Elevated blood pressure (BP) is a causal risk factor for cardiovascular disease (CVD). Epidemiological analyses have established the graded and continuous association between higher BP and CVD. Moreover, randomized clinical trials among individuals with hypertension have demonstrated, in aggregate, a reduction in CVD events by 20%, coronary heart disease (CHD) by 17%, stroke by 27%, and heart failure by 28% for every 10 mmHg systolic BP (SBP) lowering with medical therapy. Therefore, prevention, detection, treatment, and control of elevated BP, and its clinical correlate hypertension, is an important public health priority and a primary target for CVD prevention.

Although national health surveys have demonstrated improvements in hypertension awareness and treatment, strategic opportunities to improve the efficiency and efficacy of applying BP-lowering therapy in patients most likely to benefit remain. Global CVD risk assessment, using multivariable prediction models that estimate absolute CVD risk from routinely measured clinical variables, has been promulgated in several CVD prevention guidelines for cholesterol management to target the most intensive preventive therapies to those at highest absolute CVD risk. Hypertension guidelines, however, have instead relied solely on isolated BP thresholds and BP goals to guide treatment initiation and intensity. In this review, we provide a rationale for incorporating global CVD risk assessment in BP treatment decision-making and propose a framework to guide its implementation in future CVD prevention guidelines.

Role of Global CVD Risk Assessment in CVD Prevention Guidelines

Epidemiological analyses have firmly established that CVD is a multifactorial condition and that modest increases of several CVD risk factors can often lead to greater overall risk than a severe elevation of a single risk factor. Therefore, multivariable risk prediction tools have been developed to estimate CVD risk from multiple risk factors, and guideline developers have advocated for their incorporation into clinical decision-making.

The notion of matching the intensity of risk factor management to the absolute risk of CVD has been proposed for decades. In the United States, this framework was first disseminated during the 27th Bethesda Conference in 1996 and was operationalized in the 2001 Third Adult Treatment Panel cholesterol guidelines. On the basis of the continuous association between cholesterol and vascular risk and the heterogeneity of this risk at any given cholesterol level based on associated risk factors, these guidelines recommended the use of a multivariable risk prediction assessment tool to guide cholesterol-lowering treatment. This paradigm has been embraced worldwide for cholesterol management and has even been used to guide aspirin management.

CVD Risk-Based Cholesterol Guidelines

In 2013, the American College of Cardiology and American Heart Association guidelines on cholesterol treatment further advanced this paradigm by eliminating the use of low-density lipoprotein cholesterol thresholds to guide statin initiation. Instead, these guidelines identified 4 statin benefit groups in which a net benefit from statin therapy had been observed in clinical trials of individuals with clinical atherosclerotic CVD, low-density lipoprotein cholesterol ≥190 mg/dL suggestive of familiar hypercholesterolemia, diabetes mellitus, or a 10-year predicted atherosclerotic CVD risk ≥7.5% based on a combination of CVD risk factors. The final group applied to the general adult population without prevalent disease and the 7.5% risk threshold identified a risk level where clinical trial evidence suggested net benefit from statin therapy. In addition to reaffirming the importance of risk stratification, these guidelines also emphasized the importance of shared decision-making between the clinician and patient to contextualize atherosclerotic CVD risk assessment with the patient’s potential for benefit or harm from treatment, individual factors (such as family history, subclinical disease markers, or long-term risk) that could up- or down-classify risk, and the patient’s values and preferences. This risk-based approach to CVD prevention has been shown to prevent more events, while requiring treatment of fewer individuals than previous guidelines that focused on single risk factor thresholds and goals. Moreover, large meta-analyses using individual participant data from randomized clinical trials have provided empirical support for risk-based approaches to cholesterol management.
Epidemiological Data Supportive of CVD Risk-Based BP Management

Driven by the specific inclusion criteria used in landmark clinical trials of BP-lowering therapies, management of elevated BP has traditionally been anchored to discrete BP levels used to define hypertension (BP ≥140/90 mm Hg). However, the notion that a single threshold might distinguish elevated BP from normotension has been challenged from the beginning.

