therapy group. Prior studies have not shown significant benefit of dual antiplatelet therapy in patients with stable CAD, but it is

possible there may have been some benefit in this trial. Third, we are not told of the cost-effectiveness of PCI vs medical therapy. There will likely be several follow-up manuscripts. The longer-term results of the FAME 2 trial are eagerly awaited. ■

ABSTRACT & COMMENTARY

IABP for MI with Cardiogenic Shock?

By Andrew J. Boyle, MBBS, PhD
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SOURCE: Thiele H, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012; Aug 26. [Epub ahead of print.]

Patients who present with acute myocardial infarction (MI) complicated by cardiogenic shock represent a group at high risk for early mortality. Current guidelines recommend the use of intra-aortic balloon pump (IABP) for these patients, but there are few randomized, controlled trial data to support this. Thiele and colleagues studied the effects of IABP in 600 patients presenting with MI and cardiogenic shock. Patients were eligible for the study if they presented with acute MI (with or without ST elevation) and cardiogenic shock, defined as a systolic blood pressure (BP) lower than 90 mmHg for ≥ 30 minutes, or the requirement for catecholamine infusion to maintain BP > 90 mmHg, plus signs of pulmonary congestion and end-organ hypoperfusion (altered mental status, oliguria, cold clammy skin, or elevated serum lactate). Exclusion criteria included age ≥ 90 years, resuscitation from cardiac arrest for > 30 minutes, severe peripheral arterial disease precluding IABP, aortic regurgitation ≥ grade II, shock for > 12 hours, mechanical cause for shock (e.g., ruptured papillary muscle), or life expectancy < 6 months. Patients were randomized to receive IABP (n = 301) vs no IABP (n = 299) in an open-label fashion. All patients were expected to undergo early revascularization. The IABP could be inserted before or after percutaneous coronary intervention (PCI) and the mode of revascularizaton was left to the discretion of the operator. The primary endpoint was 30-day, all-cause mortality.

The baseline characteristics were similar between groups. The median age was 70 years; two-thirds were male and one-third were diabetic. The median systolic BP was 89 mmHg at study entry. There was no difference between groups in the primary endpoint of death at 30 days (39.7% in the IABP group vs 41.3% in the control group; $P = 0.69$). The authors performed intention-to-treat and per-protocol analyses of the primary outcome, as well as a multivariable analysis, and there were no differences between groups by any of these methods. There was no difference in mortality when the IABP was placed before or after PCI. Subgroup analysis revealed no difference in mortality between the IABP group and the control group when stratified by gender, diabetic status, STEMI vs non-STEMI, anterior MI vs non-anterior MI, BP above or below 80 mmHg, or first vs subsequent MI. When stratified by age, those younger than 50 years appeared to have a mortality benefit with IABP (19.4% in IABP group vs 44.1% in control group), but there was no difference in the 50-75 years group or the > 75 years group and the *P*-value for interaction with age did not reach statistical significance.

There were no differences in the rates of in-hospital stroke, recurrent MI, stent thrombosis, bleeding, sepsis, or peripheral arterial complications requiring intervention. There were no differences in the secondary endpoints of serum creatinine, C-reactive protein, and lactate levels. The authors conclude that the use of IABP did not significantly reduce 30-day mortality in patients with cardiogenic shock, complicating acute MI in those who undergo early revascularization.

■ COMMENTARY

This is a resoundingly negative study. Not only was the primary endpoint of all-cause mortality negative, the secondary endpoints were also all negative. Importantly, there were no differences whether the patient was experiencing a STEMI or non-STEMI. There was some suggestion that young patients may benefit from IABP, but this did not reach statistical significance. This study calls into question the routine use of IABP in patients with cardiogenic shock complicating MI. Should we abandon IABP completely in this setting? Or are there some patients who may still benefit from IABP in cardiogenic shock complicating MI? I think

there are still some patients who may benefit from *selective* use of IABP in this setting. First, there may be benefit for IABP in patients with impaired coronary flow after PCI, as IABP counterpulsation augments coronary perfusion. Second, the use of IABP may allow lower doses of inotropes/pressors. In some patients, such as those with arrhythmias caused by inotropes, there may be a benefit to ceasing the inotropes and IABP may be the only way this is possible. In this paper, we are not told about adequacy of coronary flow after PCI or about arrhythmias.

