REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Cardiovascular Disease Progression: A Target for Therapy?

Jay N. Cohn, MD

Cardiovascular Division, University of Minnesota Medical School, Minneapolis.

ABSTRACT

Clinical research aimed at preventing cardiovascular disease has focused on the effect of interventions to reduce risk factors on the incidence of future morbid events. Disease progression, which likely serves as a necessary prerequisite for morbid events, has not served as a target for therapy. The Rasmussen Center at the University of Minnesota has, for the past 18 years, been performing a noninvasive cardiovascular evaluation in individuals with no history of cardiovascular disease. The studies, performed in 1 hour in one room, provide a comprehensive noninvasive assessment of the severity of functional and structural abnormalities in the small arteries, the large arteries and the left ventricle, the target organs for most cardiovascular morbid events. Preliminary follow-up data have revealed a striking relationship between the Disease Score, which represents the sum of the abnormal tests, and the risk of future morbid events. In order to develop strategies to prolong cardiovascular disease-free life expectancy, studies in early stages of disease aimed at slowing disease progression should be encouraged.

 • The American Journal of Medicine (■■) ■■, ■■–■■

KEYWORDS: Cardiovascular morbid events; Early cardiovascular disease; Noninvasive testing; Risk factors

Cardiovascular disease progresses by biological processes in the arteries and heart that eventuate in myocardial infarction, stroke, heart failure, and other vascular morbid events.[1,2] Nonetheless, management has been aimed at treating or preventing the events, not at slowing the biological processes.[3-5] Reduction in deaths or morbid events has been the target of intervention trials, and these trials have formed the basis for management guidelines that drive clinical practice. Furthermore, regulatory bodies usually require morbid event reduction as a prerequisite for approval of new cardiovascular therapies. If morbid events serve as the guide to efficacy, there is no incentive to track over time the biological process that precipitates these events.

An unintended consequence of this rigorous definition of efficacy is that clinical trials, in order to accrue enough morbid events in a reasonable time frame to document efficacy, must focus on advanced stages of disease. This focus has popularized calculation of the number needed to treat to prevent a morbid event in 5 or 10 years[6] as a guide to cost-effectiveness of therapy. This calculation implies that a short-term reduction of morbid events is the optimal metric to document preventive efficacy. It fails to appreciate that a favorable effect on the cardiovascular system beginning early in the biological process may substantially prolong disease-free life expectancy. The devotion to morbid events rather than to the biological process has discouraged studies in asymptomatic individuals, when effective therapy to slow disease progression may have considerable long-term benefit. The long duration of such a trial to document effectiveness based on morbid events would be so burdensome to trialists and sponsors that such truly preventative studies are rarely undertaken.

Drug therapy has been aimed at elevated blood pressure and elevated cholesterol levels without regard to the underlying biological process in the arteries and heart. The absence of robust clinical trials to document efficacy of pharmacologic agents in asymptomatic individuals without treatable risk factor elevation has encouraged recommendation of

Funding: None.

Conflicts of Interest: Dr. Cohn holds equity in Cardiology Prevention, LLC, a corporate effort to establish cardiovascular disease prevention centers worldwide.

Authorship: The author is solely responsible for writing this manuscript.

Requests for reprints should be addressed to Jay N. Cohn, MD, Cardiovascular Division, University of Minnesota Medical School, Mayo Mail Code 508, 420 Delaware Street Southeast, Minneapolis, MN 55455.

E-mail address: cohnx001@umn.edu

0002-9343/$ - see front matter
https://doi.org/10.1016/j.amjmed.2018.03.032

lifestyle alterations as a therapeutic strategy.[7] Lifestyle changes are widely recommended to supplement drug therapy or to replace it in those without treatable risk factors, despite the lack of evidence that such advice improves outcome. Indeed, the most rigorous attempt to demonstrate that diet and exercise can reduce morbid events in high-risk individuals failed to show benefit.[8] Whether lifestyle intervention can slow the cardiovascular biological disease process has not been adequately assessed.

