Journal of the American College of Cardiology Vol. 53, No. 4, 2009

Published by Elsevier Inc.
ISSN 0735-1097/09/$36.00
doi:10.1016/j.jacc.2008.10.021

EDITORIAL COMMENT

Individualized Approach to the Management of Coronary Heart Disease

Identifying the Nonresponders Before It Is Too Late*

Peter Ganz, MD, Priscilla Y. Hsue, MD

San Francisco, California

Several therapies have proven effective in the treatment of coronary heart disease (CHD), primarily, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins), angiotensin-converting enzyme inhibitors, and antiplatelet agents (aspirin, clopidogrel). The 20% to 40% reduction in cardiovascular events achieved by each of these agents in placebo-controlled, randomized trials has been duly celebrated yet it leaves many patients unprotected. Among the highest risk CHD patients, namely, those presenting with acute coronary syndromes, 7% will suffer a myocardial infarction (MI) or CHD death within 24 months of the initial presentation despite intensive treatment to recommended guidelines (1). Thus, it is of utmost importance to identify individual patients who do not respond to therapy before adverse outcomes intervene. Several approaches to this individualized medicine are in development, including pharmacogenetic testing, measurement of inflammatory biomarkers, and assessment of endothelial function.

See page 323

Pharmacogenetics. Pharmacogenetics aims to identify the genetic determinants of interindividual variability in response to drugs (2). Pharmacogenetic approaches have been successful at improving the efficacy and safety for only a few drugs, with warfarin being the most prominent example in cardiovascular medicine (3).

Although statins reduce the risk of CHD, there is also appreciable interindividual variability in plasma lipoprotein changes and in cardiovascular outcomes. Polymorphisms in genes affecting statin pharmacokinetics (e.g., in 3-hydroxy-3-methylglutaryl-coenzyme A reductase and apolipoprotein E) are associated with variable lipoprotein responses (4,5). However, these genetic effects are relatively modest (4,5). Furthermore, for pharmacogenetic approaches to add clinical value, the genetic markers will need to predict cardiovascular outcomes and not just lipoprotein changes. Among antiplatelet agents, there is also substantial variability in effectiveness with up to 30% of subjects considered nonresponders to aspirin and 25% nonresponders to clopidogrel (2). However, specific gene variants that predict the responses to aspirin or clopidogrel remain unknown. Cardiovascular medicine of the future will mostly likely include targeted therapies based on personal genotypic information, but clearly much work remains to be done before this happens on a significant scale (2).

Inflammatory biomarkers. The inflammatory marker C-reactive protein (CRP) is the most extensively studied and the most robust predictor of cardiovascular events in apparently healthy subjects and in patients with CHD. Treatment with statins reduces CRP compared with placebo by 15% to 50% (6–8). With statin treatment, greater decreases in CRP or lower achieved levels of CRP are associated with reduced growth of coronary plaques in patients with stable CHD (7) and more favorable clinical outcomes of patients with acute coronary syndromes (6,8). While the reductions in CRP and low-density lipoprotein cholesterol (LDL-C) achieved with statins are both dose dependent (9), the response in CRP cannot be predicted from the lowering of LDL-C (6–8). Thus, a logical inference can be made for dual LDL-C and CRP goals for CHD patients, with adjustment of statin doses to achieve both. Whether or not dual low-density lipoprotein and CRP targets are justified in apparently healthy subjects treated with statins will be surmised from the recently completed JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) study (10). Committees preparing future guidelines should take note.

Endothelial function. Much progress has occurred in the understanding of the biology of the endothelium since the discovery of endothelium-dependent vasodilation by Furchgott and Zawadzki in 1980 (11) and since our first description of endothelial function testing in humans in 1986 (12). The endothelium plays a central role in the regulation of vascular tone by releasing several vasodilator substances, the key among them being nitric oxide (NO) (13–15). Nitric oxide also mediates many of the protective functions of the endothelium by limiting vascular inflammation, vascular smooth muscle proliferation, platelet aggregation, and tissue factor production (13,14).

