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INVITED REVIEW

Charting the perfect storm: emerging biological interfaces between stress and stroke

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Abstract A growing body of evidence demonstrates that psychosocial stress is an important and often underestimated risk factor for cardiovascular disease such as myocardial infarction and stroke. In this article, we map out major biological interfaces between stress, stress-related psychiatric disorders, and stroke, placing special emphasis on the fact that stress and psychiatric disorders may be both cause and consequence of cardiovascular disease. Apart from high-risk lifestyle habits such as smoking and lack of exercise, neuroendocrine dysregulation, alterations of the hemostatic system, increased oxidative stress, and inflammatory changes have been implicated in stress-related endothelial dysfunction. Heart rate provides another useful and easily available measure that reflects the complex interplay of vascular morbidity and psychological distress. Importantly, heart rate is emerging as a valuable predictor of stroke outcome and, possibly, even a target for therapeutic intervention. Furthermore, we review recent findings highlighting the role of FK506-binding protein 51 (FKBP5), a co-chaperone of the glucocorticoid receptor, and of perturbations in telomere maintenance, as potential mediators between stress and vascular morbidity. Finally, psychiatric sequelae of cardiovascular events such as post-stroke depression or posttraumatic stress disorder are highly prevalent and may, in turn, exert far-reaching effects on recovery and outcome, quality of life, recurrent ischemic events, medication adherence, and mortality.

Keywords Depression · FKBP5 · Heart rate · Psychosocial stress · Stroke · Telomerase

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Stress and cardiovascular disease (CVD)

Most soccer fans, kicking back in a comfortable recliner and looking forward to watching an exciting match, would be in stitches if they were told that, by watching soccer on television, they are indulging a perilous pastime. Notwithstanding, a Bavarian team of researchers found just that—that the incidence of cardiovascular events on days of suspenseful games during the 2006 FIFA World Cup in Munich was more than doubled [1]. The authors suggest that the thrill of an action-packed game triggered acute coronary syndromes, especially in men with pre-existing coronary heart disease (CHD) [1]. Whereas diabetes, obesity, hypertension, dyslipidemia, and smoking are nowadays firmly established as risk factors for myocardial infarction (MI) and stroke, the link between stress and cardiovascular disease (CVD) remains underrated by both clinicians and patients.

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CVD is the leading cause of death worldwide, accounting for nearly one-third of all deaths in the United States in 2013 [2]. CVD imposes a tremendous economic burden, with direct and indirect costs amounting to $316.6 billion annually in North America. Within CVD, stroke caused 6.5 million deaths globally in 2013, making it the second leading cause of death on the planet [2]. Considering the high prevalence of CVD alongside the attendant extraordinary human and economic costs, the identification and prevention of risk factors is an area of pressing clinical concern.

The Framingham cohort study was among the first to document the importance of psychosocial factors in the etiopathogenesis of coronary heart disease (CHD) [3], indicating that certain behavioral patterns (Framingham Type A behavior, e.g., impatience, hostility, and sense of time urgency) and anxiety are associated with a higher risk of CHD. Until fairly recently, research on the association between psychosocial risk factors and CVD mainly focused on the economically advanced countries in Europe and North America. However, the relationship between negative psychosocial factors and cardiovascular disease holds across a wide range of ethnic, sociodemographic, and cultural groups: The cross-national INTERHEART study, which investigated 11,119 patients from all continents, confirmed that psychosocial stress increases the risk of acute MI in all ethnic, age, and gender groups [4]. The authors report that severe global stress is an independent risk factor for cardiovascular disease, even after adjustment for potential confounders such as obesity, diabetes, and hypertension.

Similarly, in 2016, the INTERSTROKE study, which included 26,919 participants, demonstrated that chronic stress is a risk factor for stroke with a population attributable risk of 15.1% for ischemic stroke [5].