MRFIT (the Multiple Risk Factor Intervention Trial), a primary prevention trial testing the effect of a multifactor intervention program on CHD mortality in men, was one of the first studies with sufficient power to demonstrate the risk for heart disease mortality associated with modest SBP and diastolic BP elevations. Data on 316,099 white men aged 35 to 57 years who were screened and examined as part of the study were followed for 12 years for cause-specific mortality. Analyses demonstrated a graded positive association of SBP and diastolic BP with vascular disease mortality associated with modest SBP and diastolic BP elevations.6 These data were later definitively confirmed by the Prospective Studies Collaboration, which included data from 61 observational studies with individual participant data of 1 million adults.21 These analyses also demonstrated the continuous, log-linear association of SBP and diastolic BP with vascular death. For every 20/10 mm Hg higher BP, there was an associated doubling of the risk for death from heart disease, stroke, or death from other vascular causes, a relationship that continued down to a BP of 115/75 mm Hg without evidence of a threshold.21

In addition to the continuous risk from elevated BP, observational studies have also demonstrated the marked variation in CVD risk at any given BP level based on the presence of associated risk factors. Among MRFIT screenees at the highest quintile of SBP (ie, SBP ≥142 mm Hg), age-adjusted heart disease death rates varied by nearly 6-fold among men based on smoking status and cholesterol level (62.6 per 10,000 person-years among smokers with the highest quintile of cholesterol level compared with 13.7 per 10,000 person-years among nonsmokers with the lowest quintile of cholesterol level).6 Similarly, data from the Framingham Heart Study demonstrate how the relationship between BP category and 10-year CHD risk can vary not just by BP level but also by the presence of additional CVD risk factors such as elevated total cholesterol, low high-density lipoprotein cholesterol, presence of diabetes mellitus, and presence of smoking.7 Thus, for a 60-year-old man with a SBP between 130 and 139 mm Hg or diastolic BP between 85 and 89 mm Hg, 10-year CHD risk could vary between 46% and 12% based on the associated risk factor burden (Figure 1).

The importance of accounting for the presence of additional CVD risk factors has particular relevance for BP given the well-documented risk factor clustering that is seen in hypertensive individuals. In the Framingham Heart Study, for example, >80% of hypertensive individuals had ≥1 coexisting risk factor, and 55% had ≥2 risk factors.22 Additional analyses from Framingham cross-classifying BP stages with risk categories used in the Sixth Report of the Joint National Committee demonstrated that only 2.4% of individuals with high–normal or hypertensive BPs were stratified to risk group A, the lowest risk group without any CVD risk factors or target organ damage (Table 1).23 Similarly, more recent analyses from the Kaiser Permanente managed care organization demonstrated that 56% of hypertensive patients had at least 1 additional risk factor such as diabetes mellitus, hyperlipidemia, or obesity.24 Further, cumulative medical care costs increased with each additional risk factor. Thus, these analyses highlight how frequently CVD risk factors travel with elevated BP and support the notion of adopting a multifactorial framework for guiding BP management.

Unaddressed CVD Risk in the Hypertension Paradigm

Clinical practice guidelines have broadly adopted the hypertension paradigm to guide BP-related treatment decisions. In
this paradigm, individuals who have hypertension (defined by SBP ≥140 mm Hg or diastolic BP ≥90 mm Hg) are eligible for risk-reducing therapies, whereas those with lower levels are not. However, the categorization of elevated BP into hypertension and normotension, without incorporation of coexisting CVD risk factors, can lead to substantial unaddressed CVD risk.

In 2008, Lawes et al estimated that 54% of stroke and 47% of ischemic heart disease worldwide were attributable to high BP (defined as SBP ≥115 mm Hg) but only half of this burden occurred in people meeting criteria for hypertension. Data from 6859 participants in the Framingham Heart Study who were free of hypertension and CVD also demonstrated CVD risk associated with high–normal BP (BP 130–139/80–85 mm Hg). Compared with participants with optimal BP (BP <120/80 mm Hg), participants with high–normal BP had a risk factor–adjusted hazard ratio for CVD of 1.6 (95% confidence interval, 1.1–2.2) in men and 2.5 (95% confidence interval, 1.6–4.1) in women. Moreover, 80% of participants with high–normal BP had at least 1 additional CVD risk factor.

