What is the role, if any, for beta-blockers as initial therapy for uncomplicated hypertension?

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Purpose of review

Debate continues over the role of beta-blockers in the treatment of uncomplicated hypertension. Such debate has been fuelled mainly by the emerging deleterious effects of atenolol. The purpose of this review is to summarize the latest findings on vasodilating beta-blockers in terms of central effects on blood pressure (BP) and endothelial function and evidence that these agents address fundamental physiological and prognostically relevant mechanisms for the development and progression of hypertension.

Recent findings

Vasodilating beta-blockers preferentially improve central hemodynamics and reduce arterial stiffness compared with conventional beta-blockers, independent of their effects on BP reduction. Furthermore, vasodilating beta-blockers, particularly nebivolol, have positive effects on endothelial function, possibly by improving the balance between nitric oxide and peroxynitrite.

Summary

The majority of evidence suggesting that beta-blockade should not be used in uncomplicated hypertension comes from studies using atenolol. It would therefore be premature and unwise to eliminate all beta-blockers from the array of agents available to optimize BP control in patients with uncomplicated hypertension by extrapolating data based almost entirely on the conventional beta-blocker atenolol. Vasodilating beta-blockers have beneficial effects on central BP, arterial stiffening, and nitric oxide-dependent endothelial dysfunction that may contribute to their clinical benefits in patients with hypertension.

Keywords

beta-blockers, carvedilol, central blood pressure, endothelial dysfunction, hypertension, nebivolol, nitric oxide

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Introduction

Control of elevated blood pressure (BP) is crucial for optimally reducing coronary, cerebrovascular, and vascular events associated with hypertension, regardless of patient age [1]. Yet discourse and debate continue regarding the role of BP reduction *per se* versus the means used to achieve BP control (i.e., the antihypertensive therapy employed) in reducing this risk. Perhaps no class of agents has been reviewed more intensively in this regard than beta-blockers. Although data are strong and compelling for the use of beta-blockers for secondary cardiovascular disease (CVD) prevention in patients with a history of myocardial infarction and those with heart failure [2], early trials of beta-blockers in hypertension showed an apparent limited effect in primary prevention despite significant BP reductions [3,4].

It is debated whether beta-blockers should remain first-line agents in the treatment of uncomplicated hypertension [2,5,6]. A number of meta-analyses [7–9] of hypertension trials have demonstrated a relatively weak effect of beta-blockers on stroke reduction and no effect on coronary heart disease when compared with placebo or no treatment, and a clear increase in stroke risk and trend toward higher all-cause mortality compared with other antihypertensive drug classes. The risk of new-onset diabetes also appears to be more pronounced with beta-blockers compared with placebo or other classes of antihypertensive agents, particularly when used in combination with thiazide diuretics [10,11] and in patients 60 years of age and older [12,13].

The vast majority of studies [2,8,13] included in the meta-analyses that form the basis of the argument for excluding beta-blockers from first-line therapy employed atenolol as the reference drug. However, beta-blockers are heterogeneous, and individual agents vary widely in terms of parameters conventionally used to distinguish drugs within a class (e.g., pharmacokinetics, pharmacodynamics,

metabolism, and adverse events) [14]. Vasodilating beta-blockers, in particular, can be distinguished from other agents in this class on the basis of their hemodynamic profile and vascular effects [15–17]. Accumulating evidence indicates that the deleterious metabolic effects described above are not observed with newer vasodilating beta-blockers [10,12,13]. Furthermore, data on hypertension phenotypes that confer a particularly high CVD risk and the impact of reducing central pressures in modifying this risk also suggest a continued role for vasodilating beta-blockers in the treatment of uncomplicated hypertension. Similarly to certain dihydropyridine calcium channel blockers (CCBs) and inhibitors of the renin–angiotensin system (RAS) [18,19], vasodilating beta-blockers have beneficial effects on endothelial and smooth muscle cells, data that provide the most compelling evidence yet that these agents address fundamental and prognostically relevant pathophysiologic mechanisms for the development and progression of hypertension [15].

Rationale for using vasodilating beta-blockers in uncomplicated hypertension

The use of beta-blockers in the treatment of patients with hypertension is deeply rooted in our understanding of the role of the sympathetic nervous system in the pathophysiology of cardiovascular complications, including hypertension [20].

