Blood pressure management in hypertensive patients with syncope: how to balance hypotensive and cardiovascular risk

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Managing hypertension in syncope patients requires the accurate balancing of hypotensive and cardiovascular risks. On the basis of the available literature, this study analyses the complex inter-relationship between these clinical problems and presents an algorithm strategy to guide hypertension management in patients affected by syncope episodes. A SBP target of 120 mmHg is recommended in patients with a low syncope risk and a high cardiovascular risk. In patients with a high syncope risk and a low cardiovascular risk, and in older (70+) frail individuals, a less intensive treatment is advisable, targeting SBP of 140 mmHg. SBP values up to 160 mmHg can be tolerated in severe frailty or disability.

Patients with hypertension and syncope may benefit from team-based care by a 'Blood Pressure Team' including experts on hypertension and syncope and a geriatrician. The team should carry out a multidimensional assessment to balance syncope and cardiovascular risk and develop therapeutic strategies customized to individuals' frailty and functional status.

Keywords: blood pressure, hypertension, hypotension, older adults, syncope

Abbreviation: BP, blood pressure

INTRODUCTION

Hypertension is highly prevalent worldwide and is a major risk factor for cardiovascular disease, predisposing to coronary syndromes, heart failure and stroke [1–3]. Blood pressure (BP) control has been shown to significantly reduce cardiovascular morbidity and mortality, thus playing a central role in cardiovascular prevention [4,5]. Yet, intensive BP lowering may increase the risk of syncope. Indeed, in the SPRINT study [6], randomization to intensive SBP control was associated with a greater risk of adverse events involving hypotension and syncope [7]. During the 5 years of observation, in the intensive BP treatment arm, there were 5.2% patients with primary outcome events (defined as composite of myocardial infarction or acute coronary syndromes, stroke, heart failure or death from cardiovascular causes) and 3.5% patients with syncope (defined as emergency department visit or serious adverse event) and 3.4% patients with hypotension [7]. Moreover, if the SPRINT intensive BP target were applied in USA adults, we could expect 34 400 additional episodes of syncope per year and 56 100 additional episodes of hypotension in comparison with a standard treatment approach (annual risk increase 0.19 and 0.31%, respectively) [8].

Syncope may negatively affect patients' prognoses. In a recent Danish cohort study, adults hospitalized for their first syncope had an 80% higher risk of fall-related injuries within the year following discharge [9]. Consequently, the occurrence of syncope in hypertensive patients frequently results in the reduction or discontinuation of antihypertensive treatment. This, however, may potentially increase the risk of cardiovascular events.

Balancing hypotensive and cardiovascular risks may be even more challenging in older adults, particularly if they are frail. Hypotension and syncope are more common in such individuals [10] and impact more severely on health status, functional autonomy and survival [11–13]. At the same time, however, cardiovascular risk is also high in these individuals, and cardiovascular prevention through reduction of modifiable risk factors not only reduces mortality but may also help to counteract functional decline [14]. In this context, the absolute risk-benefit ratio of BP lowering may be difficult to estimate, especially in the presence of competing geriatric conditions such as frailty, disability and multimorbidity, which may have a greater impact on outcomes than cardiovascular disease.

The present study examines the complex inter-relationship between hypotensive and cardiovascular risks, in order to provide practical suggestions for optimizing the therapeutic management of hypertensive patients

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with syncope. Specifically, we address those syncope diagnoses that are more likely to be related to antihypertensive treatment and which should prompt less intensive BP control. In addition, in order to guide hypertension management in patients with syncope, we propose an algorithm strategy involving different BP targets according to the patient's hypotensive and cardiovascular risk profile.

HOW TO IDENTIFY TREATMENT-RELATED SYNCOPE

In hypertensive patients, syncope is not necessarily a treatment-related adverse event. Indeed, syncope may be caused by several etiopathogenetic mechanisms, some of which are little influenced by BP lowering.

Treatment-related syncope mainly involves the concept of hypotensive susceptibility, a tendency to vasodepression, which may be exacerbated by antihypertensive medications [15]. Hypotensive susceptibility can be defined as a vulnerability to vertical posture stress due to a gravity-induced fluid shift to the lower body, which results in a tendency to the hypotensive (vasodepressor) aspect of reflex syncope [15]. Hypotensive susceptibility plays a role in causing syncope irrespective of the cause or of the underlying mechanism [15].

