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Review

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Cardiovascular Risk Factors: It's Time to Focus on Variability!

Mallory P. Barnett, Sripal Bangalore

The Leon H. Charney Division of Cardiology, New York University School of Medicine, New York, NY, USA

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Correspondence to
Sripal Bangalore
Cardiac Catheterization Laboratory, Cardiovascular Clinical Research Center, New York University School of Medicine, New York, NY 10016, USA.
E-mail: sripalbangalore@gmail.com

ORCID iDs
Mallory P. Barnett
https://orcid.org/0000-0003-2238-4343
Sripal Bangalore
https://orcid.org/0000-0001-9485-0652

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ABSTRACT

Atherosclerotic heart disease remains a leading cause of morbidity and mortality worldwide. While extensive research supports cardiovascular risk factor reduction in the form of achieving evidence-based blood pressure, lipid, glucose, and body weight targets as a means to improve cardiovascular outcomes, residual risk remains. Emerging data have demonstrated that the intraindividual variability of these risk factor targets potentially contribute to this residual risk. It may therefore be time to define risk factor by not only its magnitude and duration as done traditionally, but perhaps also by the variability of that particular risk factor over time.

Keywords: Blood pressure; Body weight; Cholesterol; Heart rate; Mortality

INTRODUCTION

"Variability is the law of life" – Sir William Osler

Despite significant improvements in cardiovascular disease outcomes through the implementation of evidence-based management strategies, atherosclerotic disease remains the leading cause of morbidity and mortality worldwide.[1] These outcomes may be attributed to poorly controlled atherosclerotic cardiovascular disease (ASCVD) risk factors.[2] Risk calculators such as the model put forth by the Framingham Heart Study attempt to quantify the effect of risk factors such as hypertension, hyperlipidemia, tobacco use, inactivity, and obesity on clinical outcomes such as cardiovascular death, myocardial infarction (MI), and stroke. The traditional approach to these risk factors have involved assessment of the magnitude (severity) of the risk factor and the duration. The association between risk factor control and ASCVD outcomes is well described. Rothwell et al. challenged the concept of relying just on the magnitude of a single risk factor by demonstrating that visit-to-visit variability of blood pressure (BP), independent of an average BP, was predictive of future stroke risk.[3-5] Other studies have shown that variability of other risk factors such as body weight, glucose control, and cholesterol also increase ASCVD risk independent of the traditional magnitude of these risk factors.[6] Here we will review how intra-individual variability of these risk factors affects cardiovascular outcome.

Author Contributions

Supervision: Bangalore S; Writing - review & editing: Barnett MP, Bangalore S.

BLOOD PRESSURE

1. Blood pressure variability and outcomes

Hypertension is the leading cause of ASCVD death among other modifiable risk factors. Both the magnitude (severity) and duration of hypertension affects prognosis. A meta-analysis of over 60 prospective studies demonstrated a doubling of risk from death from stroke, heart disease, or other vascular disease for each 20mm Hg higher systolic blood pressure (SBP) and 10 mm Hg higher diastolic BP.[7] Others have shown that increased duration of hypertension is an independent predictor of worse outcomes.[8] On the other hand, multiple randomized trials done over the past few decades have clearly shown a reduction in the risk of adverse cardiovascular outcomes by lowering BP using antihypertensive agents.[9] However, even with aggressive antihypertensive therapy, residual risk remains.[10] Whether intra-individual variability in BP explains this residual risk has been explored recently. Intra-individual variability in BP could be very short-term (beat to beat), short-term (over 24 hours), mid-term (day to day) or long-term (visit-to-visit variability). Parati et al.[11] demonstrated that for any 24-hour mean BP, lower short0term variability (low 24-hour BP variability) was associated with a lower prevalence and severity of end-organ disease. Elevated long-term (visit-to-visit) SBP variability was subsequently found to be associated with coronary heart disease.[12] In an analysis from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT BPLA) trial of patients with hypertension, visit-to-visit variability in SBP and maximum SBP were strong predictors of stroke, independent of mean SBP. Increased residual SBP variability in patients with treated hypertension was associated with a high risk of vascular events (**Figure 1**).[13-21]

Systematic reviews and meta-analyses demonstrated that SBP variability independently predicted ASCVD mortality and incidence of coronary heart disease and stroke.[22,23] This association has been demonstrated across a range of BP reading sites and methods including in-office BP,[3-5] ambulatory BP[24-28] monitoring, and patient-measured home BP.[29,30]