Hypertension phenotypes and cardiovascular disease risk

In addition to inhibiting sympathetic outflow, beta-blockers may exert their antihypertensive effects through suppressing renin release from the juxtaglomerular cells of the kidney and by reducing catecholamine release via presynaptic beta-receptor blockade [14,15,17]. Hemodynamically, conventional nonselective beta-blockers reduce cardiac output (*CO*) via a decrease in heart rate (HR); this is accompanied by an increase in systemic vascular resistance, likely through unopposed actions on $alpha_1$-receptors [14,17]. Similarly to RAS blockers and CCBs, however, newer vasodilating beta-blockers reduce peripheral vascular resistance (PVR), increase stroke volume, and maintain or increase *CO*, and therefore may be more physiologically appropriate as antihypertensive agents than conventional beta-blockers [15–17,21].

It is becoming increasingly appreciated that hypertension is a highly heterogeneous phenotype, and such phenotypic differences may have important implications for the understanding and treatment of this condition. In younger to middle-aged populations (i.e., <55 years), the predominant phenotype is essential hypertension, manifested as either isolated diastolic hypertension (IDH) or systolic–diastolic hypertension (SDH) [22], the hemodynamic hallmarks of which are increased PVR and reduced *CO* and stroke volume [22,23]. This phenotype is considered relatively straightforward to treat, with most drugs targeted at these basic hemodynamic abnormalities [24]. Of note, it can be argued that many African–American and elderly patients can be distinguished by the presence of low-renin hypertension [14,25]; therefore, these patients may be less responsive to RAS blockers and beta-blockers [14,24].

Basic hemodynamic principles drive the progression from essential hypertension in middle age to another distinct phenotype of hypertension – isolated systolic hypertension (ISH) – in older populations. Diastolic BP (DBP), for example, rises with increased peripheral arterial resistance but falls with increased stiffness and reduced compliance of the large conduit arteries [26,27]. Age-associated increases in arterial stiffness therefore appear to drive the dominant hemodynamic abnormality in older hypertensive patients; this overrides resistance, leading to a fall in DBP, a widening in pulse pressure (PP), and, ultimately, the development of ISH [28]. The difference in aortic stiffness across hypertension subtypes has recently been confirmed in a study [29] of patients undergoing dialysis; aortic stiffness was significantly higher in patients with SDH and ISH compared with those with IDH or normal BP; it was also significantly higher in patients with ISH compared with those with SDH.

Interestingly, data in adolescents and young adults (<30 years) have shown that ISH is twice as common as diastolic hypertension in this age group [22]. As with older patients, the ISH phenotype in younger patients has been shown to be due to increased *CO*, stroke volume, and arterial stiffness [22]. Whether or not ISH in young adults represents a hypertension phenotype distinct from ISH in elderly patients remains to be determined. Age-related mechanisms responsible for aortic stiffening in older populations, such as elastin degeneration, would seem unlikely as a cause of aortic stiffening in younger age groups [22]. It is possible that sympathetic nervous system hyperactivity might contribute to ISH in adolescence and young adulthood [22]. It is also possible that functional factors regulating aortic stiffness such as changes in the endothelium – derangements of which are also commonly associated with aging – may also underlie ISH in young adults.

Perhaps of greatest clinical significance, the risk of cardiovascular morbidity and mortality is increased in patients with ISH compared with those with essential hypertension [29]. Overall, systolic BP (SBP) is superior to DBP as a predictor of CVD morbidity and mortality after 50 years of age, and the greatest benefit of hypertension control is observed in older persons and in those with ISH, predominantly through a reduction in SBP [30,31]. The heightened CVD risk associated with ISH

likely extends to the phenomenon of ISH in younger patients, as data have shown a central SBP almost 22 mmHg higher in these patients compared with their normotensive counterparts [22].