Some limitations of the study should be acknowledged. First, we are not told of the effect of IABP on other meaningful endpoints, such as heart failure and ejection fraction. If there is improvement in these parameters, there may be an indication for using IABP despite a lack of mortality benefit. Second, subjects were not blinded to which group they were in; however, the clinical events committee was blinded to the treatment group of each subject. Third, we are not told details of PCI, in particular, how many patients underwent culprit-only vs multivessel stenting. This is important as it may affect overall mortality.

This study reaffirms that the mortality associated with cardiogenic shock complicating acute MI remains very high, despite early revascularization and modern intensive medical therapy. There is a need for better treatment in this group of patients. Perhaps newer percutaneously placed left ventricular assist devices may take over from IABP in the treatment of cardiogenic shock, but this remains to be tested in adequately powered clinical trials. ■

ABSTRACT & COMMENTARY

Management of Atrial Fibrillation in Chronic Kidney Disease Patients

By John P. DiMarco, MD, PhD
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Dr. DiMarco does research for Medtronic, is a consultant for Medtronic, Novartis, and St. Jude, and is a speaker for Boston Scientific.

SOURCE: Olesen JB, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012;367:625-635.

Patients with chronic kidney disease or who have had renal replacement therapy have often been excluded from trials of anticoagulation in atrial fibrillation (AF). In this study, the authors analyzed data from hospitalized patients with nonvalvular AF in Denmark from 1997 through 2008. Patients with chronic kidney disease with and without renal replacement therapy were identified from a national registry. Pharmacotherapy was determined based on prescription data in the national patient registry. Stroke and bleeding risks were estimated using the CHA_2DS_2-VAS_C score and the HAS-BLED score, respectively. The primary outcomes in the study were hospitalization or death from stroke or systemic thromboembolism, major bleeding, myocardial infarction, and death from any cause. The analysis used a Cox proportional-hazards model with adjustment for changes in renal status or antithrombotic treatment during follow-up. The analysis was time dependent in that the renal status of patients could change during the course of follow-up if they developed chronic renal disease or began renal replacement therapy during follow-up.

During the course of the study, 146,251 patients were discharged from Danish Hospitals with nonvalvular AF. Of these, 13,879 were excluded for various reasons. In the final cohort of 132,372 patients, 96.6% had no renal disease at baseline, 2.7% had non-end-stage prior kidney disease, and 901 patients were receiving renal replacement therapy. During the course of the trial, an additional 4538 patients received a diagnosis of non-end-stage chronic kidney disease and renal replacement therapy was begun in an additional 477 patients. Among the patients with non-end-stage chronic kidney disease at baseline, 228 went on to receive renal replacement therapy during follow-up. Most patients on renal replacement therapy were receiving hemodialysis (77.9%), while 15.4% received peritoneal dialysis and 6.7% underwent kidney transplantation.

The rates of stroke or thromboembolism were increased in patients with chronic kidney disease. Among the patients with no renal disease, the event rate per 100 patient years was 3.61 compared to a rate of 6.44 in those with non-end-stage chronic kidney disease and 5.61 in those on

renal replacement therapy. Bleeding rates were also increased. These were 3.54 per 100 patient years in those with no renal disease, 8.77 in patients with non-end-stage chronic kidney disease, and 8.89 in patients on renal replacement therapy. The rates for myocardial infarction and all-cause mortality were increased about three-fold. When the rates for strokes or systemic thromboembolism were adjusted for baseline risk factors, chronic kidney disease was still independently associated with an increase in risk. The adjusted hazard ratios for patients with non-end-stage chronic kidney disease was 1.49 (95% confidence interval [CI], 1.38 to 1.59; $P < 0.001$) and 1.83 (95% CI, 1.57 to 2.14; $P < 0.001$) for those on renal replacement therapy.

Warfarin decreased the risk of stroke in all groups. The hazard ratio for warfarin therapy compared to no anticoagulant therapy was 0.59 in those with no renal disease, 0.84 in those with non-end-stage chronic kidney disease, and 0.44 in those on renal replacement therapy. Similar reductions in stroke risks were seen when both warfarin and aspirin were prescribed. Aspirin alone did not decrease, but slightly increased the risk of stroke in patients with no renal disease or non-end-stage chronic kidney disease.