Examples of syncope due to hypotensive susceptibility include the following (Table 1):

1. orthostatic vasovagal syncope with a predominant vasodepressive response, defined as syncope occurring during standing, which is reproduced during tilt testing; the test will show hypotension with a variable degree of heart rate reduction [16];
2. situational reflex syncope, occurring during or after micturition, defecation, exercise or coughing [16];
3. vasodepressive and mixed carotid sinus syndrome, defined as syncope induced by carotid sinus massage and associated with a SBP drop at least 50 mmHg [16];
4. syncope due to orthostatic hypotension, defined as syncope occurring after standing in patients with symptomatic or asymptomatic orthostatic hypotension (SBP drop $\geq$20 mmHg or to an absolute value $<$90 mmHg and/or DBP drop $\geq$10 mmHg within 3 min after standing) [16];
5. syncope due to postprandial hypotension, defined as syncope occurring during or after meals in patients with an abnormal BP drop during the meal or immediately afterwards, as may be detected by ambulatory BP monitoring or continuous beat-to-beat BP monitoring;
6. reflex syncope triggered by tachyarrhythmias, for example syncope occurring at the onset of atrial fibrillation [17] or paroxysmal supraventricular tachycardias [18];
7. in addition to the clinical forms described above, syncope is probably related to hypotensive susceptibility if recurrent severe hypotensive episodes are detected during ambulatory BP monitoring (daytime SBP $<$90 mmHg).
8. Conversely, the following clinical features and clinical forms suggest that syncope is less likely to be related to antihypertensive treatment (Table 1):
   a. syncope due to cardiac arrhythmias or to structural cardiac causes [16];
   b. syncope occurring in the supine position;
   c. vasovagal syncope triggered by emotional distress (blood phobia, instrumentation, visceral or somatic pain);
   d. cardioinhibitory reflex syncope, defined as syncope associated with reflex asystole at least 3 s and including cardioinhibitory tilt-induced syncope, cardioinhibitory carotid sinus syndrome and reflex asystolic syncope detected by means of implantable loop recorder [16]. In cardioinhibitory reflex syncope, a vasodepressive mechanism may also be present (mixed responses), thus suggesting the coexistence of a hypotensive susceptibility that may be exacerbated by BP lowering.

INTER-RELATIONSHIP BETWEEN SYNCOPE AND CARDIOVASCULAR RISK AT DIFFERENT BLOOD PRESSURE VALUES

Young hypertensive adults

Most trials investigating hypertension have demonstrated an increase in cardiovascular risk at office SBP more than 140 mmHg, thus indicating office SBP less than 140 mmHg as the first target of antihypertensive therapy [19,20]. Further risk reduction may be achieved at lower SBP values [5,21,22], and targeting office SBP less than 120 mmHg significantly reduced cardiovascular events and all-cause

TABLE 1. Clinical forms of syncope probably related/unrelated to antihypertensive treatment

Treatment-related syncope	Syncope less likely to be related to antihypertensive treatment
Orthostatic vasodepressive vasovagal syncope	Syncope occurring while supine
Situational syncope	Vasovagal syncope triggered by emotional distress
Vasodepressive carotid sinus syndrome	Syncope due to cardiac arrhythmias or to structural cardiac causes
Syncope due to orthostatic hypotension	Cardioinhibitory tilt-induced syncope[a]
Syncope due to postprandial hypotension	Cardioinhibitory carotid sinus syndrome[a]
Reflex syncope triggered by tachyarrhythmia	Reflex asystolic syncope detected by implantable loop recorder[a]
Syncope in patients with recurrent hypotension on ambulatory blood pressure monitoring	

[a]A vasodepressive mechanism may also be present, suggesting hypotensive susceptibility.

mortality in high-risk patients enrolled in the SPRINT trial [6]. Other studies, however, suggest an increase of cardiovascular risk when office SBP is lowered to values less than 120 mmHg in high-risk patients [23–25]. Given the latter findings, there seems to be a J-shaped relationship between BP and cardiovascular risk, with nadir of cumulative risk corresponding to a SBP of 120–130 mmHg [23,25] (Fig. 1a). Consistently, the European Society of Cardiology and European Society of Hypertension guidelines on hypertension indicate a SBP range as a target of antihypertensive therapy and discourage BP lowering to SBP less than 120 mmHg [20].