Endothelial dysfunction has been linked to virtually all known risk factors for atherosclerosis (16–18). It has been detected in conduit arteries and in resistance arterioles and

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiology and the Center of Excellence in Vascular Research, San Francisco General Hospital, University of California, San Francisco, California. Dr. Ganz is a consultant for Pfizer, GlaxoSmithKline, Genentech, and Bristol-Myers Squibb (total <$20,000/year), and is on the Speakers' Bureau of Pfizer (<$20,000/year).

JACC Vol. 53, No. 4, 2009
January 27, 2009:331–3

in coronary as well as peripheral arteries (13–15). This recognition of endothelial dysfunction as a systemic disorder has facilitated endothelial function testing in accessible arteries, including flow-mediated dilation (FMD) in the brachial artery (13,14).

Clinical investigations strongly support an antiatherogenic role for NO. Coronary endothelial dysfunction in cardiac transplant recipients is associated with progressive transplant vasculopathy (19). Numerous studies have shown a strong association between endothelial dysfunction and cardiovascular events. Among nearly 2,500 patients with mostly overt atherosclerosis derived from 10 studies and with a follow-up of 1 to 92 months, endothelial dysfunction conferred a nearly 3-fold increase in cardiovascular event rates (15). Endothelial dysfunction also independently predicted adverse cardiovascular outcomes among apparently healthy elderly persons (18).

Commonly used therapies in the treatment of CHD reverse endothelial dysfunction, including drugs that modify lipids and reduce blood pressure, along with smoking cessation, physical exercise, and dietary interventions (13,14,20). The observation in these studies that interventions restored normal endothelial function in some subjects but failed to do so in others suggested that endothelial function testing may be able to differentiate therapeutic responders from nonresponders. Accordingly, Modena et al. (20) investigated prospectively 400 post-menopausal women with hypertension and a low prevalence of other risk factors whose blood pressure was successfully reduced to <140/90 mm Hg. The failure to restore endothelial function to normal was associated with nearly a 7-fold increase in cardiovascular event rates during a mean 67 months of follow-up.

In this issue of the *Journal*, Kitta et al. (21) tested the hypothesis that a change in endothelial function in response to optimized medical therapy for CHD predicts cardiovascular events. They studied 251 Japanese subjects with newly diagnosed stable CHD who were not optimally treated, and demonstrated impaired endothelial function in the brachial artery (defined as FMD <5.5%). Measurement of FMD was repeated after 6 months of optimized, individualized therapy including medications and life-style changes recommended by American Heart Association/American College of Cardiology guidelines. The target for LDL-C was <100 mg/dl, hypertension control <140/90 mm Hg (or <130/80 mm Hg if diabetes mellitus was present), and hemoglobin A_{1C} <7.0% for diabetic control. All patients were advised to achieve waist circumference goals by a combination of exercise and caloric intake. The second FMD test was impaired in 104 patients (41% of all study patients) despite treatment. This continued impairment in FMD was not related to medication use or the frequencies with which therapeutic targets were achieved. After the second FMD test, all patients were followed up for as long as 36 months (mean 31 ± 4 months) for cardiac death, nonfatal MI, angina pectoris requiring revascularization, or ischemic stroke. The results were striking: 26% of patients with persistent endothelial dysfunction sustained a cardiovascular event compared with only 10% of patients with improved endothelial function. Persistently impaired endothelial function independently predicted future events with an adjusted hazard ratio of 2.9. Thus, persistent endothelial dysfunction in the brachial artery despite 6 months of standard therapy for CHD indeed identified a cohort with a high residual risk.

The authors are to be congratulated on this thought-provoking study. Yet, it is only a first step among many needed to incorporate endothelial function testing in the clinical realm to monitor the effectiveness of therapies. The treatment in this study was "optimized," but was far from optimal. For example, only 60% of the patients in this study received a statin at the second FMD test, not all patients reached the LDL-C target of <100 mg/dl, and only 20% of patients were on beta-blocker medication. The composite clinical end point was driven by revascularizations and not by the more rigorous end points of cardiac death and MIs. Thus, a larger study is now needed with defined treatment algorithms, rigorous therapeutic goals, and statistical power to capture hard end points. In addition, the available methodologies of endothelial function testing are poorly standardized and, therefore, are not ready for widespread clinical application. Although the cutoff between normal and abnormal FMD in this study was 5.5%, it was 10% in the study by Modena et al. (20). In 2,883 Framingham Heart Study participants ages 33 to 88 years, mean FMD in this relatively healthy cohort was only 3.3% in women and 2.4% in men (16).