The importance of central pressure

The clinical relevance of central (aortic and carotid) pressures is based on important physiologic and pathophysiologic distinctions between these large vessels and those in the periphery [32]. The aorta and carotid artery are large elastic-type arteries, whereas the brachial and radial arteries are smaller, muscular arteries. Afterload is determined by the aortic systolic pressure that the left ventricle (LV) encounters during systole, whereas coronary perfusion is determined by the aortic pressure during diastole [32]. Degenerative changes that characterize accelerated aging and hypertension alter the distending pressure of the central arteries to a much greater degree than they do peripheral arteries [32]. When the conduit arteries are healthy and compliant, the incident pressure wave generated by the LV and its reflection back from multiple resistance arteries (small muscular arteries and arterioles) in the periphery merge in the proximal aorta during diastole, thereby augmenting DBP and aiding coronary perfusion. When the conduit arteries stiffen (as with aging or endothelial dysfunction), pulse wave velocity (PWV) increases, accelerating the incident and reflected waves, which then merge during systole and thereby augment aortic systolic, rather than diastolic, pressure (and hence, PP) [33,34]. As a result, left ventricular afterload increases, and normal ventricular relaxation and coronary filling are compromised [32].

In addition to changes in the timing of the reflected waveforms, changes in the magnitude of the reflected wave and, thus, central pressures may result from changes in the proportion (or intensity) of the incident wave that is reflected, which in turn depends on the balance between vasoconstriction and vasodilatation in the peripheral circulation [32,35]. Decrease in PWV, wave reflection, and augmentation index (AIx) – a composite of wave reflection and systemic arterial stiffness that measures the percentage of the systolic pressure wave attributable to wave reflection – with antihypertensive therapy are all indicative of a decrease in arterial stiffness.

Another important consideration regarding the relationship between brachial and central aortic pressure is PP amplification. Typically, the diastolic and mean pressures change little across the arterial tree. However, SBP (and hence, PP) is amplified when moving from the aorta to the periphery, consequent to the progressive increase in arterial stiffness along the vascular tree as arterial and arteriolar vessels narrow [35]. PP is therefore higher in the peripheral arteries than in the aorta of healthy individuals, a mechanism that protects the heart from increased afterload [34,35]. In contrast to PWV and AIx, PP amplification declines with age, as a result of aortic stiffening. An increase in PP amplification in response to antihypertensive therapy is therefore associated with reduced central aortic PP and improved arterial function [35].

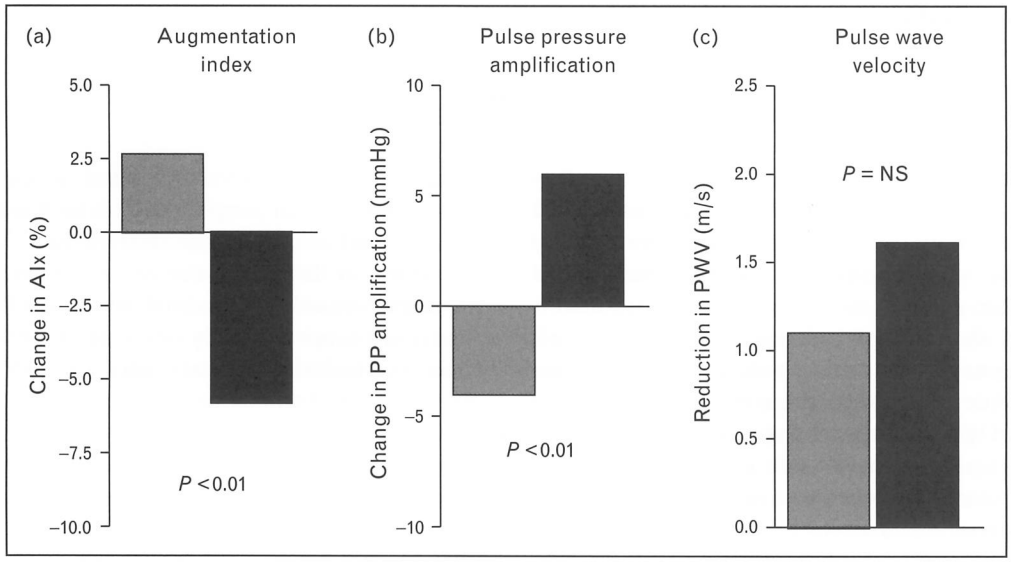
Together, these findings support the concept that increases in systolic and central aortic and carotid pressures are more sensitive than peripheral BP as biomarkers for macrovascular and microvascular dysfunction. This has been confirmed in data from the Strong Heart Study [36], a population-based longitudinal study of CVD in Native Americans (approximately one-half of whom had hypertension), which showed that central aortic PP more strongly predicted CVD outcomes than brachial pressures across a broad age range. These findings have been extended to include a geriatric population in a recent study [37] of unselected, community-dwelling geriatric normotensive and untreated hypertensive individuals, in which carotid SBP, but not brachial BP, was shown to be a strong independent predictor of CVD events, regardless of age or BP level. Other investigators have documented an overlap between brachial and central aortic pressures, such that patients classified as hypertensive on brachial BP measurement showed a large overlap, in terms of aortic pressure, with patients classified as borderline [38••]. These data suggest that central pressure cannot be reliably inferred from measurements of brachial pressure, and measuring central pressure may improve the identification and management of patients with elevated cardiovascular risk [38••].