Warfarin increased the bleeding risks in all three groups. In the proportional hazard model, the hazard ratios for bleeding were 1.28 in those with no renal disease, 1.36 in those with non-end-stage chronic kidney disease, and 1.27 in those requiring renal replacement therapy. Bleeding rates were also increased when aspirin alone was used and almost doubled in patients who received both warfarin and aspirin.

The authors note that chronic kidney disease in patients with AF is associated with increased risks for stroke, systemic thromboembolism, and bleeding. Warfarin significantly reduces the risk of systemic thromboembolism at the cost of increasing bleeding risks. They conclude that initiation of warfarin therapy requires careful thought in patients with chronic kidney disease, since the risks and benefits of therapy may well be equal.

■ COMMENTARY

In this paper, we see that in renal disease patients with nonvalvular AF, the rates for thromboembolic events off therapy and bleeding events on therapy are essentially equal. When this situation occurs, it's hard to write a firm guideline that will apply to all patients in a class. We therefore need to look at each patient's individual risk scores before making a decision. I also usually factor in that a stroke more often results in death or permanent disability than does non-CNS bleeding. Therefore, my usual first presumption is to start anticoagulation while monitoring closely for bleeding. Only in patients with a very high bleeding risk will I not make at least one attempt at oral anticoagulant therapy. ■

ABSTRACT & COMMENTARY

Stroke Risk with Warfarin Interruption

By Michael H. Crawford, MD, Editor

SOURCES: Raunso J, et al. Increased short-term risk of thrombo-embolism or death after interruption of warfarin treatment in patients with atrial fibrillation. *Eur Heart J* 2012;33:1886-1892. Hohnloser S, et al. The hazards of interrupting anticoagulation therapy in atrial fibrillation. *Eur Heart J* 2012; 33:1864-1866.

The risk of interrupting prophylactic warfarin for stroke prevention in atrial fibrillation (AF) patients is unclear. Thus, these investigators from Denmark evaluated their national health registry and found 102,591 patients > age 30 with a first-time hospitalization for AF between 1997 and 2008. Valvular AF patients were excluded. Follow-up was started 7 days after hospitalization to ensure achievement of steady-state warfarin dosing. Warfarin therapy was subsequently determined by their national pharmacy database and warfarin usage was estimated based on the supply of medications dispensed. The primary outcome was the combined endpoint of all-cause mortality or hospitalization for thromboembolism. The mean follow-up was 3.5 years. During warfarin therapy, the primary endpoint occurred in 6.9/100 patient-years. At least one treatment interruption occurred in 72% of the patients and these patients had lower CHADS2 scores compared to the no interruption group (1.34 vs 1.56, $P < 0.001$). The median duration of interrupted therapy was 36 days. Among the 16,738 primary events, 49%

occurred during the treatment interruption, for a rate of 14.2/100 patient-years. More events occurred during the first 90 days of interruption (31.6/100 patient-years) and leveled off after 180 days. The hazard ratio for treatment interruption was 2.9 (95% CI 2.8-3.0). Also, the hazard ratio was similar if death was excluded as an endpoint. The authors concluded that interruption of warfarin therapy in non-valvular AF patients increased the short-term risk of death or thromboembolism, especially during the first 90 days of treatment interruption.

■ COMMENTARY

Because of their national health systems, many European countries have very large patient databases that dwarf those at some of our single hospital systems or even multicenter trial databases. Although limited by their retrospective observational nature and the unique structure of national databases, their sheer size makes these analyses important. This study from Denmark has two interesting findings. First, the incidence of warfarin therapy interruption in AF patients is high, about three-quarters of patients, and the median length is relatively long, 36 days. Randomized AF therapy trials have noted interruptions at a frequency of 15-30%. Clearly, real-world experience is very different from trials. Second, the risk of thromboembolism or death rises three-fold in the first 90 days of interrupted therapy, then tapers off. Thus, real world patients on warfarin stroke prophylaxis for AF are often at considerable risk because of therapy interruptions.