Although cerebrovascular and cardiovascular diseases share a variety of common etiological pathways, we still need to distinguish between cerebrovascular events and MI. To take a case in point, whereas increased arousal may precipitate MI and sudden cardiac death, e.g., by inducing rupture of coronary atherosclerotic plaques or takotsubo cardiomypathy [6], there is no evidence that acute arousal constitutes an independent risk factor for stroke. Both INTERHEART and INTERSTROKE operationalized 'stress' as a multidimensional summary construct which covers stress at work and at home, financial stress, as well as major adverse life events in the preceding year. Apart from these psychological stressors, the two studies also showed that self-reported clinical depression was associated with higher risk of stroke [5] and MI [4], a remarkable epidemiological finding that has since been corroborated by several studies and meta-analyses [7–9].

Besides increasing the risk of CVD, psychosocial stress and depression exert a strong negative influence on functional outcome and recovery after stroke or myocardial infarction, an important clinical reality which is, unfortunately, frequently lost on health-care professionals.

Biological effects of stress

As illustrated in Fig. 1, there are various mechanisms by which adverse psychosocial conditions may confer an elevated cardiovascular risk. Broadly speaking, the physiological response to a stressful stimulus rests on two systems: the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenal (HPA) axis. The sympathetic 'fight and flight' reaction entails an increased heart rate, vasoconstriction, bronchial dilation, and augmented muscular blood flow [10]. Activation of the HPA axis then induces a number of adaptive catabolic processes and suppresses both the reproductive and immune systems [10].

Although the two main stress systems play an indispensable role in protecting the organism from potential harm, their dysregulation and overactivation may also have deleterious effects. In particular, many psychiatric disorders are accompanied by neuroendocrine alterations: Major depression and anxiety disorders are associated with an exaggerated activation of the HPA axis [10], whereas patients with posttraumatic stress disorder (PTSD) typically display enhanced suppression of the negative glucocorticoid feedback loop and subsequent hypocortisolism [11]. Moreover, anxiety and excessively heightened arousal, common symptoms of psychiatric disorders, are associated with an increased tone of the SNS with overshooting catecholamine production, elevated heart rate (HR), and vasoconstriction.