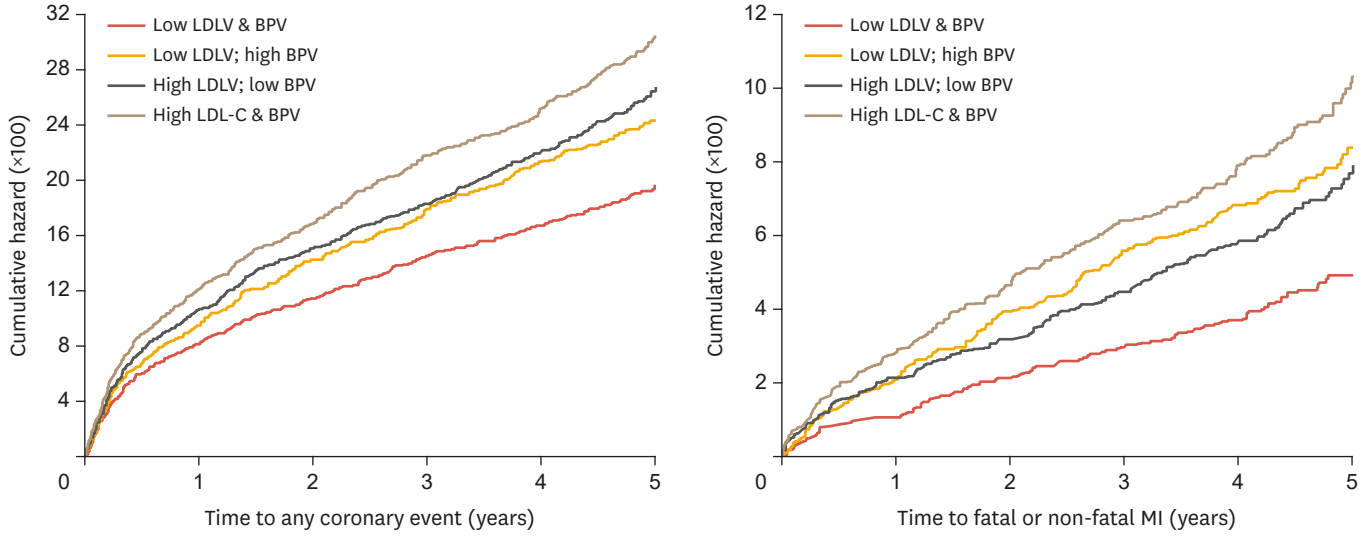

Fig. 1. LDL-C and BP variability and outcome. Compared to the group with low variability for LDL-C and SBP, the high variability group had a significant increase in any coronary event (HR_{adj}, 1.48; 95% CI, 1.30–1.70; $p<0.05$) and fatal or non-fatal MI (HR_{adj}, 1.87; 95% CI, 1.46–2.41; $p<0.05$). Reproduced with permission from Bangalore et al. Am J Cardiol 2017;119:379-87.[21]
LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; SBP, systolic blood pressure; HR, hazard ratio; CI, confidence interval; MI, myocardial infarction; BPV, blood pressure variability; LDLV, low-density lipoprotein cholesterol variability.

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2. Mechanism of adverse effects

Several hypotheses exist to explain the association between BP variability and increased cardiovascular risk. As a biologic basis, coronary atheroma progression as measured by serial intravascular ultrasonography was significantly associated with higher BP variability in a study by Clark et al.[31] Other proposed mechanisms include increased wall stress, baroreceptor dysfunction, and endothelial dysfunction in those with variable BPs. Lastly, BP variability may also be a marker for medication non-compliance and may suggest that patients spend a greater proportion of time above their guideline-recommended BP goal.

3. Implications for antihypertensive therapy

The effect of antihypertensive medications class on BP variability is heterogeneous. ASCOT-BPLA found that variability in SBP was lower in patients randomized to amlodipine when compared to atenolol through the length of follow-up (p<0.05), including individual visits and ambulatory BP monitoring.[5] BP variability in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was greatest with lisinopril, improved with chlorthalidone, and lowest with amlodipine.[32] This may explain why stroke rates were significantly higher in the lisinopril treatment group when compared to chlorthalidone or amlodipine groups.[33]

Similarly, in a meta-analysis of BP trials, SBP variability was reduced by calcium-channel blockers (CCBs) (ratio of the variances, 0.81; 95% confidence interval [CI], 0.76–0.86; p<0.05) and thiazides (0.87; 95% CI, 0.79–0.96; p<0.05). but was increased by angiotensin converting enzyme (ACE) inhibitors (1.08; 95% CI, 1.02–1.15; p<0.05), angiotensin receptor blockers (1.16; 95% CI, 1.07–1.25; p<0.05), and beta-blockers (1.17; 95% CI, 1.07–1.28; p<0.05).[34] Lastly, Parati et al.[35] demonstrated that lercanidipine (a CCB) alone or in combination with enalapril reduced BP variability but enalapril alone did not.

