REVIEW ARTICLE

Orthostatic hypotension and cardiovascular risk

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ABSTRACT
Orthostatic hypotension (OH) is a cardinal sign of cardiovascular (CV) autonomic dysfunction as a result of autonomic nervous system failure to control the postural hemodynamic homeostasis. The proportion of individuals with OH increases with aging and chronic conditions, such as neurodegenerative diseases, hypertension, heart failure, diabetes, renal dysfunction, autoimmune diseases, and cancer. In individuals over 70 years of age, more than 20% can be affected. It is now increasingly recognized that there is a direct relationship between OH and each step of the CV disease continuum, eventually leading to end-stage heart disease and CV death. In particular, prevalent OH is associated with cardiac functional and structural remodeling, left ventricular hypertrophy, elevated levels of circulating markers of inflammation, increased intima-media thickness, subclinical atherosclerosis, and thrombosis. Beyond subclinical changes, the presence of OH independently predicts coronary events, stroke, atrial fibrillation, heart failure, and CV mortality. Furthermore, OH is associated with syncope, falls, and fragility fractures, presenting hurdles to be overcome in the delivery of the best management of CV risk factors. Taken together, OH heralds disruption of global circulatory homeostasis and flags overt autonomic dysfunction. The presence of OH is also an independent risk factor for mortality and CV disease; however, until now, the importance of this highly prevalent disorder has been given insufficient attention by clinicians and other healthcare providers. Consequently, more studies are needed to find effective treatment for this troublesome condition and to identify preventive measures that could reduce the burden of CV risk in OH and autonomic dysfunction.

Introduction Orthostatic hypotension (OH) is a cardinal sign of cardiovascular (CV) autonomic dysfunction (FIGURE 1),[1-4] and, in particular, a clinical expression of sympathetic failure.[5] The term was first used by Laubry and Doumer[6] in 1930s, although the characteristic symptoms of postural hypotension were reported earlier by Bradbury and Eggleston.[7] According to an international consensus, endorsed by major cardiac societies, OH is diagnosed when a sustained decrease in systolic blood pressure (SBP) of 20 mm Hg or higher or in diastolic blood pressure (DBP) of 10 mm Hg or higher during active standing or head-up tilt test is present.[8-10] There are some variants of this generally accepted definition, such as inclusion of an absolute standing SBP value of less than 90 mm Hg,[9] higher diagnostic thresholds in hypertension (SBP/DBP decline >30 mm Hg /15 mm Hg),[8,11] or relying on SBP decline only for the diagnosis using the international consensus.[9,12]

Orthostatic hypotension is a result of the autonomic nervous system failure to preserve the postural hemodynamic homeostasis, a process that involves complex adaptive mechanisms, including the most important one, the baroreceptor reflex (FIGURE 1).[13] When the central arterial pressure declines and cerebral perfusion as well as cerebral tissue oxygenation become critically compromised during orthostasis, patients may report fatigue, blurred vision, dizziness, and, finally, suffer loss of consciousness,[14] sometimes presenting as a traumatic fall of unexplained origin.[15-18]

Orthostatic hypotension is more common than usually believed. Its prevalence has been studied in both the general population and specific diseases. The proportion of individuals who meet the diagnostic criteria of OH increases with

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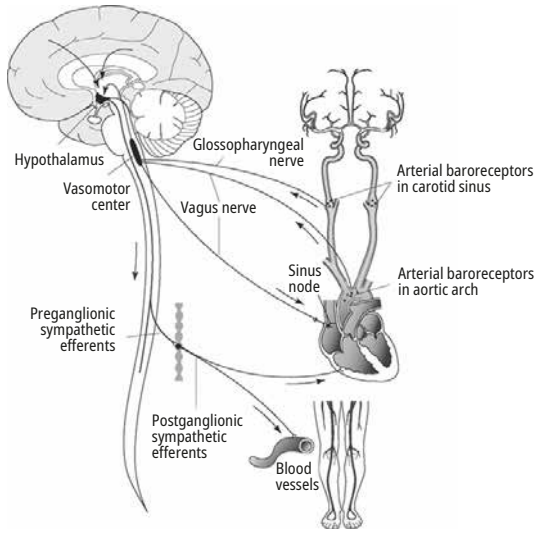
Hypertension
Nondipping / reverse dipping
Sympathovagal imbalance
Dysregulation of cerebral circulation