With regard to syncope, the risk is known to increase at low BP values, and is therefore located on the left side of the J-shaped relationship between BP and adverse events (Fig. 1a). Sim *et al.* [26] reported a significant increase in serious falls and syncope in treated hypertensive patients with minimum or mean SBP less than 110 mmHg [odds ratio (OR) 2.18, 95% confidence interval (95% CI) 2.11–2.25 and 1.54, 95% CI 1.43–1.66, respectively]. In the SPRINT trial, a higher incidence of hypotension and syncope was reported in the intensive treatment group [6], suggesting that the risk of syncope significantly increases at SBP less than 120 mmHg. Therefore, the cumulative risk of syncope and cardiovascular events seems to reach its nadir at a SBP of 120 mmHg (Fig. 1a).

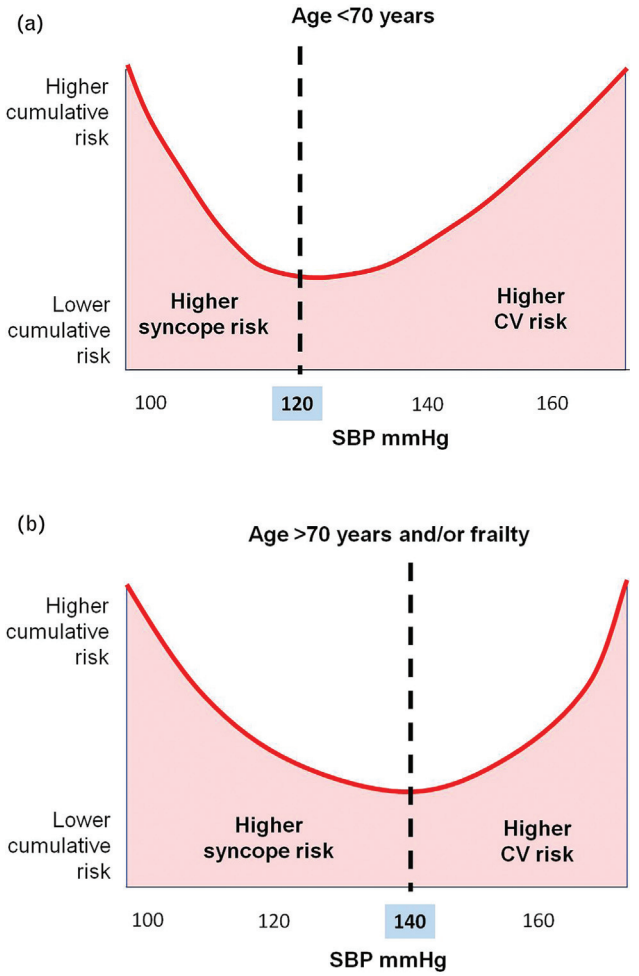

FIGURE 1 Cardiovascular and syncope risk according to SBP values in younger adults (a) and in older frail adults (b). The risk curve is schematic and without a scale, merely aimed at illustrating the concept. CV, cardiovascular.

Older and frail hypertensive adults

In the SPRINT study, the benefits of intensive BP control (SBP target <120 mmHg) on cardiovascular events and mortality were also confirmed in older frail hypertensive patients [27]. However, other observational studies suggest that the association between BP values and cardiovascular risk modifies at advanced age. In the JATOS study, the primary endpoint including cardiovascular disease displayed a similar incidence in older patients randomized to a SBP target less than 140 or 140–160 mmHg [28]. Instead, SBP less than 140 mmHg and DBP less than 90 mmHg were found to be associated with reduced survival in hypertensive adults aged at least 80 years in a study by Oates *et al.* [29] (hazard ratio 0.82 for a 10-point increase in SBP up to 139 mmHg, 95% CI 0.74–0.91; hazard ratio 0.85 for a 10-point increase in DBP up to 89 mmHg, 95% CI 0.78–0.92). Of note, SBP values more than 140 mmHg were not associated with mortality. The prognostic role of BP seems to modify also in older individuals at high cardiovascular risk. Indeed, in the ZODIAC study, SBP and DBP were inversely related to both all-cause and cardiovascular mortality in older hypertensive patients with diabetes [30]. However, some studies suggest that a U-shaped risk curve still exists at older age [31,32]. BP lowering to SBP less than 160 mmHg seems to be beneficial [33,34], with a risk nadir at SBP 140 mmHg [35].