Interestingly, there were no subgroup differences in the incidence of the primary event whether stratified by age, sex, duration of therapy, or CHADS2 score. Also, excluding death as an endpoint did not appreciably alter the results, suggesting that the important events were thromboembolism. This raises the question of the etiology of the increase in events. One possibility is that warfarin is preventing strokes and after its withdrawal the stroke rate returns to its natural state (the so-called catch-up phenomenon). Another is that there is a warfarin withdrawal phenomenon that actually increases the rate of thromboembolism over what it would naturally be. Although there are some experimental data showing that coagulation factors transiently rise above normal levels after warfarin withdrawal, there are no clinical mechanistic data to support this theory. Finally, it is possible that whatever occasioned the interruption in therapy was the cause of the event, such as surgery (confounder). Unfortunately, this study is not able to sort out these potential mechanisms.

Other studies have shown that warfarin can be interrupted for clinical reasons such as surgery or due to patient decisions unrelated to their health conditions. This study does not specify the reasons and we have no clinical data such as INR values. Also, we do not know if the interruptions were transient or the patients stopped therapy. Although the median duration of interruption was 36 days, the 75th percentile was 207 days. Specific guidelines exist for medical issues such as high INR values, episodes of major bleeding, and surgery, which should minimize the risks of thromboembolism, so one could conclude that the majority of the interruptions that lead to events were in the patient decision category. If so, it behooves us to emphasize the importance of continuous therapy to our patients. Perhaps the use of the newer oral anticoagulants, which do not require INR-based management, will improve patient compliance. ■

ABSTRACT & COMMENTARY

Riata ICD Lead Defects

By John P. DiMarco, MD, PhD

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SOURCE: Liu J, et al. Fluoroscopic screening of asymptomatic patients implanted with the recalled riata lead family. *Circ Arrhythm Electrophysiol* 2012;5: 809-814.

More than 200,000 Riata family implantable cardioverter-defibrillator (ICD) leads from St. Jude Medical were implanted worldwide. Recently, the FDA issued a Class I recall on this lead because of the appearance of defects in the lead insulation that may lead to externalization of the conductor wires. Although the initial company statement

estimated the frequency of conductor problems with Riata leads at less than 1%, subsequent reports have reported much higher rates of externalization. In this study, the authors offered voluntary fluoroscopic and electrical screening of their ICD leads to all patients who received Riata lead implants in the University of Pittsburgh Medical Center network of hospitals. Of 369 active Riata lead patients, 245 agreed to screening and were included in the study. Cine fluoroscopy of the lead was performed in three views. Lead conductor externalization was defined as the appearance of conductors outside the lead body in one or more of the views. Lead electrical performance was analyzed using standard techniques. Isometric testing was also performed to look for electrogram abnormalities that might be detected by this technique.

Among the 245 patients screened, 190 (78%) leads showed no conductor separation, 53 (22%) leads exhibited clear externalization, and in two patients the fluoroscopic imaging was inconclusive. Externalization was not seen in leads that had been implanted for less than 3 years, in 13% of leads with implant durations of 3 to 5 years, and in 26% of those with implant durations of longer than 5 years. Riata lead externalization was seen in all projections in 59% of patients, but was missed in at least one view in the remaining 41%. Patients with externalized conductors tended to be younger (62 ± 13 years or 66 ± 12 years), but this difference is not clinically helpful. Externalized leads showed a trend toward a decrease in R-wave amplitude, but this and other measures of electrical integrity remained in the normal range. Only one patient with externalized cables exhibited new noise on the right ventricular electrogram during isometric maneuvers. Far field noise was common in patients both with externalized cables and without externalized cables.

The authors conclude that cine fluoroscopic screening of asymptomatic patients with Riata leads will yield more than 20% rates of cable externalization. This appears to be a time-dependent phenomena. The relationship of externalized conductors to true electrical failure is still uncertain.

■ COMMENTARY

Over the last few years, we have seen several large scale Class 1 recalls of ICD leads or generators. Clinical decision making in such patients is often difficult since a number of factors must be carefully weighed. These include the expected rate of failure, the consequences of a failure, the risks of intervention, and the clinical characteristics of the patient. Intuitively, one might think generator recalls to be less problematic since the surgery required for replacement is fairly simple, but even with generator changes the risk for infection, erosion, or lead damage are not trivial. Lead replacements involve yet higher risks whether the lead is extracted. With previous recalls, more patient deaths and permanent injuries were caused by attempts at extraction than were documented to be due to the lead failures themselves. It should also be remembered that the longer a lead is in place, the greater the risk for extraction, so extracting early may be an attractive option, particularly at the time of an elective generator replacement in some situations.