It is also becoming apparent that agents that preferentially reduce central pressure over brachial pressure may have an advantage in reducing CVD outcomes in patients with hypertension. Evidence in this regard is provided by the Conduit Artery Function Evaluation (CAFE) substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which showed that central PP was significantly lower (by 3 mmHg) throughout the study with amlodipine-based therapy compared with atenolol-based therapy, despite a slightly lower brachial PP with amlodipine-based therapy [39]. Two other biomarkers showed important treatment differences; a significant increase in PP amplification was observed in patients treated with amlodipine-based therapy relative to atenolol-based therapy in CAFE; [39] likewise, a decrease in AIx was observed with amlodipine relative to atenolol [39,40•]. These findings potentially explain the results of ASCOT, which showed that amlodipine-based therapy prevented significantly more major cardiovascular events compared with atenolol-based therapy [4].

Beneficial impact of vasodilating beta-blockers on central pressure and arterial stiffness

Although antihypertensive agents can differ in their effects on larger artery stiffness and pulse wave reflection,

Figure 1 The effect of atenolol and nebivolol on arterial hemodynamics



Changes in (a) AIx, (b) PP amplification, and (c) PWV after 4 weeks of treatment with atenolol 50 mg (▭) or nebivolol 5 mg (■) (mean values ± SEM). AIx, augmentation index; PP, pulse pressure; PWV, pulse wave velocity. Adapted from Mahmud and Feely [35].

it is possible that some of these effects are related to the passive effect of lowered arterial BP [21], and, in regard to beta-blockers, reduction in sympathetic tone that may accompany systemic administration of these agents [40•]. Two recent studies provide preliminary data suggesting that a vasodilating beta-blocker can preferentially improve central hemodynamics and reduce arterial stiffness compared with a conventional beta-blocker in patients with essential hypertension [35] or ISH [40•], and these effects are independent of BP reduction. In both studies [35,40•], the vasodilating beta-blocker nebivolol was compared with atenolol in terms of peripheral and central hemodynamics, as well as determinants of arterial stiffness (PWV and AIx). In the study on patients with essential hypertension, brachial PP was reduced to a similar extent by both drugs; however, aortic PP fell by 16 mmHg with nebivolol and by 11 mmHg with atenolol ($P = 0.04$) [35]. Both agents also significantly reduced PWV (from 11.5 ± 0.5 to 9.8 ± 0.5 m/s with atenolol and from 11 ± 0.4 to 9.9 ± 0.5 m/s with nebivolol, both $P < 0.001$ from baseline); however, only nebivolol reduced AIx (from 35 ± 5 to $28 \pm 2\%$, $P < 0.05$), and this change remained significant when corrected for baseline BP (Fig. 1) [35]. In addition, although PP amplification decreased with atenolol therapy (from 10 ± 1 to 7 ± 1 mmHg, $P < 0.01$), it increased with nebivolol therapy (from 8 ± 1 to 14 ± 3 mmHg, $P < 0.01$).

Similarly to the report by Mahmud and Feely [35], the effects on peripheral hemodynamics (brachial systolic, diastolic, mean, and PPs) did not differ significantly between nebivolol and atenolol in the study of patients with ISH [40•]. However, aortic PP was 4 mmHg higher after treatment with atenolol than after nebivolol ($P = 0.02$) [40•]. This is similar to the differences in aortic PP between atenolol-based and amlodipine-based regimens reported by the CAFE investigators [39]. Although PWV also decreased to a similar extent following treatment with either beta-blocker (-1.0 ± 0.3 m/s for nebivolol and -1.2 ± 0.2 m/s for atenolol), AIx increased less with nebivolol than with atenolol (6 ± 1 versus $10 \pm 1\%$, respectively; $P = 0.04$), regardless of the reductions in HR that were seen with both drugs [40•]. Taken together, both studies [35,40•] suggest that the beneficial effects of nebivolol on central pressure may be related to the reductions in arterial wave reflection.