Antihypertensive treatment seems to significantly influence the association between BP and adverse outcomes. In the PARTAGE study, SBP values less than 130 mmHg were associated with a two-fold increased risk of mortality in nursing home residents receiving two or more medications. Conversely, individuals with similarly low BP values but receiving no or one antihypertensive medication showed a lower mortality rate [36]. The Leiden 85+ study reported consistent results [37], indicating that the negative prognostic impact of low BP mainly applies to individuals receiving antihypertensive medications.

Little evidence is available on BP treatment in frailer individuals. In the SPRINT, frailty did not modify treatment effects [27], but the study mainly included people with mild-to-moderate frailty [38]. However, there is now a large body of literature indicating that the relationship between BP and adverse events is influenced by frailty and functional status [39,40]. In the SNAC-K study, SBP less than 130 mmHg was associated with higher mortality in older people suffering from either cognitive or mobility impairment, while mortality was reduced in those with low BP and preserved mobility and cognitive performance [41]. The SHEP trial yielded similar results. Indeed, BP treatment targeting a SBP less than 160 mmHg or a 20-mmHg reduction from the baseline was not protective against cardiovascular mortality in older adults with functional impairment, unlike in fit patients. Conversely, antihypertensive treatment reduced the risk of stroke regardless of functional status [42].

In parallel with limited cardiovascular benefits, BP lowering in older adults is also associated with a higher risk of hypotension and syncope, particularly in frail individuals and those with cognitive impairment [43–45]. Indeed, several factors predisposing to hypotensive susceptibility

usually coexist at advanced age, including reduced baroreceptor sensitivity [46], poor hydration, deconditioning, comorbidities and hypotensive medications. In addition, fall-related complications are common in this population and impact more severely on patients' functional status and survival [13]. In this context, less intensive BP control is advisable in order to minimize the risk of syncope and its related complications. Consistently, in the stop-VD study, syncope recurrence was reduced in older patients after the reduction/withdrawal of BP therapy that targeted a SBP of 140 mmHg [47].

Similarly, intensive BP control should also be avoided in older people with a history or a high risk of falls, regardless of their cause. Indeed, syncope is a recognized cause of nonaccidental falls in older adults [16,48] and hypotension may further predispose to falling in patients with gait and balance impairment.

Given all of the above, in older frail adults, the nadir of cumulative risk corresponds to higher SBP values than in younger adults (Fig. 1b).

BOP

Several observational studies support the hypothesis that a J-curve also exists for DBP, particularly in high-risk patients [24,25,49]. Indeed, DBP less than 60–70 mmHg has been shown to significantly increase cardiovascular risk, probably as a result of reduced coronary perfusion [24,49–51].

The association between DBP and syncope has been poorly investigated in the literature. Regarding orthostatic hypotension, SBP seems to play a greater role [52,53], but we may suppose that low DBP could also contribute to hypotensive symptoms. Therefore, in view of its potential unfavourable consequences on both cardiovascular and syncope risk, avoiding excessive DBP lowering seems to be a reasonable approach in hypertensive patients with syncope.

ALGORITHM FOR HYPERTENSION MANAGEMENT IN PATIENTS WITH SYNCOPE

Treatment-related syncope does not always require a reduction of antihypertensive therapy. In these patients, risk stratification should be carried out in order to assess both syncopal and cardiovascular risk. Risk stratification is aimed at determining which of the two risk components is prevalent and should guide the approach to BP treatment.

Features indicating a high risk of syncope and cardiovascular events are detailed in Table 2 [54]. Cardiovascular risk is defined according to the European Society of Cardiology/European Society of Hypertension guidelines [20]. Regarding syncope, high risk is defined as recurrent and/or severe syncope (Table 2), while low risk is defined by the presence of single or rare episodes.

In young hypertensive patients presenting with high cardiovascular risk and low risk of syncope (Table 2), a SBP target of 120–130 mmHg can be recommended. SBP values less than 120 mmHg should be avoided, being associated with a significant increase in both cardiovascular and syncope risk.