In this paper, the authors show a high rate of externalized conductor wires in the Riata family of ICD leads. My laboratory and several others have made similar observations. Several questions, however, still remain. Will the rate of externalization continue to increase over longer implant durations? This seems likely but the authors here suggest a plateau may have been reached after about 6 years. What fraction of externalized conductors will actually go on to fail electrically? The externalized Riata lead conductor at least initially has a second layer of ETFE insulation and it's possible this may provide sufficient insulation long term. Careful longitudinal follow-up data from leads with externalized conductors are certainly needed. The recent FDA statement advises either fluoroscopic screening or chest radiography, but my experience and the data here suggest a plain chest X-ray is not sufficiently accurate. Should everyone have fluoroscopy and, if so, how frequently? Is the high frequency of externalized conductors just a sign that the silicone insulation in this lead will be dangerously susceptible to both "inside-out" abrasion from lead motion and "outside-in" abrasion from contact with other leads, the generator, ligaments or bone? Until we get the better answers to all these questions, managing patients with Riata leads will remain largely guesswork. ■

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5. Once the evaluation is received, a credit letter will be sent to you. ■

CME Questions

1. Lead insulation failure in Riata ICD leads can be seen by fluoroscopy in about what percent of patients?
   a. 5%
   b. 10%
   c. 20%
   d. 30%

2. Chronic kidney disease in patients with atrial fibrillation increases the risk of:
   a. stroke.
   b. bleeding.
   c. systemic embolism.
   d. All of the above

3. Invasive fractional flow reserve measures of ischemia-guided percutaneous coronary interventions vs best medical therapy:
   a. reduces death.
   b. reduces myocardial infarction.
   c. reduces subsequent urgent revascularization.
   d. All of the above

4. In acute MI complicated by cardiogenic shock treated with percutaneous coronary interventions, intra-aortic balloon counterpulsation:
   a. reduces mortality.
   b. reduces stroke rates.
   c. reduces stent thrombosis.
   d. None of the above

5. Significant interruptions in warfarin therapy for stroke prevention in atrial fibrillation patients are:
   a. uncommon.
   b. associated with increased thromboembolic events.
   c. associated with less bleeding.
   d. All of the above

CME Objectives

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

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

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By Louis Kuritzky, MD

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

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Refining the Relationship Between Thyroid Hormones and Left Ventricular Mass

Source: Iida M, et al. *J Am Soc Hypertens* 2012;6:261-269.

Animal studies have shown that thyroid hormones (T3 and T4) induce hypertrophy of cardiac myocytes through stimulation of both structural and regulatory myocyte genes, which can be prevented by ACE inhibitors or beta-blockers. Such observations have led to the question of whether there might be a relationship between cardiac mass and thyroid hormones, even within the range currently defined as normal.

Hypothyroidism and hyperthyroidism are each considered a potential secondary cause of hypertension: the former through endothelial dysfunction that leads to vasoconstrictor hyperresponsiveness and subsequent increased peripheral resistance, and the latter through increased sympathetic tone. Iida et al investigated hypertensive subjects (n = 293) who had no known thyroid disease and whose thyroid function tests (T3, T4, and TSH) were within normal limits.

Among these euthyroid hypertensive study subjects, multiple linear regression found a positive relationship between T3 and T4 and ventricular mass (the higher the thyroid hormones, the greater the ventricular mass), and an inverse relationship between TSH and ventricular mass. When compared with normotensive controls, no such relationship could be identified. This would lead to consideration that in persons with hypertension, higher levels of thyroid hormone — even within the normal range — may be related to the development of left ventricular hypertrophy. ■

The ORIGIN Trial: Basal Insulin vs Standard Care for Early Type 2 Diabetes

Source: The ORIGIN Trial Investigators. *N Engl J Med* 2012;367:319-328.