Baroreceptor dysfunction

Reduced heart rate variability
Inappropriate sinus tachycardia
Postural orthostatic tachycardia syndrome
Chronotropic insufficiency
Coronary dysfunction

Orthostatic hypotension
Periphery circulatory dysfunction

FIGURE 1 Spectrum of cardiovascular autonomic disorders and the global circulatory homeostasis in relation to orthostatic hypotension. Symptoms of cardiovascular autonomic dysfunction may mimic other disorders and are often termed "idiopathic" or "essential" due to lack of a generally accepted mechanistic disease model and unexplained etiology (modified from Ricci et al[1] and Spallone et al[4]).

advancing age and chronic conditions, such as neurodegenerative diseases, hypertension, heart failure, diabetes, renal dysfunction, autoimmune diseases, and cancer.[19-22] The prevalence of age-dependent OH ranges from less than 5% in younger individuals (<50 years of age) to 20% and higher in those older than 70 years.[23,24] However, the majority of individuals who meet the OH criteria at screening are asymptomatic or unaware of the problem.[25,26] The most important chronic conditions with high OH occurrence are Parkinson disease (approx. 50%),[27-29] hypertension (approx. 15%–30%),[11,24,30] heart failure (8%–83%),[31] diabetes (approx. 20%–30%),[24,32-34] and kidney failure (up to approx. 40%),[35] conditions all known to be associated with increased risk of CV events.

In this review, we discuss the current understanding of how the occurrence of OH aggravates the risk of CV disease and death in the general population.

Detection of orthostatic hypotension More than 80 years ago, Shellong described the active standing test as a simple method of CV autonomic evaluation, an approach that is still in use today.[36] Modern solutions include both noncontinuous automatic blood pressure (BP) measurement and more detailed noninvasive continuous technology,[37] applied during both active standing and head-up tilt examination.[38,39] The former is preferably used in population-based studies[25] and in the busy emergency department, hospital ward, or private practice, whereas the latter is a very important prerequisite for CV autonomic evaluation in syncope clinics and autonomic laboratories.[25,40,41] Detailed information on how to perform orthostatic tests can be found in the current European guidelines on syncope.[9,38]

Cardiovascular risk in orthostatic hypotension The concept of a CV disease continuum framed as a chain of events, initiated by a number of related and unrelated risk factors, and progressing through numerous physiologic pathways and processes at both molecular and cellular levels up to the development of end-stage heart disease, has been proposed and validated through the evidence that an intervention at any point along this chain can modify the course of the disease and deliver cardioprotective effects.[42] Notably, it is now increasingly recognized that a direct relationship exists between OH and each step of the cascade of pathophysiologic and clinical events in the CV disease continuum (FIGURE 2 and TABLES 1 and 2).

Cardiovascular risk factors and circulatory complications Orthostatic hypotension is a relatively common condition among hospitalized patients, although it is likely that asymptomatic OH remains unrecognized in the majority of patients in clinical practice. The condition is associated with several adverse clinical outcomes, including syncope, falls, and fragility fractures.[43-45] The high prevalence of OH among institutionalized patients likely reflects the presence of multiple risk factors, namely, the combination of aging, diabetes, hypertension, carotid artery disease, use of vasoactive medications, atrial fibrillation, renal dysfunction, and hypotensive susceptibility.[46] All these risk factors have in common the potential to impair regulation of baroreflex function, which predicts excess CV morbidity and mortality.[47-49]

The prototypical patient with OH is elderly, frail with multiple comorbidities, and taking numerous medications.[50] Diabetes may be present in up to 40% of OH patients, as this is