While several studies have proven that BP variability differs among various antihypertensive medications, no study to date has demonstrated that the reduction of BP variability in and of itself improves outcomes.

CHOLESTEROL

1. Cholesterol variability and outcomes

Over thirty years of epidemiologic data have demonstrated a positive relationship between low-density lipoprotein cholesterol (LDL-C) levels and cardiovascular events. Statin therapy lowers LDL-C and improve outcomes. However, in the randomized trials of statins, residual risk remains. More recent data seem to suggest that intra individual visit to visit variability of LDL-C levels is potentially harmful. Intraindividual variability in LDL-C levels have been shown to occur on a short term basis (for example, between meals), an intermediate basis (for example, week to week), or more long-term (for example, from visit to visit).[36,37]

In patients without known ASCVD from the Framingham Heart Study visit-to-visit variability in cholesterol was strongly associated with the risk of future adverse cardiovascular events.[38] Similarly, in the Treating to New Targets (TNT) trial, we demonstrated that among 9,572 patients, each 1-standard deviation (SD) increase in LDL-C variability increased the risk of any cardiovascular event by 11% (hazard ratio [HR], 1.11; 95% CI, 1.07–1.15; p<0.05),death by 23% (HR, 1.23; 95% CI, 1.14–1.34; p<0.05), MI by 10% (HR, 1.10; 95% CI, 1.02–1.19; p<0.05)

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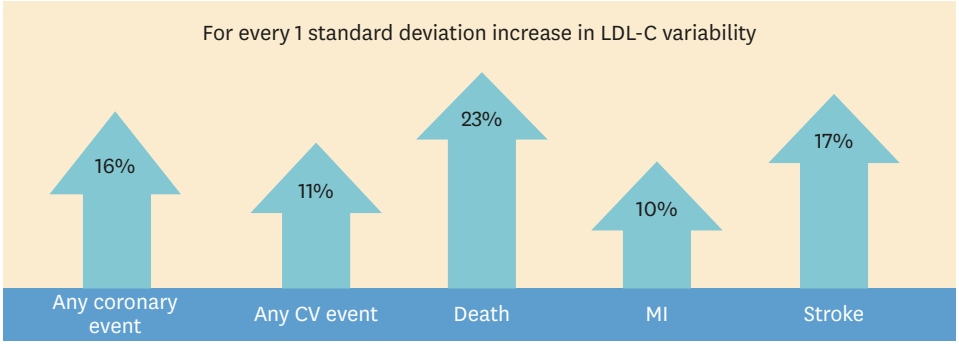

Fig. 2. LDL-C variability and outcome. Visit-to-visit LDL-C variability was defined as between visit variability in LDL-C values of the 9,572 patients in the TNT trial. Arrows pointing up indicate the relative risk of the specified outcome in the highest versus the lowest quintile of variability in LDL-C. Reproduced with permission from Bangalore et al. J Am Coll Cardiol 2015 21;65:1539-48.[39]
LDL-C, low-density lipoprotein cholesterol; TNT, Treating to New Targets; CV, cardiovascular; MI, myocardial infarction.

and stroke by 17% (HR, 1.17; 95% CI, 1.04–1.31; p<0.05). Findings were independent of absolute LDL-C levels (**Figure 2**).[39] Although statin non-adherence is strongly associated with visit-to-visit LDL-C variability, the association between poor outcomes and LCL-C variability persisted even after adjustment for medication adherence.[39,40] A large study examining 3.65 million subjects in Korea also found that high lipid level variability was associated with adverse outcomes including all-cause mortality, MI, and stroke.[41] The residual risk we see in patients with below-goal LDL-C levels may in fact be explained by variability.