Besides neuroendocrine alterations, behavioral factors play a fundamental role in the development of CVD: psychosocial stress and mental disorders favor high-risk lifestyle habits such as smoking, drinking, lack of exercise, and unhealthy eating [12–14], which, in turn, constitute risk factors for CVD. In addition, stress may cause a relevant hemostatic imbalance, as it promotes hypercoagulability in tandem with reducing fibrinolysis (for review, see [15]). An evolutionary explanation of increased clotting during acute emotional arousal could lie in the fact that, during much of human history, a moderate increase in coagulability in a sticky situation, so to speak, may have helped avert and minimize more serious harm. Most interestingly, the precise patterns of activation seem to differ between healthy subjects and CVD patients: In healthy controls, acute stress causes parallel stimulation of coagulation and fibrinolytic systems within a physiological range, whereas, in patients with CVD, the pro-coagulant reaction seems to
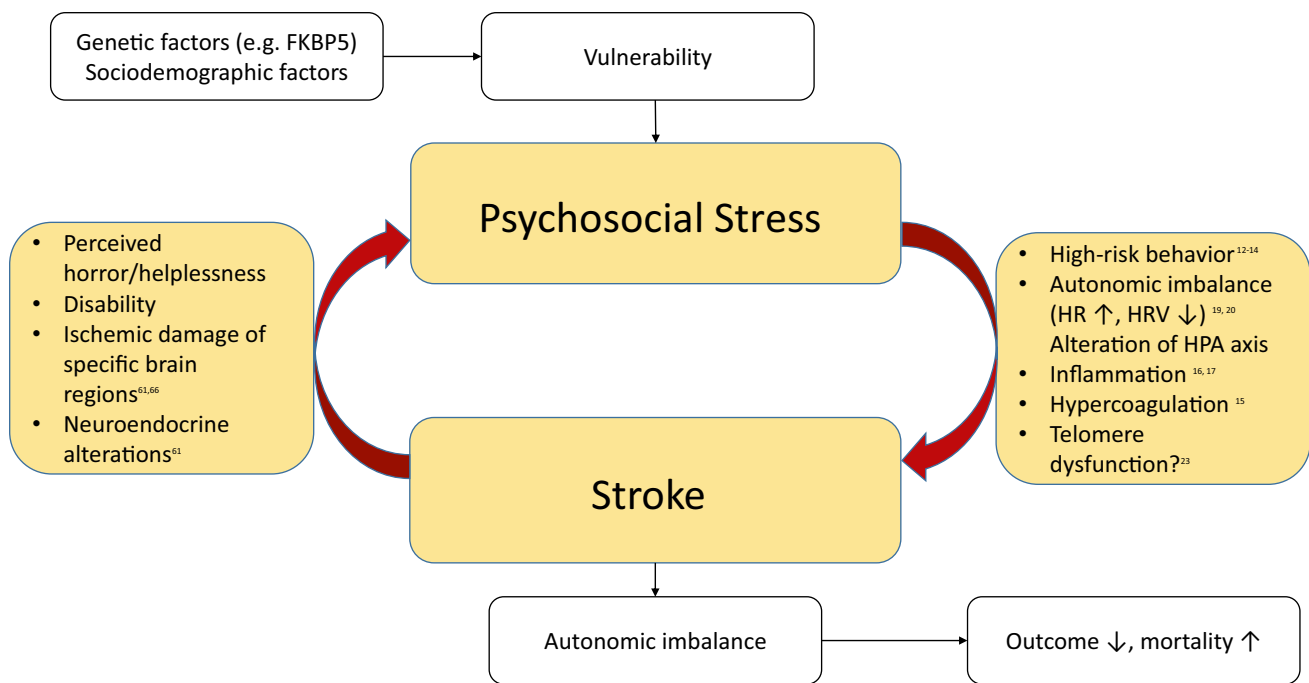
Fig. 1 Psychosocial stress and stroke—a bidirectional relationship. *FKBP5* FK506 binding protein 5, *HR* heart rate, *HRV* heart rate variability, *HPA axis* hypothalamic-pituitary-adrenal axis

predominate—possibly due to endothelial dysfunction and secondary insufficiency of fibrinolysis [15].

Systemic inflammatory and oxidative processes also contribute to stress-induced atherosclerosis. Psychosocial stress leads to increased plasma concentrations of cell adhesion factors and pro-inflammatory cytokines and lowers anti-inflammatory cytokines [16, 17], a mechanism that may promote CVD and immunological diseases. Acute inflammation may lead to a significant reduction of endothelium-dependent vasodilation, suggesting that endothelial dysfunction is one of the key mechanisms underlying stress-related cardiovascular risk [18]. Aside from the direct effects of inflammation on the vascular endothelium, centrally mediated changes in autonomic function may also be relevant [19, 20]. After induction of acute systemic inflammation by Typhim vaccination, an increase in the ratio of low-to-high frequency changes in heart rate (HR) variability was observed, suggesting an inflammatory modulation of the baroreflex with an increase in diastolic blood pressure [19].

Finally, psychosocial stress has been linked with elevated levels of reactive oxygen species (ROS), which may induce cellular injury, development of atherosclerotic plaques, and endothelial damage in the brain. Increased ROS concentrations have been demonstrated in humans after severe

life experiences such as childhood abuse, divorce, or war, as well as in rodent models including predator exposure or maternal separation [21].

Telomere biology

Telomeres are found on each end of eukaryotic chromosomes; they consist of repetitive hexamer DNA and multiple protein components, providing protection from degradation and maintaining chromosomal stability. Telomeres play a crucial rule in cellular senescence as they become shorter with each cell division, followed by a DNA damage response and, in the end, p53-mediated apoptosis [22]. The main function of the telomerase enzyme, a reverse transcriptase composed of a protein component (TERT) and an RNA component (TERC), is the elongation of telomeres and, hence, cellular regeneration and restoration.