More recent analyses among middle-aged participants from the Framingham Offspring and Atherosclerosis Risk in Communities studies demonstrate similar findings and suggest a potential role for multivariable risk assessment in identifying at-risk individuals. At 10 years of follow-up, approximately half of excess atherosclerotic CVD events attributable to nonoptimal SBP (defined as SBP ≥120 mm Hg) occurred at levels not currently eligible for BP-lowering treatment initiation or treatment intensification (Table 2). However, multivariable risk estimation with the American College of Cardiology/American Heart Association Pooled Cohort equations provided a strategy for identifying people likely to benefit from risk-reducing therapies across the full spectrum of SBP, particularly among those who were not already treated with BP-lowering medications (Figure 2). These findings have even greater relevance for future strategies to reduce BP-related disease with national trends from 2003 to 2012, demonstrating an increase in the prevalence of prehypertension from 27% to 33%.

Analyses From Clinical Trials Supportive of Risk-Based BP Lowering

Although epidemiological analyses have provided a rationale for adopting a risk-based framework to manage elevated BP, secondary analyses of BP-lowering clinical trials and prospective clinical trials have been instrumental in demonstrating the benefits of intensive BP-lowering therapy in high-risk groups.

The SHEP study (Systolic Hypertension in the Elderly Program) was one of the first studies to suggest a role for pretreatment risk stratification to maximize treatment benefit. In a post hoc analysis, Ferrucci et al used the American Heart Association Multiple Risk Factor Assessment equation to stratify 4189 SHEP participants without CVD into 4 risk quartiles. Relative risk reduction from stepped BP-lowering therapy with chlorthalidone was similar across

Table 1. Proportion of Adults in the Framingham Heart Study Classified Into Each JNC-VI Risk Group by Blood Pressure Stage

<table>
<thead>
<tr>
<th>Blood Pressure Stage</th>
<th>Risk Group A, n (%)</th>
<th>Risk Group B, n (%)</th>
<th>Risk Group C, n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High–normal (130–139/85–89 mm Hg)</td>
<td>23 (3.4)</td>
<td>441 (66.1)</td>
<td>203 (30.4)</td>
<td>667 (100)</td>
</tr>
<tr>
<td>Stage 1 (140–159/90–99 mm Hg)</td>
<td>24 (3.8)</td>
<td>410 (64.1)</td>
<td>206 (32.2)</td>
<td>640 (100)</td>
</tr>
<tr>
<td>Stages 2 and 3 (≥160/≥100 mm Hg or treated)</td>
<td>21 (1.4)</td>
<td>807 (54.3)</td>
<td>659 (44.3)</td>
<td>1487 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>68 (2.4)</td>
<td>1658 (59.3)</td>
<td>1068 (38.2)</td>
<td>2794 (100)</td>
</tr>
</tbody>
</table>

Risk groups as defined by Sixth Report of the Joint National Committee (JNC-VI): risk group A, no cardiovascular disease (CVD) risk factors, clinical CVD, or target organ damage; risk group B, at least 1 CVD risk factor (excluding diabetes mellitus); and risk group C, diabetes mellitus, CVD, or evidence of target organ damage. Data derived from Lloyd-Jones et al.

Table 2. Excess ASCVD Events at 10 Years by Baseline Systolic Blood Pressure Category

<table>
<thead>
<tr>
<th>Baseline SBP, mm Hg</th>
<th>ASCVD Events (n)</th>
<th>Expected ASCVD Events (n)</th>
<th>Excess ASCVD Events (n)</th>
<th>% of Excess ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated (n=14856)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;120</td>
<td>135</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>120–129</td>
<td>114</td>
<td>52</td>
<td>62</td>
<td>31.6</td>
</tr>
<tr>
<td>130–139</td>
<td>77</td>
<td>30</td>
<td>47</td>
<td>24.1</td>
</tr>
<tr>
<td>140–149</td>
<td>38</td>
<td>15</td>
<td>23</td>
<td>11.8</td>
</tr>
<tr>
<td>150–159</td>
<td>33</td>
<td>7</td>
<td>26</td>
<td>13.2</td>
</tr>
<tr>
<td>≥160</td>
<td>45</td>
<td>6</td>
<td>39</td>
<td>19.6</td>
</tr>
<tr>
<td>Total</td>
<td>442</td>
<td>110</td>
<td>197</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Treated (n=4042) |                  |                            |                         |                          |
| <120                | 59               | 20                         | 39                      | 16.9                    |
| 120–129             | 61               | 16                         | 45                      | 19.5                    |
| 130–139             | 43               | 12                         | 31                      | 13.4                    |
| 140–149             | 41               | 8                          | 33                      | 14.2                    |
| 150–159             | 35               | 5                          | 30                      | 13.1                    |
| ≥160                | 58               | 5                          | 53                      | 22.9                    |
| Total               | 297              | 67                         | 230                     | 100.0                   |