2. Mechanism of adverse effects

A post hoc analysis of nine clinical trials using intravascular ultrasound may provide a hypothetical explanation for the association between lipid level variability and clinical outcomes. Clark et al.[42] found that the SD of atherogenic lipid particles among individual patients is significantly associated with progression of atheroma volume. It is possible that this variation in lipid efflux may lead to vascular wall instability, impairing plaque stabilization, and potentially increasing plaque vulnerability and risk of rupture. These findings emphasize the importance of achieving consistently low atherogenic lipoprotein levels to promote plaque regression and improve clinical cardiovascular outcomes.

3. Implications for lipid-lowering therapy

We demonstrated that high-dose atorvastatin (80 mg/day) was found to be associated with lower LDL-C variability when compared to lower dose atorvastatin (10 mg/day) in the TNT trial (SD, 12.03±9.70 vs. 12.52±7.43; p<0.05).[39] Knowledge regarding the association of LDL-C variability and cardiovascular risk is important when considering intermittent statin dosing, which is a common practice used to minimize statin side effects such as myalgias.

BODY WEIGHT

1. Body weight variability and outcomes

Obesity is a well-known independent risk factor for cardiovascular death and disease. While cardiovascular prevention guidelines recommend to maintain weight loss, many patients struggle to do so, resulting in fluctuations known as “weight cycling.”[43-45] As a result, weight loss is often followed by weight gain. The Western Electric study demonstrated that such

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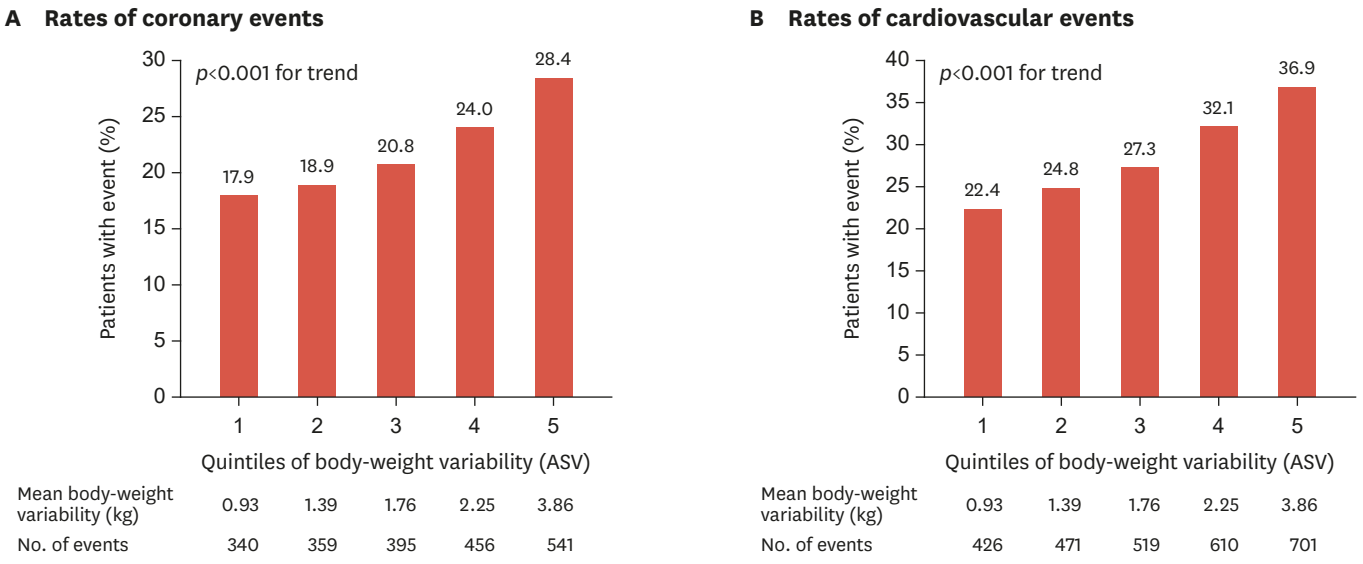

Fig. 3. Body weight variability and rates of coronary and cardiovascular events. A coronary event was defined as a composite of death from coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, revascularization, or angina. A cardiovascular event was defined as a composite of any coronary event or cerebrovascular event, peripheral vascular disease, or heart failure. Reproduced with permission from Bangalore et al. N Engl J Med 2017;376:1332-40.[49]
ASV, average successive variability.

fluctuations in weight increase the risk of developing coronary heart disease. Over a 25-year period, the risk of coronary death was 26% in the "gain and loss" group, 15% in the "gain only" group, 14% in the "no change" group, and 17% in the remaining subjects.[46] Two cohort studies, however, did not find a significant association between weight fluctuations and mortality.[47,48] We recently demonstrated that in those with known coronary artery disease, body weight variability was associated with higher rates of cardiovascular events and mortality independent of traditional cardiovascular risk factors (**Figure 3**).[49] Among patients in the quintile with the highest variation in body weight in this study, the risk of coronary events was 64% higher, the risk of cardiovascular events 85% higher, death 124% higher, MI 117% higher, and stroke 136% higher than the risk among those in the quintile with the lowest variation in body weight in adjusted models.