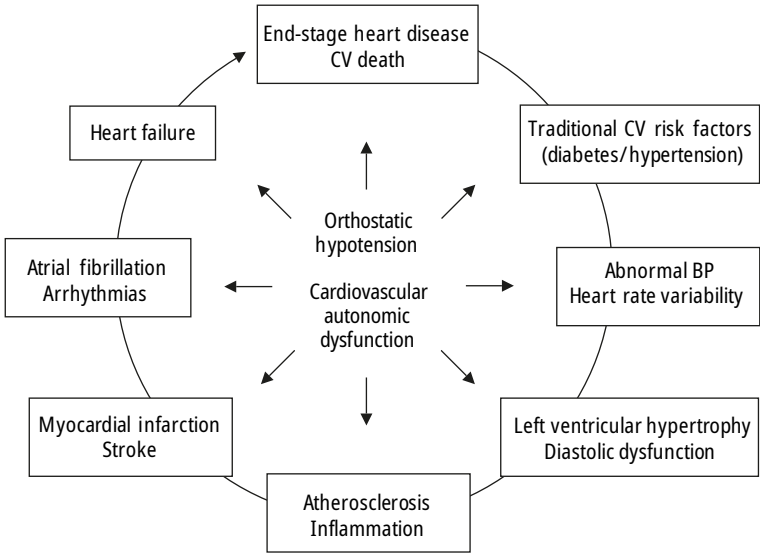


FIGURE 2 Cardiovascular (CV) disease cascade and autonomic dysfunction. Orthostatic hypotension has been associated with different mechanisms involved in CV disease progression, from a strong relationship with traditional CV risk factors and subclinical changes on functional level to increased risk of CV death.

Abbreviations: BP, blood pressure

the most common cause of peripheral and autonomic neuropathy. However, hypertension, especially supine hypertension,[51] is by far the most common comorbidity in OH patients, ranging up to 70%, and complicating their management because treatment of one can worsen the other.[46]

Although antihypertensive treatment is usually considered to be a risk factor for OH,[52] results from the HYTE (Hypertension Heredity in Malmö Evaluation) study cohort showed that antihypertensive medications may reduce the impaired orthostatic response; specifically, the use of angiotensin-converting enzyme inhibitors in hypertensive patients was associated with lower frequency of OH.[11] Accordingly, in the ACCORD BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure) trial, hypertensive diabetics treated to an SBP goal of less than 120 mm Hg did not show a higher prevalence or incidence of OH than those treated to an SBP goal of less than 140 mm Hg. On the contrary, a tendency to a decreased incidence of OH was seen.[53,54] Importantly, putting these findings in a broader context, there is consistency across large trials (ASK [African American Study of Kidney Disease and Hypertension]

TABLE 1 **Summary of population-based studies on the association between prevalent orthostatic hypotension and mortality (continued on the next page)**

First author, study cohort	Year	Country	Study population	Sample size, n	Follow-up, y	Mean age, y	Summary
Raiha et al[88]	1995	Finland	Population-based, elderly individuals	318	10	74	OH was common in this unselected elderly population. No predisposing factors other than hypertension. Diastolic, but not systolic, OH, but not systolic OH, predicted excess vascular mortality.
Masaki et al,[83] HHP	1998	Hawaii	Population-based, Japanese elderly individuals	3522	4	71–93[a]	OH is a significant independent predictor of all-cause mortality. A linear dose-response relation between orthostatic ΔSBP and mortality; threshold effect with orthostatic ΔDBP >5 mm Hg.
Hossain et al[92]	2001	United States	Nursing home residents	673	1	84	Neither OH alone nor variability of supine SBP is associated with mortality outcome.
Sasaki et al[35]	2005	Japan	Predialysis individuals	304	4	63	OH at the introductory phase of hemodialysis is an independent predictor of all-cause mortality.
Cohen et al[91]	2006	Israel	Emergency room individuals	814	1	57	On age-adjusted analysis, patients aged >75 years with OH had a significantly higher rate of mortality.
Rose et al,[23] ARIC	2006	United States	Community-living, middle-aged individuals	13 152	13	54	OH predicts mortality in middle-aged adults. This association is only partly explained by traditional risk factors for CV disease and overall mortality.
Weiss et al[90]	2006	Israel	Acute geriatric inpatients	471	3	81	OH is relatively common in elderly patients discharged from acute geriatric wards, but has no impact on all-cause and cause-specific mortality.
Verwoert et al,[87] Rotterdam Study	2008	The Netherlands	Community-living individuals	5064	7	68	OH increases the risk of coronary heart disease and all-cause mortality in elderly people. The risk of CV disease and mortality is higher in younger and very old subjects.