Converging findings from animal and human studies suggest a close link between psychosocial stress and telomere biology. First, quite a number of studies have found that patients with psychiatric disorders such as major depression, 'chronic mood disorders' or bipolar disorder have shorter telomeres than healthy controls [23]. Similarly, prenatal and early life stress have been associated

with shortened telomeres [23]. It has, therefore, been hypothesized that psychiatric patients are prone to accelerated telomere attrition, ultimately translating into premature senescence. However, a crucial question for which evidence has so far remained inconclusive concerns the relationship between telomerase activity and psychosocial stress: While some authors assume that decreased telomerase activity underlies telomere shortening in psychiatric disease, other studies have reported an increase in telomerase activity, suggesting a compensatory function of this enzyme [23].

The effect of stress on telomere biology and vascular senescence deserves special consideration as a potential mediator of increased cardiovascular risk. Although telomerase activity and telomere length have already been studied quite thoroughly in leukocytes, comparable knowledge of telomere biology in endothelial cells remains scant. Human aortic endothelial cells show telomere shortening with each cell division in vitro. Moreover, forced expression of TERT extends endothelial lifespan and attenuates phenotypic characteristics of cellular senescence such as reduced expression of endothelial NO synthase or increased binding of monocytes to endothelial cells. Together, these findings strongly suggest a crucial role of telomeres and TERT in vascular aging [24]. It has also been shown that inhibition of telomerase leads to a reduction in neointimal growth, a finding which implies that telomerase is also involved in the metabolism of the vascular smooth muscle cell [24]. Finally, in-vivo studies of human aortic endothelial cells revealed a reduction of telomere length with age [25].

Recent findings from animal studies provide further insight into the biological functions of telomerase. Mice null for TERT display a normal phenotype in the first generation, but their telomeres shorten in each successive generation [26]. Moreover, the later generations show a shorter lifespan and a diminished capacity to react to stresses such as wound healing and hematopoietic ablation [26]. After occlusion of the middle cerebral artery (MCAo), TERT knockout mice exhibit significantly larger infarct volumes and worse functional outcome along with elevated production of pro-inflammatory factors and a higher vulnerability to oxidative stress than littermate controls [27].

Animal models of chronic stress and stroke

A variety of rodent stress models have been established which enable the assessment of the interplay between stress, depression, and vascular risk [28, 29]. The chronic stress model (CS) developed by Strekalova et al. [30] is a valid mouse model of anhedonia, one of the core symptoms of depression: Mice are exposed to a procedure consisting

of several mild stressors (tail suspension, restraint, and predator-based stress) for 28 days. It has been shown that, after CS, mice consume less sucrose (a behavioral correlate of anhedonia) and show more anxiety-like behaviors [30]. In an adaptation of the procedure, we investigated the effects of chronic stress on endothelial function and stroke [28, 31]. Mice subjected to the CS procedure showed significantly enlarged brain lesions and impaired endothelium-dependent vasorelaxation after MCAo. The vascular effects of CS were at least partially mediated by glucocorticoid signaling as demonstrated by the fact that they were reversed by administration of glucocorticoid receptor (GR) antagonist mifepristone [31]. Interestingly, selective heart rate reduction (HRR) via the If channel inhibitor ivabradine also attenuated the detrimental effects of CS on endothelial function and thereby reduced the size of experimental infarcts after MCAo [28]. Our results are further corroborated by studies of apolipoprotein E$^{-/-}$ mice showing decreased aortic atherosclerotic lesion size, reduction of oxidative stress, and improved endothelial function after ivabradine administration [32].