Type 2 diabetes reflects insulin insufficiency. Early in the disease process, plasma insulin levels may actually be higher than normal, but insufficient to maintain euglycemia. By the time of formal diagnosis, approximately half of beta cell mass has been lost, and as the disease progresses, insulin levels continue to fall.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized subjects with prediabetes or early diabetes (n = 12,537) to insulin glargine (GLAR) or standard treatment (STND) for 6.2 years (mean). The objective of the trial was to determine whether early institution of basal insulin, as compared to STND, improves cardiovascular outcomes. Standard treatment was simply treatment of diabetes as per the treating clinician's choice; by the end of the trial, only 11% of the STND group was receiving insulin. Eighty percent of the GLAR group was on insulin at the end of the trial.

There was no difference in cardiovascular outcomes between the two treatment groups. One notable difference between treatments was the likelihood of progression from prediabetes to diabetes. The GLAR group was 28% less likely to progress than the STND group; however, there was also more hypoglycemia and weight gain in the GLAR group.

Increased incidence of cancer — a concern generated by earlier insulin trial data — was *not* seen in this large trial, and hence should be very reassuring. ■

Bronchodilators in COPD and Arrhythmias

Source: Wilchesky M, et al. *Chest* 2012; 142:298-304.

For chronic obstructive pulmonary disease (COPD), except for the provision of oxygen in late-stage disease, no pharmacologic intervention has been confirmed to save lives. Nonetheless, since bronchodilators improve symptoms, quality of life, and exercise capacity, and reduce acute exacerbations of COPD, they play an important role in routine care. Concerns about the potential capacity for arrhythmogenicity of bronchodilators has arisen from clinical COPD trials such as the Lung Health Study (n = 5887), in which short-acting ipratropium bromide was associated with a three-fold greater incidence of arrhythmia than comparator groups. Other smaller trials have not confirmed these findings, hence clarification is needed.

Wilchesky et al analyzed data from the province of Saskatchewan, Canada, to identify COPD subjects (n = 6018) and compare the incidence of arrhythmia in new users of ipratropium, beta-agonists (short- and long-acting), and methyhlxanthines to non-users.

Short-acting anticholinergics were

associated with a 2.4 relative risk of arrhythmia, and long-acting beta-agonists with a 4.5 relative risk. No statistically significant increased risk was seen with short-acting beta-agonists or methylxanthines. Despite these concerns, the authors remind us that the absolute risk increase was very small, and "in most cases would be outweighed by the therapeutic benefit accrued through symptomatic relief and consequent improvements to quality of life." ■

Reversible Dementia from Corticosteroid Therapy

Source: Cipriani G, et al. *Clin Geriatrics* 2012;20:38-41.

Although there are many clinical situations in which corticosteroids (CTS) are disease modifying and life saving, one aspect of CTS that has not received much attention is the potential for central nervous system (CNS) adverse effects. CTS may be largely subgrouped into mineralocorticoids exemplified by aldosterone, and glucocorticoids (GLC) like prednisone, the latter of which is the object of this case report.

There are at least two types of CTS receptors in the brain: type I (mineralocorticoid receptors) and type II (glucocorticoid receptors). Type II receptors are found in the hippocampus as well as diffuse other sites throughout the brain. The hippocampus is required for voluntary recollection of learned information, such as recalling what you had for dinner last night. Even low doses of GLC have been shown to impair hippocampal function, despite being used for short time periods: doses of prednisone of 80 mg/day have been shown to alter cognitive function within 4-5 days.

The authors include discussion of a report detailing six cases of dementia-like cognitive decline (distinct from steroid psychosis) in patients whose cognitive function was restored upon GLC discontinuation.

Clinicians should be vigilant for decline in cognitive function in persons receiving GLC treatment, even over the short-term. ■

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Could Thinner be Worse for Newly Diagnosed Diabetics?

Source: Carnethon MR, et al. *JAMA* 2012;308:581-590.

Usually, we anticipate a direct relationship between overweight and cardiovascular adversity, attributed to increases in blood pressure, lipids, glucose, insulin resistance, and sympathetic tone that are associated with obesity. There appears to be some exception to this general rule in reference to diabetes. For instance, in the TRIAD study, diabetics who were normal weight at entry to the study had a *higher* mortality than overweight/obese study subjects; similarly, in the PROactive trial, normal weight subjects or those who lost weight had *higher* mortality than overweight subjects. Because these two studies included confounding issues such as diabetes of varying duration and pre-existing cardiovascular disease, a more clear-cut relationship between body mass index (BMI) and outcome in diabetes could be discerned by selecting newly diagnosed diabetics.