ASCVD event defined as nonfatal myocardial infarction, coronary heart disease death, nonfatal stroke, and fatal stroke. Excess ASCVD events are calculated as the difference between observed and expected ASCVD events, using the ASCVD event rate in the group with untreated SBP <120 mm Hg as the reference (Expected in stratum, n in stratum×event rate in untreated SBP <120 mm Hg. Excess, observed in stratum–expected in stratum). ASCVD indicates atherosclerotic cardiovascular disease; and SBP, systolic blood pressure. Reprinted from Karmali et al with permission of the publisher. Copyright © 2015, Wiley, Inc.
the 4 risk quartiles; however, incidence rates for CVD events were greater in each successive risk quartile, and consequently, numbers needed to treat for 4.5 years to prevent 1 CVD event were progressively smaller, decreasing from 160 to 100, to 48, and to 37. A principal limitation of this analysis, however, was that mean age among trial participants was 72 years, and average BP was 172/77 mm Hg, limiting the generalizability of these findings to the broader population.

To account for these limitations and extend the evidence base to lower-risk individuals with a broader range of BPs, the Blood Pressure Lowering Treatment Trialists’ Collaboration recently completed a meta-analysis of individual participant data from 51,917 participants from 11 randomized clinical trials who received active/more intensive BP-lowering treatment or placebo/less intensive treatment. Trials included those that used standard BP thresholds to determine study eligibility and trials such as the HOPE study (Heart Outcomes Prevention Evaluation) and the ADVANCE study (Action in Diabetes and Vascular Disease) that used high-risk status independent of specific BP entry criteria. This meta-analysis demonstrated that BP-lowering therapy provided similar relative risk reductions across patient groups with markedly different levels of baseline CVD risk but progressively greater absolute risk reductions at higher levels of baseline risk (Table 3). This same pattern was seen in a range of secondary analyses for specific CVD outcome subtypes after adjusting for differences in baseline and achieved BP levels. In other words, the Blood Pressure Lowering Treatment Trialists’ Collaboration meta-analysis provided empirical evidence that the absolute benefits achieved with BP-lowering therapy were driven by the combination of CVD risk factors determining risk of a CVD event rather than just the initial BP level in isolation. The clinical implications of these findings are demonstrated in Figure 3 and provide support for the notion that the most intensive BP-lowering therapies should be directed to those at highest CVD risk.

This principle was recently tested prospectively by the SPRINT (Systolic Blood Pressure Intervention Trial), which randomized 9361 high-risk, nondiabetic participants to intensive SBP reduction <120 mm Hg compared with conventional SBP reduction <140 mm Hg. For participants who were at high risk because of age ≥75 years, chronic kidney disease, clinical or subclinical CVD, or global 10-year CVD risk ≥15% by Framingham risk score, intensive SBP reduction of ≈15 mm Hg was associated with a 25% reduction in CVD events and a 27% reduction in all-cause mortality. This resulted in numbers needed to treat for 3.3 years to prevent 1 CVD event and 1 all-cause death of 61 and 90, respectively. Importantly, benefits of BP reduction were not observed in HOPE-3 trial (Heart Outcomes Evaluation-3), a clinical trial testing a fixed-dose combination therapy with candesartan and

