MARC S. PENN, MD, PhD
Director, The Earl and Doris Bakken Heart-Brain Institute, Cleveland Clinic, Cleveland, OH

EARL E. BAKKEN, MD (HonC), DSc (3 Hon), DHL (2 Hon)
Founder and Director Emeritus, Medtronic, Inc., Minneapolis, MN; Founder, The Earl and Doris Bakken Heart-Brain Institute

Heart-brain medicine: Update 2009

Last October, the 2009 Heart-Brain Summit—the fourth annual summit of this type presented by the Bakken Heart-Brain Institute—was held in Chicago and built on the the first three summits' tradition of open-minded discussion, out-of-the-box thinking, scholarly activity, and engagement of attendees from varied backgrounds.

DEPRESSION AND HEART DISEASE: A WATERSHED YEAR, OR JUMPING THE GUN?

The year leading up to the 2009 summit may be remembered as a watershed period for the field of heart-brain medicine, in light of the American Heart Association's (AHA's) inclusion of the recommendation to screen patients with coronary artery disease (CAD) for depression in its science advisory on depression and CAD.[1] As has been discussed at prior Heart-Brain Summits, there is incontrovertible evidence in the literature that CAD patients with depression have a worse prognosis than do their counterparts without depression.[2–6] While the link is clear, the etiology or mechanism behind depression's association with worse CAD outcomes is debated. Possible reasons for the association range from greater nonadherence with medical therapy[7] to increased systemic inflammation related to the decreased vagal tone associated with depression.[8] Furthermore, there is clear evidence that patients with depression and CAD can be treated for their depression safely with cognitive and pharmacologic therapy.[5,9] What is lacking, however, is convincing data that the treatment of depression in patients with CAD leads to improved outcomes.[10]

The topic for the first half of the opening day of the 2009 summit was whether the AHA has gotten ahead of itself in its science advisory[1] and whether we should require demonstrable benefits from the treatment of depression in CAD patients before screening for depression is recommended in all patients with CAD. This is a critically important question for the field as well as for the Bakken Heart-Brain Institute, which under our leadership has been advocating for a clinical trial to address this very issue. Cardiologists addressing this question were well reminded that logical therapeutic targets without proven end points have failed us in the past. For instance, it was a rational concept that the suppression of premature ventricular contractions in patients with a history of acute myocardial infarction would lead to decreased ventricular tachycardia and death. Unfortunately, when this concept was put to the test in a randomized clinical trial, increased death was observed in the treatment group.[11] More recent examples—and perhaps more applicable to depression, given its chronic nature—come from recent clinical trials demonstrating that tight blood sugar control is associated with higher mortality than moderate blood sugar control in critically ill patients[12] and that intensive blood pressure control does not yield greater reductions in cardiovascular events compared with moderate blood pressure control in patients with type 2 diabetes.[13]

So we are faced with a chronic disease state—depression—that is clearly linked to adverse outcomes and death in patients with CAD. In the context of this association, we also know the following:

- The AHA science advisory recommends that we screen all CAD patients for depression.
- Treating depression in heart disease patients is safe.
- There is no clear proof that treating depression will reverse the increased risk associated with depression in patients with CAD.
- There is a community of physicians who treat CAD patients who are skeptical about therapies that do not have outcomes data.

The summit's first morning concluded with a debate on whether now is the time for a large-scale multicenter randomized trial, which raised several important issues:

- The limited effectiveness of treatment for depression (approximately 30% to 40%)
- The ethics of randomizing a patient with depression to placebo
- The required size of the trial, given the efficacy of antidepressant therapy
- Measures to define response to therapy
- The utility of surrogate markers for adverse events in CAD versus a mortality end point.

The discussion and presentations were excellent and animated. In the end, each attendee was left to reach his or her own conclusion. Personally, one of us (M.S.P.) was surprised to be left with the conclusion that we are not ready for a definitive clinical trial.

In the cardiovascular medicine literature we were faced with a similar situation regarding the management

doi:10.3949/ccjm.77.s3.01

of patients with atrial fibrillation. In the AFFIRM trial, patients were randomized to conservative treatment (rate control and warfarin) or aggressive treatment (rate control, warfarin, and any and all therapies to convert to and maintain normal sinus rhythm).[14] Ultimately there was no difference between the groups, with a trend toward improved outcomes in the conservatively treated patients. What we really learned was that our therapies to convert to and maintain normal sinus rhythm were inadequate, and that in the case of atrial fibrillation at least we could clearly identify which patients did not respond to therapy.[14] These findings ultimately may have led the field astray, as we still do not know if we have efficacious therapies for the treatment of atrial fibrillation and whether patients would benefit.