Carnethon et al performed a pooled analysis of five longitudinal cohort studies (n = 2625) to examine the relationship between mortality and BMI for persons with newly diagnosed diabetes. Overall, only 12% of study subjects had a BMI < 25 at the time of diagnosis, but the relative risk for total mortality during follow-up (up to 15 years) was essentially doubled in this population compared to overweight individuals.

The mechanism(s) by which lower BMI increases mortality risk are unknown. Clinicians must not be falsely reassured that this lower-BMI phenotype, which is commonly seen in Asian-Americans, portends a favorable future. ■

The Impact of Exercise on Depression in Heart Failure

Source: Blumenthal JA, et al. *JAMA* 2012;308:465-474.

It is estimated that 5 million Americans have chronic heart failure (CHF), and almost half of these patients fulfill diagnostic criteria for depression. Subsyndromal depression is present in as many as 75%. Notwithstanding the burden of depression on quality of life, a direct impact on mortality has been shown in post-myocardial infarction patients, and even in patients with hypertension in the Systolic Hypertension in the Elderly Program. Unfortunately, to date the information on the impact of treating depression is both limited and generally disappointing. For instance, a clinical trial of sertraline in depressed patients with CHF found no cardiovascular event outcomes benefit.

Exercise is a treatment for depression, and exercise has been shown to provide event reduction in CHF patients. Whether it might improve depression and cardiovascular events in CHF patients was the object of the HF-ACTION trial (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training).

More than 2000 patients with stable CHF were randomized to an aerobic exercise program. The exercise subjects enjoyed a statistically significant 11% reduction in mortality over the next 30 months. Although the mean score on the Beck Depression Inventory was statistically significantly lower in the exercise group, the improvement was sufficiently modest to be of uncertain clinical impact. Exercise in CHF reduces mortality and may have a modest effect on depression. ■

PHARMACOLOGY WATCH

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Statins and Cognition — More to the Story?

In this issue: Side effects of statins; effects of cannabis use; antihypertensives and lip cancer; and FDA actions.

Review challenges FDA warning

Do statins cause changes in cognition? In February, the FDA added warnings to statin labels regarding the risk of reversible memory loss and confusion. But a new review from the *Journal of the American College of Cardiology* reviews the evidence given to the FDA and concludes "that there is no increased risk of cognitive decline" with statin use. The State-of-the-Art Paper was a comprehensive review of case reports, observational research, and randomized, controlled trials of statins and cognitive change, as well as risk of cancer and diabetes. Most of the evidence for cognitive changes came from individual case reports, many of which were self-reported by consumers to the FDA. Observational studies gave mixed results on cognition with four of nine studies showing statins improved cognition, while three showed no change, and two studies found an increased risk of cognitive impairment. The authors suggest that these studies are inconclusive and prone to selection bias. Two large, randomized, controlled clinical trials specifically looked at the effect of statins on cognitive function as the major secondary endpoint. In both, no significant differences were seen between the study and control groups with regard to cognitive decline. Twelve smaller studies showed mixed results with the majority showing no change and only one in 12 showing a detrimental effect of statins on cognitive function, while two studies showed a benefit. Along with lack of evidence to suggest statins lead to cognitive decline, the authors also found no evidence that statins increase the risk of cancer. They did, however, find a small risk for development of diabetes, which they felt was "outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended" (*J Am Coll Cardiol* published online August 15, 2012). ■

Cannabis use and cognitive decline

Persistent cannabis use — particularly in adolescence — may lead to permanent cognitive decline, according to a new study. Researchers looked at a birth cohort of 1037 healthy individuals in New Zealand who underwent neuropsychological testing in the mid 1980s before the onset of cannabis use, and then again in 2010-2012 after some had developed a persistent pattern of cannabis use. Persistent cannabis use over 20 years (at least 4 days per week) was associated with neuropsychological decline, with greater decline evidence for more persistent users. This effect was only seen in adolescent-onset cannabis users and was associated with an average 8 point loss in IQ by age 38. The effect persisted after controlling for education, other drugs, or tobacco. The effects were not seen among adult-onset cannabis users. The authors conclude that increasing efforts should be directed toward delaying the onset of cannabis use by young people, "particularly given the recent trend of younger ages of cannabis use initiation in the United States and