TABLE 1 Summary of population-based studies on the association between prevalent orthostatic hypotension and mortality (continued from the previous page)

First author, study cohort	Year	Country	Study population	Sample size, n	Follow-up, y	Mean age, y	Summary
Fedorowski et al,[85] MPP	2010	Sweden	Population-based, middle-aged individuals	32 068	23	46	OH can be detected in 6% of middle-aged individuals and is frequently associated with hypertension and diabetes. OH independently increases mortality and risk of CV disease.
Alagiakrishnan et al,[82] CHS	2013	United States	Population-based, elderly individuals	5273	13	74	Among community-dwelling older adults, OH had no significant association with all-cause mortality or other incident CV events. However, compared with those without OH, matched participants with symptomatic OH had higher risk of all-cause mortality and CV events.
Fedorowski et al,[78] CPP	2013	Sweden	Community-living hypertensive patients	8788	6	52	After adjustment for traditional risk factors, the presence of OH was associated with the increased risk of incident cerebrovascular events and tended to predict the composite event of death and manifest CV disease.
Chou et al,[89] Taiwan NHIRD	2015	Taiwan	Population-based, middle-aged adults	13 486	4	54	OH was found to be an independent risk factor for ischemic stroke and all-cause mortality.
Fleg et al,[54] ACCORD BP	2016	Canada / United States	High-risk participants with hypertension and T2DM	4266	4	62	Consensus OH occurred at ≥1 of the 3 time points in 20% of participants. OH incidence was unrelated to assigned SBP treatment group. Occurrence of OH was an independent marker of total mortality and HF death or hospitalization but not nonfatal MI, stroke, CV death, or their composite.
Ricci et al,[84] MPP	2017	Sweden	Population-based, middle-aged individuals	32 628	27	46	Hospital admissions caused by OH independently predict CV mortality, but not all-cause mortality.
Juraschek et al,[55] AASK	2018	United States	Black hypertensive adults with CKD	1094	4	54	OH is associated with increased risk of nonfatal and any CV disease, but not all-cause mortality.
Juraschek et al,[43] ARIC	2018	United States	Community-dwelling middle-aged adults	9139	26	54	OH identified in community-dwelling middle-aged adults was associated with all-cause mortality, future CV events, and subclinical atherosclerotic CV disease.
Yasa et al,[73] MDCS	2018	Sweden	Population-based, middle-aged individuals	30 528	15	58	Hospital admissions for OH, previously seen as benign events, herald a higher risk of CV morbidity and all-cause mortality and convey independent prognostic information. OH hospitalization is associated with 14% increased mortality.

a Age range

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACCORD BP, Action to Control Cardiovascular Risk in Diabetes Blood Pressure; ARIC, Atherosclerosis Risk in Communities; CHS, Cardiovascular Health Study; CKD, chronic kidney disease; CPP, Captopril Preventive Project; CV, cardiovascular; DBP, diastolic blood pressure; HF, heart failure; HHP, Honolulu Heart Program; MDCS, Malmö Diet and Cancer Study; MI, myocardial infarction; MPP, Malmö Preventive Project; NHIRD, National Health Insurance Research Database; OH, orthostatic hypotension; SBP, systolic blod pressure; T2DM, type 2 diabetes mellitus

in African Americans with chronic kidney disease[55]; SPRINT [Systolic Blood Pressure Intervention Trial] in individuals without stroke or diabetes[56]; and the blood pressure cohort of the SPS3 trial [Secondary Prevention of Small Subcortical Strokes] in adults with a recent stroke [<6 months])[55] that a lower SBP goal reduced OH without affecting orthostatic symptoms. One