STRATEGIES FOR MODULATING HEART-BRAIN INTERACTIONS

In line with the need for more effective strategies to modulate heart-brain interactions, the summit went on to review and discuss the role of biofeedback. If the effects of depression, post-traumatic stress disorder, and other psychological modulators of vagal tone are the mechanism of action for adverse outcomes in these patient populations, then methods to directly modulate vagal tone may prove efficacious.[15] Within the Bakken Heart-Brain Institute we recently committed half a million dollars to fund a biofeedback program. The program's goal is to investigate the efficacy of biofeedback in improving outcomes within and across several states of cardiovascular disease and chronic disease. We believe that rigorous and standardized delivery and quantification of the effects of biofeedback are critical in order to robustly determine the role of biofeedback in the treatment of patients with chronic disease.

The group of experts assembled at this year's summit presented further evidence of the potential importance of biofeedback for the control and treatment of multiple disorders, including heart failure, epilepsy, and chronic headache. As the mechanisms underlying brain interactions with end-organ innervations and systemic inflammation are dissected, it is clear that this field of medicine will have greater impact on the outcomes of many patient populations.

CROSS-FERTILIZATION OF TREATMENT APPROACHES

The summit abounded with evidence and examples of how neurology, cardiology, and psychiatry continue to cross-fertilize one another and foster interdisciplinary innovation. We were fortunate to have Brian Litt, MD, from the University of Pennsylvania return for the 2009 summit to update us on the progress of detecting, mapping, and extinguishing early seizure activity before there is clinical evidence of a seizure. The lessons learned and clinical advancement of internal cardiac defibrillators offer insights and great hope for this potentially important advancement in the treatment of seizure disorders. Similarly, Irving Zucker, PhD, from the University of Nebraska reviewed how neuromodulation through the baroreceptors can be targeted to modulate arterial blood pressure. Clearly there is great potential for device-based therapies to augment the treatment of chronic hypertension and improve outcomes in clinical populations at risk.

A LOOK AHEAD

Many of the topics reviewed above are discussed in detail in the proceedings supplement that follows. We continue to be excited and gratified by the progress being made in the field of heart-brain medicine. The continuing commitment to the rigorous multidisciplinary approach that has served this field well to date will continue to advance our understanding of disease and improve outcomes in our patients. We hope you will join us September 23–24, 2010, at the Lou Ruvo Center for Brain Health in Las Vegas, Nevada, for the 2010 Heart-Brain Summit, our fifth annual gathering.

REFERENCES

1. **Lichtman JH, Bigger JT Jr, Blumenthal JA, et al.** Depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Psychiatric Association. Circulation 2008; 118:1768–1775.
2. **Frazier L, Vaughn WK, Willerson JT, Ballantyne CM, Boerwinkle E.** Inflammatory protein levels and depression screening after coronary stenting predict major adverse coronary events. Biol Res Nurs 2009; 11:163–173.
3. **Connerney I, Shapiro PA, McLaughlin JS, Bagiella E, Sloan RP.** Relation between depression after coronary artery bypass surgery and 12-month outcome: a prospective study. Lancet 2001; 358:1766–1771.
4. **Davidson KW, Schwartz JE, Kirkland SA, et al.** Relation of inflammation to depression and incident coronary heart disease (from the Canadian Nova Scotia Health Survey [NSHS95] Prospective Population Study). Am J Cardiol 2009; 103:755–761.
5. **Summers KM, Martin KE, Watson K.** Impact and clinical management of depression in patients with coronary artery disease. Pharmacotherapy 2010; 30:304–322.
6. **Kendler KS, Gardner CO, Fiske A, Gatz M.** Major depression and coronary artery disease in the Swedish Twin Registry. Arch Gen Psychiatry 2009; 66:857–863.
7. **Albert NM, Fonarow GC, Abraham WT, et al.** Depression and clinical outcomes in heart failure: an OPTIMIZE-HF analysis. Am J Med 2009; 122:366–373.
8. **Khawaja IS, Westermeyer JJ, Gajwani P, Feinstein RE.** Depression and coronary artery disease: the association, mechanisms, and therapeutic implications. Psychiatry (Edgmont) 2009; 6:38–51.
9. **Glassman AH, O'Connor CM, Califf RM, et al.** Sertraline treatment of major depression in patients with acute MI or unstable angina. Sertraline Antidepressant Heart Attack Randomized Trial (SADHART) Group. JAMA 2002; 288:701–709.
10. **Shapiro PA.** Depression in coronary artery disease: does treatment

help? Cleve Clin J Med 2008; 75(suppl 2):S5–S9.
11. **Echt DS, Liebson PR, Mitchell LB, et al.** Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991; 324:781–788.
12. **Finfer S, Chittock DR, Su SY, et al.** Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009; 360:1283–1297.
13. **Cushman WC, Evans GW, Byington RP, et al.** Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010; 362:1575–1585.
14. **Wyse DG, Waldo AL, DiMarco JP, et al.** A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347:1825–1833.
15. **Penn MS, Bakken EE.** Heart-brain medicine: update 2008. Cleve Clin J Med 2009; 76(suppl 2):S5–S7.

Correspondence: *Marc S. Penn, MD, PhD, Director, Bakken Heart-Brain Institute, Cleveland Clinic, 9500 Euclid Avenue, J2-4, Cleveland, OH 44195; pennm@ccf.org*