In the United States, nearly half of adults will eventually succumb to cardiovascular disease.[9] The demand for short-term benefit, such as a reduction in 10-year event rate, does not adequately capture the long-term goal of cardiovascular preventive efforts, which should include prolonging event-free cardiovascular health through the 9th or 10th decades of life. Because a study duration of 30 or more years is unrealistic, surrogate end-points that document slowing the biological process without adverse effects would be essential. The projected cost-benefit and side-effect profile of therapeutic intervention in such a population could then serve as a guide to management.

CLINICAL SIGNIFICANCE

- Cardiovascular morbid events are a consequence of progressive functional and structural abnormalities of the arteries and heart.
- Reliance on morbid event reduction as a guide to efficacy of treatment discourages study of preventive therapy in early disease.
- Disease progression can be monitored by efficient noninvasive testing of the health of the arteries and heart.
- Therapy that slows disease progression may be effective in delaying cardiovascular morbid events until the 9th or 10th decades of life.

The purpose of this treatise is to explore the known relationship between demonstrable, functional, and structural abnormalities of the vasculature or the heart and the future occurrence of morbid events. We will contrast this strategy with the current practice of risk factor assessment and management to identify and treat individuals statistically at risk for future morbid events. We will also assess the evidence that therapeutic interventions that reduce the risk for morbid events also favorably affect the vascular or cardiac abnormalities that underlie these events. Such analyses are critical in proposing that disease markers might supplement morbid events as a guide to therapeutic effectiveness in asymptomatic, early stages of cardiovascular disease.

MECHANISMS OF MORBID EVENTS

Cardiovascular morbid events occur in the setting of abnormal structure and function of the small microvascular arteries, the large conduit arteries, or the left ventricle.[1,2] Abnormalities of these 3 target organs underlie myocardial ischemia or infarction, lethal arrhythmias, left ventricular dysfunction or failure, strokes, transient cerebral ischemic events and dementia, claudication, and renal failure. These morbid events are usually preceded by years of progression of the structural and functional abnormalities. Although some of the events may be precipitated by superimposed clots or hemorrhages, the fact that the severity of the underlying disease is a powerful predictor of future morbid events[10] confirms that progression of the structural and functional abnormalities is usually a prerequisite. Can abnormalities of these 3 target organs be efficiently detected in order to identify individuals at risk for future morbid events, and can the progression of these abnormalities be tracked over time to monitor the effectiveness of therapeutic intervention?

RISK FACTOR ASSESSMENT AND MANAGEMENT

Preventive cardiology has been dominated by the dedication to identifying risk factors and promoting, when appropriate, their management. The landmark Framingham study and subsequent analyses of large clinical databases have confirmed the statistical association between readily available clinical assessment measurements and the risk for future morbid events.[11,12] Age, sex, resting blood pressure, cholesterol levels, a smoking history, a prescription for antihypertensive drugs, and a history of diabetes have been the most commonly used risk factors in these algorithms. The calculation provided for most of these algorithms is the 10-year risk for a morbid event.

These risk factors bear a strikingly heterogeneous relationship to cardiovascular disease. Age and blood pressure are the most powerful predictors, but for very different reasons. The age-dependent progression of structural changes in the arteries and heart mandates that chronological age will be a powerful but nondiscriminating risk factor, whereas blood pressure serves not only as a statistical risk factor but as a marker for the vascular disease that thickens and stiffens the small and large arteries. An elevated blood pressure itself will also accelerate the pathological process in the artery wall.[13] Smoking and diabetes are potent contributors to cardiovascular risk, whereas cholesterol levels, including their low-density lipoprotein and high-density lipoprotein fractions, have proven to be less discriminating.[14] Thus, some risk factors may be viewed as manifestations of the cardiovascular disease itself or as contributors to the disease progression, whereas others serve as, at best, markers for risk.