### Table 3. Relative and Absolute Effects of Blood Pressure Reduction on CVD Events by Different Levels of CVD Risk

<table>
<thead>
<tr>
<th>5-Year CVD Risk</th>
<th>Risk Ratio (95% CI)</th>
<th>Risk Difference (95% CI)</th>
<th>CVD Events Prevented per 1000 Treated (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;11%</td>
<td>0.82 (0.73, 0.93)</td>
<td>−1.41 (−2.05, −0.77)</td>
<td>14 (8, 21)</td>
</tr>
<tr>
<td>11 to &lt;15%</td>
<td>0.85 (0.75, 0.96)</td>
<td>−1.95 (−3.09, −0.82)</td>
<td>20 (8, 31)</td>
</tr>
<tr>
<td>15 to &lt;21%</td>
<td>0.87 (0.78, 0.98)</td>
<td>−2.41 (−4.04, −0.77)</td>
<td>24 (8, 40)</td>
</tr>
<tr>
<td>≥21%</td>
<td>0.85 (0.76, 0.95)</td>
<td>−3.84 (−6.06, −1.61)</td>
<td>38 (16, 61)</td>
</tr>
<tr>
<td>P value</td>
<td>0.30</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

CVD events defined as myocardial infarction, stroke, heart failure, and CVD death. CI indicates confidence interval; and CVD, cardiovascular disease. Data derived from Sundström et al.
hydrochlorothiazide in 12,705 intermediate-risk participants (10-year CVD risk ≈10%) who achieved only a 6 mm Hg SBP reduction.33 Taken together with SPRINT, HOPE-3 highlights the need both for high CVD risk status and intensive SBP reduction to avoid CVD events.

Implications of a CVD Risk Reduction Treatment Paradigm

The potential merits of a risk-based paradigm for BP management have been demonstrated by several simulation studies and cost-effectiveness analyses.34-38 One such study proposed that use of risk prediction tools to guide risk factor management provided a mechanism for individualized guidelines that could improve outcomes while at the same time reducing healthcare costs.35

More recent modeling by Sussman et al37 directly compared a treat-to-target BP treatment approach with a multivariable risk-based strategy called a benefit-based tailored approach. In the treat-to-target approach, BP-lowering therapy was initiated and titrated toward a fixed BP target of 140/90 mm Hg (or 130/85 mm Hg for participants with diabetes mellitus). In contrast, for the benefit-based tailored approach, the Framingham risk score was used to estimate 10-year absolute risk of a CVD event, and expected net benefit from treatment was calculated using expected relative risk reductions and treatment harms from BP-lowering therapy (both obtained from randomized trial evidence). In Markov modeling of 5 years of treatment, the benefit-based tailored approach prevented 900,000 more CVD events, saved 2.8 million more quality-adjusted life-years and used 6% fewer medications compared with the treat-to-target approach in a nationally representative sample of American adults without prevalent CVD.37 Furthermore, among those individuals treated differently by each strategy, those treated by the benefit-based tailored approach had twice the benefit compared with the treat-to-target approach (saving 159 quality-adjusted life-years per 1000 treated versus 74 quality-adjusted life-years per 1000 treated).

Limitations of CVD Risk in BP Management

Any proposal for greater use of absolute CVD risk assessment in BP management must also account for potential limitations of this approach. First, in contrast to cholesterol levels where there are no clear health risks or symptoms from intensive low-density lipoprotein cholesterol reduction in higher-risk individuals, this is not the case with BP. Given the importance of BP for tissue perfusion and known risks of excessively low BPs such as symptomatic hypotension, treatment-related falls, and renal dysfunction, there is, not surprisingly, a floor to BP reduction in high-risk individuals, which may also vary from individual to individual. Second, given the strong effect of age on short-term CVD risk estimation, CVD prediction algorithms that use 5- or 10-year time horizons often shift treatment eligibility to elderly individuals at the expense of younger ones. Thus, younger adults with markedly elevated BPs may be unlikely to reach risk-based treatment thresholds in spite of higher lifetime risk for CVD related to their elevated BP. Conversely, older adults with relatively normal BP levels may reach treatment thresholds because of their age in spite of little BP-related CVD risk.39 The risks of modestly elevated BP levels during young adulthood have been shown in longitudinal cohort studies such as the Coronary Artery Risk Development in Young Adults. This study has shown greater amount of coronary artery calcification and worsened left ventricular mass and cardiac mechanical dysfunction in middle-aged adults who had higher cumulative exposure to nonoptimal BP levels during young adulthood.40-42 Third, although multiple analyses have demonstrated that the absolute risk reductions from
BP-lowering therapies may increase with increasing CVD risk, other meta-analyses have shown that residual risk (ie, risk of a vascular event that occurs in spite of BP-lowering treatment) also increases with baseline CVD risk. These findings highlight the limitations of BP-lowering therapies to completely reverse CVD risk that has been accrued over time and has led some to propose earlier treatment in low-risk individuals with mild BP elevations to maximize longer-term benefits from treatment.41,42