TABLE 2 Breakdown of adverse outcomes reported in longitudinal cohort studies

First author, study cohort	Year	Death, any cause	CV death	HF	CAD/MI	Stroke	Atrial fibrillation	Subclinical ASCVD/TOD
Raiha et al[88]	1995	+	+		+	+		
Masaki et al,[83] HHP	1998	+						
Eigenbrodt et al,[80] ARIC Stroke	2000					+		
Hossain et al[92]	2001	+			+	+		
Sasaki et al[35]	2005	+						
Cohen et al[91]	2006	+						
Rose et al,[23] ARIC	2006	+	+					
Weiss et al[90]	2006	+						
Verwoert et al,[87] Rotterdam Study	2008	+		+	+	+		
Fedorowski et al,[85] MPP	2010	+			+	+	+	
Fedorowski et al,[81] MPP HF	2010			+				
Jones et al,[93] ARIC HF	2012			+				
Agarwal et al,[74] ARIC	2013						+	
Alagiakrishnan et al,[82] CHS	2013	+		+	+	+		
Casiglia et al,[76] LEOGRA	2013			+	+	+	+	
Fedorowski et al,[78] CPP	2013	+			+	+		
Chou et al,[89] Taiwan NHIRD	2015	+			+	+		
Magnusson et al,[68] MPP	2015							+
Fleg et al,[54] ACCORD BP	2016	+	+	+	+	+		
Ricci et al,[84] MPP	2017	+	+					
Juraschek et al,[55] AASK	2018	+		+	+	+		
Juraschek et al,[43] ARIC	2018	+	+	+	+	+		+
Ko et al,[75] FHS	2018						+	
Yasa et al,[73] MDCS	2018	+	+	+	+	+	+	

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; FHS, Framingham Heart Study; HF, heart failure; HHP, Honolulu Heart Program; LEOGRA, Last Evidences of Genetic Risk Factors in the Aged; MI, myocardial infarction; TOD, target organ damage; others, see TABLE 1

possible explanation is that reducing supine hypertension by antihypertensive drugs may lead to a narrower BP swing window on standing and a lower detection rate of OH in otherwise autonomically affected patients. It should be also remembered that "one size does not fit all," and that older hypertensive patients with multiple comorbidities should be treated with caution taking into consideration an a priori increased risk of falls in this patient group.[57]

It has been proposed that injurious falls and syncope incidence may have been underreported in interventional studies such as SPRINT.[58] In this context, bedtime administration of antihypertensive treatment, addressing both supine hypertension and an increased risk of BP fall during morning hours, seems to be less harmful, more optimal in reducing CV risk, and might be a standard approach in the future.[59] Finally, it is important to acknowledge that the identification of any optimum SBP therapeutic goal must not only balance OH, falls, syncope, and CV risk but also consider cerebral perfusion status and the range of individualized cerebral autoregulation activity.[57] In patients with OH and syncope, discontinuation of vasodepressors might be the only acceptable option to prevent falls and trauma,[60] as emphasized by the current European guidelines on syncope.[9] Thus, although antihypertensive treatment may diminish OH occurrence in hypertensive patients, it may also increase the vasovagal reflex tendency and fall risk in susceptible individuals.

Atherosclerotic cardiovascular disease In the middle-aged community-dwelling population of the ARIC study (Atherosclerosis Risk in Communities), OH was strongly associated with subclinical CV disease, that is, higher levels of high-sensitivity cardiac troponin T and N-terminal fragment of the prohormone brain natriuretic peptide, carotid intima-media thickness (IMT),

and presence of plaques, as well as a higher risk of incident myocardial infarction, heart failure, and stroke, regardless of traditional CV risk factors. Interestingly, baseline carotid IMT of individuals with and without OH was identical (0.80 mm vs 0.73 mm) both in the MDCS-CC trial (Malmö Diet and Cancer Study Cardiovascular Cohort)[61] and in the ARIC[62] population (mean age, 58 years and 54 years, respectively), suggesting strong external validity. In the MDCS--CC study, OH was also independently associated with increased plasma levels of fibrinogen, where an increment of 1 g/l conferred an almost doubled risk of all-cause mortality, coronary artery disease, and stroke.

Orthostatic hypotension is a condition of impaired hemodynamic homeostasis associated with prolonged orthostatic stress setting off a chain reaction leading to hyperactivation of the endothelin system and activation of compensatory neuroendocrine adaptive mechanisms, eventually promoting, in the long term, a state of "orthostatic hypercoagulation"[63] and atherothrombotic events in susceptible individuals.[64,65] Taken together, these 2 well established predictors of CV mortality and morbidity, that is, increased IMT and elevated fibrinogen level, offer a plausible explanation for the increased risk of various fatal and nonfatal events observed in OH.[61] Furthermore, accumulating data suggest an extensive bidirectional cross-talk between impaired hemostasis and inflammation (which are both downstream events regulated by OH) in the pathophysiology of atherothrombosis.[66,67]