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evidence that fewer adolescents believe that cannabis use is associated with serious health risk." (*Proc Natl Acad Sci U S A* published online August 27, 2012). This study and others are increasingly important as cannabis, the most widely used illicit drug in the world, is being considered for more medicinal uses as well as legalization. ■

Antihypertensives and lip cancer

Two photosensitizing antihypertensives, hydrochlorothiazide and nifedipine, may increase the risk for lip cancer in non-Hispanic white patients, according to a new study from Kaiser Permanente in California. From a large cohort of patients, 712 were identified with lip cancer along with nearly 23,000 matched controls. At least a 5-year supply of the drug resulted in the following odds ratios for lip cancer (95% confidence intervals) — hydrochlorothiazide 4.22 (2.82-6.31), hydrochlorothiazide-triamterene 2.82 (1.74-4.55), nifedipine 2.50 (1.29-4.84), and lisinopril 1.42 (0.95-2.13). When atenolol was given without other hypertensives, the odds ratio for lip cancer was 0.54 (0.07-4.08). The authors suggest that while antihypertensive therapy outweighs the risk of lip cancer, preventive measures should be taken for those at increased risk because of fair skin and long-term sun exposure (*Arch Intern Med* published online August 06, 2012). ■

FDA actions

The FDA has approved a delayed-release form of prednisone for the treatment of endocrine, inflammatory, and neoplastic conditions. Delayed-release prednisone should be taken once a day with timing to be determined by the disease being treated. For example, 10 p.m. dosing is recommended for rheumatoid arthritis, as it is more effective than immediate-release prednisone taken in the morning for treating morning stiffness associated with the disease. Dosing is based on the theory that both cytokines and endogenous cortisol follow a circadian rhythm, and that dosing the drug based on the condition being treated may afford more effective treatment than immediate-release prednisone. The new product delays the release of prednisone by approximately 4 hours. Side effects are the same as short-acting prednisone. Delayed-release prednisone will be marketed as RAYOS by Horizon Pharma.

The FDA has approved a new chlorofluorocarbon (CFC)-free, over-the-counter inhaled racepinephrine product for the treatment of asthma. The new product takes the place of the banned Primatene Mist, which was taken off the market at the end of 2011 because it contained CFCs. Inhaled epinephrine has been used for the treatment of asthma for more than 100 years. Marketed as Asthmanefrin, the new product will be sold as a starter kit and refill package. The starter kit will include 10 vials of racepinephrine along with the EZ Breathe Atomizer. The refill kit will include 30 vials of the drug. The drug is not without controversy, however, with many asthma experts feeling that the side effects of epinephrine are serious and well-documented, and over-the-counter use goes against published guidelines for treating asthma. Asthmanefrin will be marketed by Nephron Pharmaceuticals.

The FDA has approved linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The drug is the first guanylate cyclase (GC-C) agonist that acts locally in the gut with minimal systemic exposure. The drug is taken once daily on an empty stomach at least 30 minutes before the first meal of the day. Safety and efficacy in the management of irritable bowel syndrome with constipation was established in two double-blind studies of nearly 1300 patients who were randomly assigned to linaclotide or placebo for 12 weeks. Patients taking the drug experienced more complete spontaneous bowel movements than those taking placebo. The drug should not be used in patients 17 years or younger. Linaclotide will be jointly marketed by Ironwood Pharmaceuticals and Forest Pharmaceuticals as Linzess.

Montelukast (Singulair), Merck's popular asthma and allergy medication, will soon be available as a generic. The leukotriene receptor antagonist will be manufactured by 10 generic companies in tablet form, oral granules, and chewable tablets. The FDA warns that montelukast should not be used for relief of sudden asthma attacks and further warns that patients should contact a clinic immediately if they are experiencing behavior and mood-related changes such as aggression, depression, or hallucinations.

The FDA has approved the first generic version of pioglitazone (Actos). The drug is approved along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This happens as thiazolidinediones have generally fallen out of favor for use in type 2 diabetes due to side effects including worsening heart failure and edema. The FDA also recently issued a warning for pioglitazone regarding increased risk of bladder cancer if the drug is taken for more than 1 year. The first generic pioglitazone will be manufactured by Mylan Pharmaceuticals. ■