While cardiovascular mortality associated with weight cycling is certainly of concern, cognitive function may also be at risk. The Israel Ischemic Heart Disease study found that those with greatest weight variability were at greater risk for dementia when compared with those with the w most stable weight, even after adjustment for diabetes, height, and socioeconomic status.[50]

2. Mechanism of adverse effects

Based on current data, it is unclear if the association of weight cycling and adverse outcomes is due to causality or is a marker of pre-existing illness. For example, those with systolic heart failure often have wide swings in body weight on the basis of body-fluid volume status. However New York Heart Association class IIIB and IV patients were excluded from our study that demonstrated higher rates of cardiovascular events in those with higher body-weight variability.[49] We also performed a sensitivity analysis excluding patients with a history of heart failure at baseline, and the results were similar to those in the larger trial population. It is therefore likely that an unknown physiologic mechanism for these findings exists. The identification of these mechanisms may expand our understanding of the obesity paradox in

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which cardiovascular mortality is lower in obese or overweight patients when compared to those of normal weight.[51]

3. Implications for weight loss counseling

We should continue to recommend not only weight loss, but weight loss maintenance as recommended by current guidelines.[43] However given the known adverse effects of yoyo dieting, weight reduction strategies that minimize weight cycling should be recommended over those that are known to result in weight cycling.

GLUCOSE CONTROL

1. Glycemia and variability

Individuals with type 2 diabetes, particularly those with poor glucose control, are at elevated cardiovascular risk. Aggressive treatment of diabetes has been demonstrated to reduce ASCVD events; however residual risk remains even among those with well-controlled glucose levels.[52] Hirakawa et al.[53] demonstrated that among patients with intensive glucose control visit-to-visit variability, defined as a 5-SD measurement of glycosylated hemoglobin (HbA_{1c}) over a 3-24 month period, was associated with a higher risk of macrovascular events and death. Therefore consistency of glycemic control, in addition to reaching HbA_{1c} targets, is important to reduce the risk of vascular events and death in those with type 2 diabetes.

A study examining inpatients revealed that elevated variability of admission glucose appeared more significant than absolute glucose level on admission and prior glucose control in predicting 1-year adverse events in post-MI patients.[54] Findings were replicated in a meta-analysis of 21 studies (7 including type 1 diabetic patients and 13 including type 2 diabetic patients), which demonstrated that HbA_{1c} variability was associated with microvascular complications, macrovascular complications, and mortality, all independent of the absolute HbA_{1c} levels.[55] Most of the studies in the metanalysis were retrospective, did not adjust for potential confounders, and differed in terms of their definition of variability. High variability in fasting glucose levels was found to be an independent predictor of mortality and cardiovascular events in a 6.7 million patient study from the Korean National Health Insurance System.[8] Similar to weight, glycemic variation in those with type 2 diabetes has been suggested to contribute to brain atrophy and cognitive decline.[56]

2. Mechanism of adverse effects

It has been demonstrated that glycemic variability (GV) results in greater endothelial dysfunction, perhaps related to higher oxidative stress, when compared to stable glucose levels. Wide swings in glucose may also result in increased platelet activation, aggregation, and distortions in autonomic function.[57-60]

3. Implications for diabetes therapy

The data suggest that diabetes therapy should target swings in glucose in addition to mean glucose levels and HbA_{1c}. Oral hypoglycemics with glucose-dependent mechanism of actions have the potential to stabilize fluctuations in glucose. The dipeptidyl-peptidase-4 enzyme inhibitor class has been shown to decrease GV in several trials.[61-64] For example sitagliptin reduced GV compared to the sulfonylurea glimepiride in patients with poorly controlled T2DM on background metformin.[61] Despite improved GV, outcome trials studying dipeptidyl-peptidase-4 enzyme inhibitors have failed to demonstrate superiority in reducing ASCVD

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events.[65-67] Preliminary data suggests that glucagon-like peptide 1 analogues modulate fluctuations in glucose.[68-70] And while the sodium-glucose co-transporter 2 inhibitor class of hypoglycemics has demonstrated impressive benefits on ASCVD outcomes, studies examining their effect on GV are limited.[71,72] Regarding insulin, an observational study demonstrated improved GV with glargine when compared to Neutral Protamine Hagedorn Insulin.[73] Future trials examining diabetes treatment should continue to focus on identifying therapies with the most consistent glucose control.