Given this lack of agreement on what constitutes a normal result, standardization of the FMD method based on age, sex, ethnicity, laboratory technique, and analysis will be required. Other approaches to assessing endothelial function are still in development (13–15). When these obstacles are overcome, rigorous biostatistical and pharmacoeconomic methods will be essential to establish that endothelial function testing adds further value and cost effectiveness to the monitoring approaches we already employ. Lastly, it is not yet known how the information from endothelial function testing would alter therapy (e.g., titration or addition of drugs or consideration of revascularization) and whether any intensification of treatment guided by endothelial function testing would improve clinical outcomes. Despite these hurdles, the study by Kitta et al. (21) is an encouraging proof of principle. In the past, the lack of patient-to-patient uniformity in the improvement in endothelial function with various therapies represented an "inconvenient truth." In the future, reinforced with the much needed improvements we have outlined, it may lead to more effective, personalized treatments.

Reprint requests and correspondence: Dr. Peter Ganz, San Francisco General Hospital, 1001 Potrero Avenue, 5G1, San Francisco, California 94110. E-mail: ganzp@medsfgh.ucsf.edu.

REFERENCES

1. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–504.
2. Giacomini KM, Brett CM, Altman RB, et al. The pharmacogenetics research network: from SNP discovery to clinical drug response. Clin Pharmacol Ther 2007;81:328–45.
3. Schwarz UI, Ritchie MD, Bradford Y, et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 2008;358:999–1008.
4. Chasman DI, Posada D, Subrahmanyan L, Cook NR, Stanton VP Jr., Ridker PM. Pharmacogenetic study of statin therapy and cholesterol reduction. JAMA 2004;291:2821–7.
5. Thompson JF, Man M, Johnson KJ, et al. An association study of 43 SNPs in 16 candidate genes with atorvastatin response. Pharmacogenomics J 2005;5:352–8.
6. Morrow DA, de Lemos JA, Sabatine MS, et al. Clinical relevance of C-reactive protein during follow-up of patients with acute coronary syndromes in the Aggrastat-to-Zocor Trial. Circulation 2006;114: 281–8.
7. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29–38.
8. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005;352:20–8.
9. Kinlay S, Timms T, Clark M, et al. Comparison of effect of intensive lipid lowering with atorvastatin to less intensive lowering with lovastatin on C-reactive protein in patients with stable angina pectoris and inducible myocardial ischemia. Am J Cardiol 2002;89:1205–7.
10. Ridker PM. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. Circulation 2003;108:2292–7.
11. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980;288:373–6.
12. Ludmer PL, Selwyn AP, Shook TL, et al. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. N Engl J Med 1986;315:1046–51.
13. Deanfield JE, Halcox JP, Rabelink TJ. Endothelial function and dysfunction: testing and clinical relevance. Circulation 2007;115:1285–95.
14. Ganz P, Vita JA. Testing endothelial vasomotor function: nitric oxide, a multipotent molecule. Circulation 2003;108:2049–53.
15. Lerman A, Zeiher AM. Endothelial function: cardiac events. Circulation 2005;111:363–8.
16. Benjamin EJ, Larson MG, Keyes MJ, et al. Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. Circulation 2004;109:613–9.
17. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990;81:491–7.
18. Yeboah J, Crouse JR, Hsu FC, Burke GL, Herrington DM. Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. Circulation 2007;115: 2390–7.
19. Davis SF, Yeung AC, Meredith IT, et al. Early endothelial dysfunction predicts the development of transplant coronary artery disease at 1 year posttransplant. Circulation 1996;93:457–62.
20. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 2002;40:505–10.
21. Kitta Y, Obata J-e, Nakamura T, et al. Persistent impairment of endothelial vasomotor function has a negative impact on outcome in patients with coronary artery disease. J Am Coll Cardiol 2009;53: 323–30.

Key Words: endothelium ■ prognosis ■ coronary artery disease ■ risk factor.