Potential mechanisms underlying central hemodynamic effects of vasodilating beta-blockers

A number of pathobiologic factors are associated with arterial stiffness and are believed to contribute to it, including endothelial dysfunction, altered vascular smooth muscle cell function, vascular inflammation, and genetic determinants [26]. The body of evidence that vasodilating beta-blockers have positive effects on endothelial function in animal models and in patients with hypertension is extensive [41–45] and continues to grow [46–48]. Both carvedilol and nebivolol (but not atenolol) have been shown to significantly increase flow-mediated dilation (FMD) in patients with

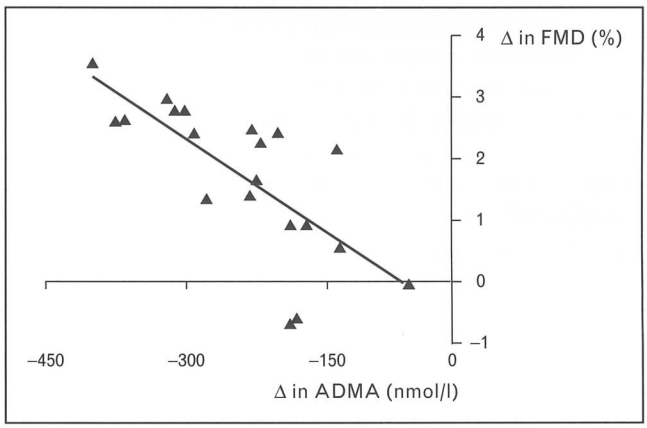
hypertension, independent of their effects on systemic BP [46–48]. In one study [49], treatment with nebivolol in 36 patients, most of whom were overweight or obese, was also found to reverse the ischemic effects produced by the cold pressor test. Moreover, only three patients (8.3%) still had abnormal results on the basis of myocardial perfusion single-photon emission computed tomography following 28 days of treatment with 5 mg/day nebivolol [49].

The improved endothelial activity and vascular function associated with vasodilating beta-blockers (particularly nebivolol) is believed to be mediated via nitric oxide-dependent pathways [19,48,50,51], specifically, an increase in nitric oxide bioavailability and a decrease in oxidative stress. Recent experimental data using a nanotechnological approach to simultaneously monitor nitric oxide and peroxynitrite ($ONOO^-$) in aortic endothelial cells from Wistar–Kyoto rats have confirmed that endothelial nitric oxide synthase (eNOS) uncoupling is observed with aging, manifested by a three-fold decrease in nitric oxide and a three-fold increase in $ONOO^-$ [52]. Increased eNOS uncoupling has also been observed in human umbilical vein endothelial cells from healthy African–Americans and Mexican–Americans, two ethnic groups suspected of having greater impairment in endothelial function compared with healthy white counterparts, effects that were reversed with nebivolol but not with atenolol [43,44]. In the recent study reported by Pasini *et al.* [48] evaluating the effects of nebivolol and atenolol on FMD in patients with hypertension, nebivolol, but not atenolol, was associated with a decrease in circulating levels of asymmetric dimethylarginine (ADMA), a naturally occurring amino acid that inhibits eNOS production. Of note, there was a significant and direct inverse correlation between changes in circulating ADMA levels and changes in FMD during nebivolol treatment ($r=0.62$, $P<0.01$; Fig. 2) [48]. The effects of nebivolol on ADMA are similar to those seen with a statin and an angiotensin-converting enzyme inhibitor in two separate studies [53,54].

Antioxidant effects of vasodilating beta-blockers have also been observed in cholesterol-fed rabbits, with nebivolol inducing a consistent increase of endothelial reactivity and aortic eNOS expression compared with control animals ($P<0.05$) and those receiving carvedilol ($P<0.05$) [55]. Moreover, the oxidative stress induced in human umbilical vein endothelial cells with oxidized low-density lipoprotein cholesterol was reversed by nebivolol, but not by atenolol, via downregulation of genes involved in the initiation and progression of atherosclerosis [56].