Overall, this evidence suggests that OH is strongly associated with both clinical and subclinical CV disease, such that its identification in ambulatory middle-aged adults may warrant further consideration of CV risk stratification, which may yet provide an incremental prognostic value.[43] Nevertheless, it remains to be established whether OH is a prognostic marker of a generally increased risk of poor outcome, an intermediate variable in the causal pathway of CV risk factors, a simple measure of disease severity, or an independent causal mechanism.[65]

Left ventricular hypertrophy and structural heart remodeling Orthostatic hypotension is a harbinger of structural and functional cardiac changes including left ventricular hypertrophy (LVH), diastolic dysfunction, and a reduction in right ventricular preload, independently of traditional risk factors among middle-aged adults.[68-71]

Left ventricular hypertrophy in OH can be explained by: 1) pronounced diurnal BP variability and nocturnal hypertension; 2) arterial hypertension; and 3) upregulated neuroendocrine mechanisms leading to an increase of left ventricular mass through direct action on the myocardium or through their action on the vasculature. Together with increased arterial stiffness, LVH is likely to be responsible for the impaired diastolic function in patients with OH.

Atrial fibrillation Incident atrial fibrillation has been consistently related with the presence of OH at baseline in a series of independent epidemiological studies.[72-76] Both cardiac remodeling and abnormal neuroendocrine activation due to BP instability are believed to underlie this association. Although a causal association is difficult to prove, further research is warranted to explore whether interventions to prevent and treat OH may improve atrial fibrillation–related CV outcomes.

Coronary artery disease and myocardial infarction Increased incidence of coronary events has been observed among patients with OH in large longitudinal population-based cohort studies as well as in patients with hypertension.[25,43,73,77,78] It is hypothesized that neuroendocrine and inflammatory activation, coronary dysfunction, LVH, supine hypertension,[79] and other factors that are not yet recognized contribute to an increased risk of coronary events in OH.

Stroke Stroke has a similarly increased incidence among patients with OH as coronary artery disease,[43,73,77,78,80] probably due to the same mechanisms, with an expected right-shifted age-dependent incidence.

Heart failure Heart failure, as the common end stage of the CV disease continuum, is logically predicted by the occurrence of OH both in the general population and in patients with hypertension and diabetes.[43,54,73,81,82] Here, as depicted in FIGURE 2, all factors involved in the detrimental CV disease cascade and associated with the presence of CV autonomic failure promote progressive changes in the myocardium, consequently leading to overt heart failure.

All-cause and cardiovascular mortality There have been multiple studies[25,35,43,54,55,65,73,78,80,82-92] as well as a meta-analysis[65] uniformly pointing to the increased mortality among patients in whom OH was detected, either by screening (population-based cohorts) or through characteristic symptoms confirmed by autonomic testing (TABLE 1). However, this issue has hitherto not been given sufficient priority in research activities. As for October 31, 2019, PubMed search for articles with the keywords "diabetes," "hypertension," "orthostatic hypotension" plus "mortality," yielded 63 038, 58 140, and 445 records, respectively, showing a clear disparity between the 2 former conditions and OH. Thus, there is a huge gap in knowledge where observational studies point at a clearly increased risk of death in OH or CV autonomic dysfunction, in general, while basic research and interventional studies are lacking.

Conclusions Orthostatic hypotension is a cardinal sign of CV autonomic dysfunction. It is now increasingly recognized that, regardless of symptoms, there is a direct relationship between OH and each step of the CV disease continuum, eventually leading to CV death. Orthostatic hypotension is also associated with adverse clinical outcomes, including syncope, falls, and fragility fractures, the fact that strongly complicates preventive treatment of CV risk factors in patients with OH. Nevertheless, this aspect of CV health has not been given proper attention. Further research is greatly needed to determine interventions that may prevent OH and its complications without causing more harm to this vulnerable and common patient population.

ARTICLE INFORMATION

CONFLICT OF INTEREST AF reports personal fees from Medtronic, Inc. and Biotronik outside the submitted work. RS reports personal fees and other from Medtronic, Inc. and Abbott Laboratories outside the submitted work. RS is a member of the speaker's bureau of Abbott Laboratories and a shareholder in Boston Scientific, Edwards Lifesciences, and AstraZeneca Plc. The authors declare no other relationships or activities that could appear to have influenced the submitted work.

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