Risk factor algorithms have proven to be powerful tools in identifying populations at near-term risk for morbid events. Based on arbitrary thresholds of statistical risk, these algorithms have been widely utilized to identify populations of individuals in whom risk factor intervention is justified by their 10-year risk for morbid events. Identifying the disease process in the arteries and heart should provide a more individualized assessment of risk, but the relative benefit of this early detection effort for predicting morbid events must be

verified before such evaluation can be advocated to supplement or replace risk factor algorithms.

DETECTION OF EARLY DISEASE

The most popular assessment tool for coronary disease has been quantitation of calcium in atherosclerotic plaques in the coronary arteries.[15] This technique clearly identifies individuals at near-term risk for a coronary event. Its weakness is not only the radiation dose required for its detection, but also the frequency of noncalcified plaques in younger individuals with premature coronary disease.[16] Ultrasound of the carotid arteries has been used as a predictor of myocardial infarctions and strokes,[17] but its predictive value has been disappointing.[18] Carotid plaques observed by ultrasound also provide a potential window into the atherosclerotic process in other conduit arteries. Echocardiography offers insight into functional and structural abnormalities of the left ventricle that should long precede symptomatic heart failure.[19] Our early studies of heart failure demonstrated the survival benefit of therapy that slowed the left ventricular remodeling process and the failure of drug therapy that did not slow remodeling.[20-22]

Do any of these measures allow tracking of disease progression that would be useful for prognosis or to document the effectiveness of therapy? The United States Preventive Services Task Force has concluded that these supplemental measures do not provide adequate enhanced discrimination to justify their routine use.[23]

Biomarkers have been widely evaluated as guides to disease and its progression.[24] Management of heart failure has been improved by monitoring the levels of components of the natriuretic peptide system that are released in the setting of increased left ventricular wall stress.[25] Ischemic injury and heart failure progression are associated with elevated circulating levels of troponin.[26] A host of other biomarkers appear to be elevated in certain disease processes, but their value in tracking disease progression has not been documented. Whether any biomarker can serve as a reliable guide to disease progression or to a favorable therapeutic response remains uncertain.

A comprehensive noninvasive approach to assessing disease severity and response to therapy has been in use in our Center at the University of Minnesota for more than 15 years.[27] It consists of a series of 10 tests that evaluate the health of the small arteries, the large arteries, and the left ventricle. The total score of these 10 tests has been demonstrated to be a sensitive guide to the occurrence of future morbid events,[9] and has also been demonstrated to respond appropriately to therapeutic interventions that improve outcomes.[28-30] These data support the hypothesis that abnormalities of the arteries and heart can serve as a surrogate for future morbid events. Does this global assessment of cardiovascular function and structure in individuals provide a more effective guide to the need for, and response to, treatment than counting morbid events? The merits of this approach must be assessed in future clinical trials.

It is time to enhance the effort to track the biological basis for the progression of cardiovascular disease. Clinical trials aimed at preventing morbid events should include rigorous efforts to monitor and document the biological process that precipitates these events. Our long-term goal must be to preserve cardiovascular health in all individuals, not just those destined to suffer morbid events in the short term. Such a goal can only be achieved by documenting the effectiveness of interventions on a measurable and mechanistic guide to the progression of disease that precipitates morbid events. Statistical benefit on morbid events in a heterogeneous population should never be accepted as an ideal tool for individualized medical management.

The potential of the new science of genetic polymorphisms to advance our quest for more effective individualized medicine will be dependent on a marriage between the molecular medicine of the present and the physiologic and biochemical insights that drove advances in the recent past. A focus on the molecular, cellular, and organ responses that characterize disease progression may provide the insights that can lead to early recognition and effective management of the chronic cardiovascular diseases that burden our current health care system.