In patients at a high risk of syncope who have suffered severe and/or recurrent episodes (Table 2), the syncopal risk probably exceeds the cardiovascular risk, and less intensive BP control is advisable. A SBP target of 130–140 mmHg can be recommended in these patients, thus minimizing the risk of syncope recurrence without significantly increasing cardiovascular risk.

Given the age-related increase of many risk factors for hypotension such as orthostatic BP impairment and white-coat effect, leading to BP overestimation at the time of a clinic visit [55,56], hypotensive risk can be expected to become more relevant above the age of 70, even if the identification of such an age threshold is not supported by strong scientific evidence but mostly by clinical experience. On the basis of these considerations, in individuals who are frail and/or aged at least 70 years, a SBP of 130–140 mmHg might then be recommended as a safer treatment target. A similar approach is also recommended in older people with a history or a high risk of falls. SBP values up to 160 mmHg can be accepted in individuals with severe frailty and/or disability, in view of the extremely high risk of syncope and falls and the limited evidence supporting BP lowering. Frailty status can be assessed using rapid frailty measures such as the Fried frailty phenotype [57] or the Clinical Frailty Scale [58]. The former defines frailty as the presence of at least three of the following: weight loss, self-reported exhaustion, weakness, low gait velocity and reduced physical activity [57]. The Clinical Frailty Scale is a visual numeric scale providing a frailty assessment, which is based on clinical judgement, with frailty defined by a score of at least 5 [58]. Both these tools are easy to perform in routine clinical practice and have been previously suggested for frailty assessment in hypertensive adults [59,60].

On the basis of the above-described evidence and in agreement with the risk curve (Fig. 1) and risk stratification (Table 2), we propose an algorithm to guide BP management in patients with hypertension and syncope (Fig. 2).

TABLE 2. Clinical features indicating a high risk of syncope and cardiovascular events

High risk of syncope Antihypertensive treatment-related syncope AND one of the following	High risk of cardiovascular events[a]
At least three syncope episodes over the previous 2 years	Clinical cardiovascular disease (coronary artery disease, stroke/TIA, peripheral artery disease)
Syncope-related fracture or intracranial bleeding	Diabetes mellitus with target organ damage
Recurrent hypotensive presyncope with a significant impact on quality of life	Severe chronic kidney disease
Syncope due to orthostatic hypotension[b]	Calculated 10-year SCORE[c] $\geq$10%

[a]Defined in accordance with Williams *et al.* [20].
[b]Defined as per Brignole *et al.* [16] by the presence of a symptomatic abnormal BP fall and history of syncope highly suggestive of orthostatic hypotension.
[c]Available at: http://www.escardio.org/Guidelines-&-Education/Practice-tools/CVD-prevention-toolbox/SCORE-Risk-Charts [54].