A Potential Framework for Future BP Treatment Guidelines

We propose that future clinical practice guidelines for BP management should move away from sole consideration of BP thresholds and goals to guide treatment decisions. Instead, future BP guidelines should adopt a more holistic view of elevated BP, one that accounts for the presence of concomitant CVD risk factors that are routinely measured in clinical practice. These multiple risk factors modify an individual’s absolute CVD risk and, therefore, his or her potential for treatment benefit. However, rather than adopting an entirely risk-based approach, we also think that there is a continued role for BP levels to guide treatment thresholds for individuals at low short-term risk and treatment floors for individuals at high short-term risk.

Long-term follow-up from epidemiological studies have consistently shown that many young and middle-aged adults with SBP levels ≥160 mm Hg may have low short-term CVD risk because of their younger age but high lifetime CVD risk during ≥20 years of follow-up.45,46 Such an observation provides guidance for a potential SBP treatment threshold, above which young individuals might receive BP-lowering treatment because of high lifetime CVD risk regardless of their low short-term risk status. Among these younger individuals, there is also a need for additional research to identify interventions that may blunt the vascular and myocardial alterations that occur from cumulative exposure to elevated BP, even in the normotensive range. Conversely, the known health risks from excessive BP reduction and limited clinical trial experience with SBPs <120 mm Hg provide guidance for a potential floor for SBP reduction.

Thus, for individuals with SBP levels in the broad middle range (ie, SBP 120–159 mm Hg), we think that future BP treatment guidelines might incorporate multivariable absolute CVD risk assessment and risk-based treatment thresholds that are defined by observed treatment benefits in clinical trials to guide BP-lowering treatment decisions. In a manner similar to the American College of Cardiology/American Heart Association cholesterol guidelines, these guidelines should also emphasize the importance of shared clinician–patient decision-making to contextualize a patient’s CVD risk information with expected benefit from BP-lowering therapies, potential for adverse effects, and individual preferences.47 In this paradigm, a clinician provides expert guidance and modifies the strength of recommendation based on a patient’s clinical profile, but treatment decisions for primary prevention are made jointly, respecting the autonomy of an informed patient to make a choice that aligns with his or her values and preferences.47

In an era of precision medicine, advances in functional genomics, transcriptomics, proteomics, and metabolomics provide novel opportunities to further characterize individuals beyond simple risk factor measurements.48 Although, at present, such data have lacked the statistical power to be incorporated into CVD risk prediction equations, they may hold promise to not only refine risk assessment but also personalize BP-lowering treatment strategies to maximize therapeutic response and minimize the potential for adverse effects.49 Importantly, risk-based treatment strategies using traditional risk factors and novel biomarkers at the individual level must be complemented by broad-based, public health strategies to promote primordial prevention of elevated BP to improve overall cardiovascular health in the population.50

Conclusions

In conclusion, the current hypertension paradigm does not account for the continuous risk associated with elevated BP or the multifactorial nature of CVD, the primary consequence of elevated BP. Adopting a risk-based framework to enrich BP-lowering treatment decisions would not only provide a strategy to account for these risk factors but also align BP treatment guidelines more closely with cholesterol treatment guidelines in primary prevention. In addition, using CVD risk assessment to guide treatment thresholds and intensity would help move BP management away from arbitrary cut-points to a personalized treatment strategy geared toward the CVD risk and potential for benefit of the individual.

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None.

References


Global Risk Assessment to Guide Blood Pressure Management in Cardiovascular Disease Prevention
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