References

1. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. *Circ Res*. 2012;110(8):1097-1108.
2. Lakatta EG, Levy D. Arterial and cardiac aging: major shareholders in cardiovascular disease enterprises: Part I: aging arteries: a "set up" for vascular disease. *Circulation*. 2003;107(1):139-146.
3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. *Circulation*. 2014;129(suppl 2):S1-S45.
4. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520.
5. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused update of the 2013 ACC/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70:776-803.
6. Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med*. 1988;318:1728-1733.
7. Eckel RH, Jakicic JM, Ard JD, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2960-2984.
8. Wing RR, Bolin P, Brancati FL, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med*. 2013;369:145-154.
9. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*. 2016;133:e38-e360.
10. Duprez DA, Florea N, Zhong W, et al. Vascular and cardiac functional and structural screening to identify risk of future morbid events: preliminary observations. *J Am Soc Hypertens*. 2011;5:401-409.
11. Goff DC Jr, Lloyd-Jones DM, Bennett G, American College of Cardiology/American Heart Association Task Force on Practice Guidelines, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart

Association Task Force on Practice Guidelines. *Circulation*. 2014;129(25 suppl 2):S49-S73.
12. D'Agostino RB, Vasan RS, Pencia MJ, et al. General cardiovascular risk profile for use in primary care: The Framingham Heart Study. *Circulation*. 2008;117:743-753.
13. Cohn JN. Is it the blood pressure or the blood vessel? *J Am Soc Hypertens*. 2007;1(1):5-16.
14. Fernández-Friera L, Fuster V, López-Melgar B, et al. Normal LDL-cholesterol levels are associated with subclinical atherosclerosis in the absence of risk factors. *J Am Coll Cardiol*. 2017;70:2979-2991.
15. Polonsky TS, McClelland RL, Jorgensen NW, et al. Coronary artery calcium score and risk classification for coronary heart disease prediction. *JAMA*. 2010;303(16):1610-1616.
16. Carr JJ, Jacobs DR, Terry JG, et al. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol*. 2017;2(4):391-399.
17. O'Leary DH, Polak JF, Kronmal RA, et al. for the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med*. 1999;340(1):14-22.
18. Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. *JAMA*. 2012;308(8):796-803.
19. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685-691.
20. Cintron G, Johnson G, Francis G, et al. for the V-HeFT VA Cooperative Studies Group: Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. *Circulation*. 1993;87:VI17-VI23.
21. Wong M, Staszewsky L, Latini R, et al. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. *J Am Coll Cardiol*. 2002;40(5):970-975.
22. Konstam MA, Udelson JE, Anand IS, Cohn JN. Ventricular remodeling in heart failure: a credible surrogate endpoint. *J Card Fail*. 2003;9:350-353.
23. Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U. S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(7):496-507.
24. McCarthy CP, McEvoy JW, Januzzi JL Jr. Biomarkers in stable coronary artery disease. *Am Heart J*. 2018;196:82-96.
25. Eapen DJ, Manocha P, Patel RS, et al. Aggregate risk score based on markers of inflammation, cell stress and coagulation is an independent predictor of adverse cardiovascular outcomes. *J Am Coll Cardiol*. 2013;62:329-337.
26. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation*. 2012;125:280-288.
27. Cohn JN, Hoke L, Whitwam W, et al. Screening for early detection of cardiovascular disease in asymptomatic individuals. *Am Heart J*. 2003;146:679-685.
28. Duprez DA, Florea ND, Jones K, Cohn JN. Beneficial effects of valsartan in asymptomatic individuals with vascular or cardiac abnormalities: the DETECTIV Pilot Study. *J Am Coll Cardiol*. 2007;50:835-839.
29. Saul SM, Duprez DA, Zhong W, et al. Effect of carvedilol, lisinopril and their combination on vascular and cardiac health in patients with borderline blood pressure: the DETECT study. *J Hum Hypertens*. 2013;27:362-367.
30. Duprez DA, Florea N, Duval S, et al. Effect of nebivolol or atenolol vs. placebo on cardiovascular health in subjects with borderline blood pressure: the EVIDENCE study. *J Hum Hypertens*. 2018;32:20-25.