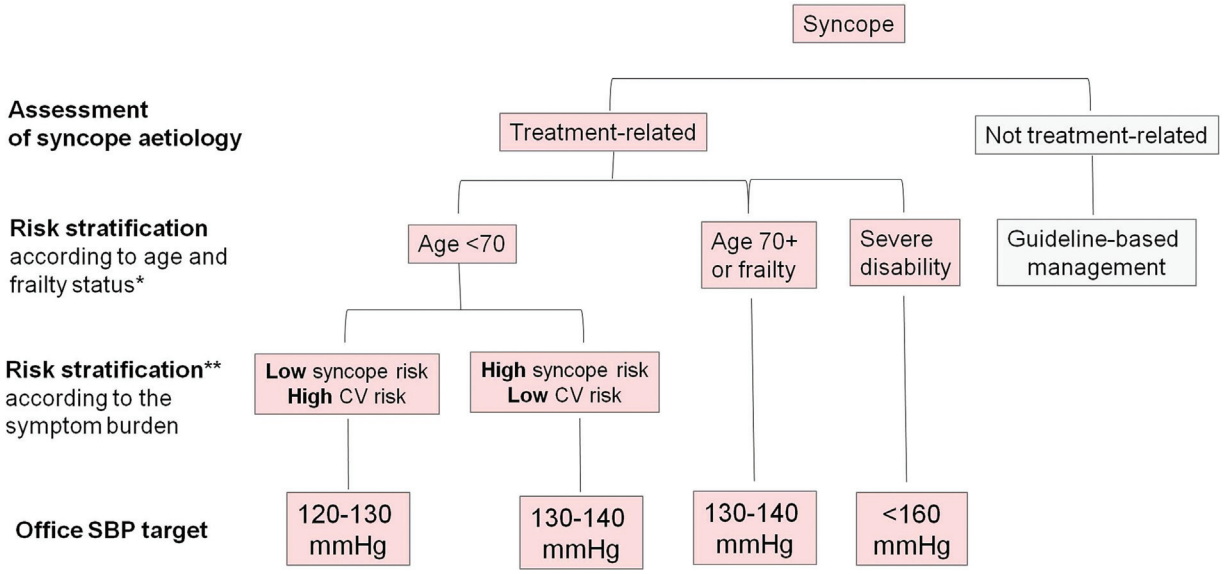

FIGURE 2 Algorithm strategy to guide blood pressure management in patients with hypertension and syncope. [a]Defined according to the Fried Frailty Phenotype [52] or the Clinical Frailty Scale [53]. [b]See Table 2 for details on syncope and CV risk. CV, cardiovascular.

If syncope episodes are not related to antihypertensive treatment, guideline-based BP management should be provided.

PRACTICAL ADVICE TO OPTIMIZE MEDICAL THERAPY IN PATIENTS WITH HYPERTENSION AND SYNCOPE

In addition to customized BP targets, some practical suggestions for medical therapy optimization may be helpful to reduce the risk of treatment-related syncope in hypertensive patients (Table 3).

In order to avoid excessive BP lowering, in patients suffering from syncope, antihypertensive treatment should preferably be started with monotherapy at a low dose, followed by a gradual dose titration. If BP targets are not achieved with a single drug, combination therapy can be considered, starting from the lowest available dose of the combined drugs. Alpha-blockers, beta-blockers and diuretics should be avoided, unless specifically indicated, as they may exacerbate patients' hypotensive susceptibility. Irrespective of the selected drug class, drug dosage should be adjusted according to renal function, to avoid an excessive increase in drug plasma levels.

TABLE 3. Practical advice to optimize medical therapy in patients with hypertension and syncope

1. Start treatment with monotherapy at a low dose;
2. In the case of suboptimal BP control, perform gradual dose titration or consider combination therapy, starting from the lowest available dose;
3. Avoid alpha-blockers, beta-blockers and diuretics, unless specifically indicated;
4. Review potentially hypotensive noncardiovascular medications, for example benzodiazepines, antipsychotics and tricyclic antidepressants, and consider withdrawal or reduction to the lowest effective dose;
5. Prefer bedtime administration of short-lasting antihypertensive medications – with the exception of diuretics – in patients with selective elevation of night-time BP;
6. Adjust drug dosage as appropriate according to renal function.

It is noteworthy that some noncardiovascular medications, for example benzodiazepines, antipsychotics and tricyclic antidepressants, may have hypotensive effects and predispose to treatment-related syncope. Therefore, medical therapy optimization in patients with syncope should also include a review of potentially hypotensive noncardiovascular medications. Indications for their prescription should be reassessed and drug withdrawal considered, whenever possible. In case these medications are needed, drug dosage should be reduced to the lowest effective dose.

Antihypertensive medications with short duration of action should be administered at bedtime in patients with selectively elevated night-time BP. Indeed, nocturnal hypertension may exacerbate pressure natriuresis and induce volume depletion, thus predisposing to orthostatic hypotension in the morning [61]. Diuretic administration at bedtime should instead be avoided, as it induces nocturia and potentially increases the risk of situational syncope.

A significant inter-individual variability exists in the balance between syncope and cardiovascular risk; this is even greater when advanced age, frailty, disability and multimorbidity also play a role. Therefore, patients with hypertension and syncope may benefit from integrated decision-making by a 'Blood Pressure Team' including experts on hypertension and syncope and a geriatrician. The team should carry out a comprehensive multidimensional assessment aimed at balancing syncope and cardiovascular risk according to health and functional status. In addition, the team should develop reasonably optimized treatment strategies, customized to the individual's frailty and functional level.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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