The limited data available on the endothelial effects of metoprolol are conflicting. One study [52] showed that, similarly to L-arginine, metoprolol (but not atenolol) increased the production rate and concentration of nitric oxide and increased the overall ratio of nitric oxide to $ONOO^-$. In another study [57], the downregulation of genes involved in inflammatory processes, oxidative stress, and smooth muscle cell proliferation in human coronary artery smooth muscle cells observed with nebivolol was not seen with metoprolol. In general, the limited experimental data on metoprolol do not appear to be supported by clinical data; a recent study [58] in mildly hypertensive patients showed no change in FMD or aortic PWV following 3 months of metoprolol treatment.

Figure 2 The effect of nebivolol on flow-mediated dilation and circulating asymmetric dimethylarginine levels



Correlation between changes in FMD and in circulating ADMA levels in nebivolol-treated patients ($r=0.62$, $P<0.01$). ADMA, asymmetric dimethylarginine; FMD, flow-mediated dilation. Adapted from Pasini *et al.* [48].

Clinical implications and future issues

Clinically, vasodilating beta-blockers have been proven extremely effective in lowering elevated BP [16,59], including in subgroups such as the elderly [60] and African–Americans [61], populations traditionally considered resistant to the effects of conventional beta-blockers, perhaps because of their low renin levels [14]. It is possible that the beneficial vasodilatory effects mediated via nitric oxide may contribute to the clinical findings with nebivolol and carvedilol. Improvements in endothelial effects have also been hypothesized to contribute to the apparently improved adverse event profile – particularly related to metabolic effects and sexual dysfunction – of vasodilating beta-blockers compared with older agents in this class [62–66]. For example, a recent study [67] showed that nebivolol, but not metoprolol, improved the endothelial function of the corpus cavernosum in apolipoprotein E-knockout mice.

Moreover, the beneficial effects of nebivolol and carvedilol on central BP suggest that these agents may serve an important role in the treatment of older patients with hypertension and patients with ISH, the latter of which is a significant proportion of the hypertensive population. Data from the third National Health and Nutrition Examination Survey (1988–1994) showed that three out of four adults with hypertension were 50 years of age or older, and approximately 80% of untreated and inadequately treated individuals with hypertension aged 50 years and older had ISH [68]. Furthermore, the high frequency of ISH in the hypertensive population makes ISH the most common hypertensive subtype in persons with metabolic syndrome [69]. Of note, a recent study [70] showed a mean reduction of 28 mmHg in SBP in patients with ISH treated with nebivolol.

Conclusion

Although expert groups, such as the American Heart Association's Council for High Blood Pressure Research and the National Institute for Clinical Excellence in England and Wales, no longer endorse beta-blockers as first-line treatment for uncomplicated hypertension [71,72], the 2007 guidelines from the European Society of Hypertension/European Society of Cardiology (ESH/ESC) emphasize that beta-blockers may still be considered an option for initial antihypertensive treatment strategies [10]. Moreover, although the ESH/ESC cautions against using conventional beta-blockers in hypertensive patients with multiple metabolic risk factors, including the metabolic syndrome and its major components, the group makes special note that this recommendation does not apply to vasodilating beta-blockers such as carvedilol and nebivolol [10]. Other experts caution against 'throwing the baby out with the bathwater' when it comes to vasodilating beta-blockers [9,14,20], a position that is supported by recent clinical and experimental data on these agents. Although there are relatively few clinical outcome data from primary prevention hypertension trials using beta-blockers other than atenolol, data in heart failure have shown beneficial effects of carvedilol and nebivolol on morbidity and mortality [73–76]. Although randomized, controlled trials comparing vasodilating beta-blockers with conventional beta-blockers and other antihypertensive agents in terms of hypertensive clinical end points might validate these findings, it is unlikely that such trials will be undertaken, as, on the basis of current evidence, it would be unethical to randomize hypertensive patients to atenolol. Although vasodilating beta-blockers are still 'on trial,' atenolol has already been tried and found guilty of ineffectiveness, and, at worst, harm. It is high time that clinicians and patients now pass the appropriate sentence.

References and recommended reading

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 383).

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