HEART RATE VARIABILITY

High resting heart rate is a risk factor for ASCVD. However, unlike BP and other cardiovascular risk factors, variability of heart rate has actually been proven to be protective against adverse cardiovascular events. Kleiger et al. demonstrated that reduced heart rate variability (HRV) was associated with higher mortality rates over thirty years ago.[74] Several other studies have shown similar findings, particularly among patients with coronary heart disease and heart failure. Notably, the protective effect of HRV has been shown to be independent of non-sustained ventricular tachycardia and left ventricular ejection fraction.[8,75,76]

The association of reduced HRV and mortality has even been demonstrated in patients without known ASCVD. For example, the Framingham Heart Study showed that among 2,501 patients, a 1-SD decrease in HRV was associated with a 1.45 HR for cardiac events (95% CI, 1.13–1.85; $p<0.05$), when adjusted for age, sex, cholesterol, and clinical risk factors.[77] Similarly, the Atherosclerosis Risk In Communities (ARIC) study, which enrolled patients without typical cardiac risk factors such as hypertension or diabetes, found that reduced HRV on a 2-minute electrocardiogram strip was associated with increase all-cause mortality (HR, 1.69; 95% CI, 1.11–2.57).[78]

1. Mechanism of heart rate variability

Cardiac autonomic neuropathy is a proposed mechanism to explain HRV. Similar to the peripheral neuropathy seen in those with type 2 diabetes, sympathetic and parasympathetic fibers of the autonomic system may also be affected. As a result, poor HRV reflects the autonomic nervous system's inability to adjust to any given physiologic state.[79]

2. Implications for therapy

While many cardiac medications including beta blockers, spironolactone, ACE inhibitors, statins, and ivadribine have all been shown to increase HRV, the clinical significance of this finding is uncertain.[80,81]

CONCLUSIONS

While the literature reviewed suggests an association between risk factor variability and adverse cardiovascular outcomes, there has yet to be a proof of causation. English epidemiologist Sir Austin Bradford Hill defined the Hill criteria for causation in 1965 to be used to establish evidence of a causal relationship.[82] It is possible that the variability we see of risk factors in the aforementioned studies may be a result of publication bias or statistical analysis. However, several pathophysiologic hypotheses do exist to suggest that

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the findings are in fact not simply a statistical phenomenon. With ongoing research on risk factor variability, we may soon fulfill Hill's criteria for causality, move forward with targeted therapies to decrease variability, and ultimately improve clinical outcomes.[82]

As clinicians, how should risk variability affect the way we counsel our patients? Medication compliance should always be strongly encouraged in order to limit variability in risk factors such as high BP, hyperglycemia, and hyperlipidemia. However, we should understand that medication adherence does not fully explain variability seen in practice and in published studies. For example, in the ALLHAT trial, BP variability was only explained in small part by adherence to anti-hypertensive therapy.[33] We should commend our patients for their weight loss; however, provide them with tools to ensure weight loss maintenance. High-potency statins should be encouraged over low-moderate intensity statins for hyperlipidemia, and calcium channel blockers should be the preferred agents for BP control over ACE inhibitors.

A paradigm shift has occurred with regard to risk management for the prevention of cardiovascular disease. Cardiac risk factors should no longer simply be defined by magnitude (*i.e.* a single LDL-C measurement or the absolute HbA_{1c}) and duration. Rather, we must now define risk factor by magnitude, duration, and equally important, the variability of that particular risk factor over time. The risk factors discussed in this review, including BP, LDL-C, glucose control, and body weight, are surrogate markers that often vary in parallel with clinical cardiovascular endpoints. While a reduction in the magnitude of these surrogate markers has often translated into protection from adverse outcomes in published trials, we have yet to see an intervention trial demonstrate that a reduction in variability per se, independent of the risk factor magnitude is associated with a similar benefit. As we eagerly wait for such trials to be conducted, it is reasonable for clinicians to target reduction of both the risk factor magnitude and variability in an attempt to maximize cardiovascular benefit for our patients.

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