FK506-binding protein 51

To this day, it has largely remained a mystery why some individuals are more susceptible to the adverse effects of psychosocial stress than others. Researchers in the field are grappling with how to unravel the complex interplay between genetic and epigenetic modulation, sociodemographic and environmental risk factors (e.g., childhood abuse and neglect, social support), and neurochemical pathways [33]. Recently, the FK506-binding protein 51 (FKBP5), a co-chaperone of the glucocorticoid receptor (GR) complex, has come into focus as a critical intracellular regulator of the stress response [34]. FKBP5 modulates the reactivity of the GR by inhibiting ligand binding and translocation of the receptor complex to the nucleus. As activation of the GR leads to increased FKBP5 transcription, this creates an ultra-fast negative feedback loop [35]. Emerging evidence points to the importance of FKBP5 in the development of stress-related mental disorders such as depression, anxiety disorders, and PTSD [36, 37]. Although the precise mechanisms remain to be elucidated, it appears safe to assume that epigenetic modulation and polymorphisms of FKBP5 contribute to the neuroendocrine alterations of the HPA system, which have been identified as a hallmark feature of stress-related mental illness. For example, it has been demonstrated that polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes [36]. Moreover, several polymorphisms in the FKBP5 locus have been shown to significantly interact with the severity of child abuse to predict the development

of PTSD symptoms in adulthood [37]. Furthermore, neuroimaging has revealed structural changes in emotion-processing brain areas in healthy individuals with experience of childhood abuse carrying the risk allele of the FKBP5 gene [38], suggesting one possible anatomical pathway for the increased vulnerability of those subjects towards stress. Findings from animal studies also support an important role of the co-chaperone in the stress response: While FKBP5$^{-/-}$ mice do not differ from their littermates in behavior under basal conditions, they display increased resilience to stressful stimuli including more active coping behavior and reduced HPA axis reactivity [39]. In sum, these findings indicate that FKBP5 might be a very promising target for pharmacological manipulation in depression, PTSD, and anxiety disorders. Importantly, with regard to vascular disease, a study of healthy humans demonstrated interactions between adverse early life events and certain FKBP5 risk genotypes leading to an alteration of the heart rate response to mental stress [40], providing further evidence for the importance of gene–environment interactions in the pathogenesis of cardiovascular disease. Moreover, FKBP5 risk allele carriers exposed to a pre-learning stress condition display a significantly impaired performance in learning and memory compared to non-carriers [41], possibly due to a negative effect of certain FKBP5 polymorphisms on GR-mediated synaptic plasticity. The influence of FKBP5 polymorphisms on cognitive function seems to be even more pronounced in the elderly [42]. This finding is of particular interest for stroke patients, as learning deficits after stress exposure might have far-reaching consequences for neurological and psychological outcomes in the medium and long term.

Another important question concerns the possible interplay between FKBP5 polymorphisms and prior stressful/traumatic experiences in shaping the outcome of an incident stroke. Research into this issue is barely out of the gate, but may hold great promise in the related fields of personalized and preventive medicine.

Heart rate (HR), stroke risk, and stroke outcome

While age, stroke severity, and blood pressure are widely established as predictors of stroke mortality, the value of HR as a prognostic indicator has so far been underappreciated. HR is an easily accessible measure on clinical examination. A relationship between HR and cardiovascular morbidity has been demonstrated in different patient populations such as patients with severe hypertension, heart failure, coronary artery disease, and even in healthy men [43–45]. A number of studies [46–48] have investigated the link between HR and ischemic stroke: in acute stroke patients without atrial fibrillation, higher HR on admission is associated with higher mortality, heart failure, and higher degree of dependence after 90 days [46, 49]. Similarly, a post hoc analysis in the PERFORM study population found that in patients with a recent noncardioembolic ischemic cerebral event, elevated HR is a negative prognostic factor and is associated with higher risk for MI [46, 49]. Since a rapid HR reflects, at least to a certain extent, increased levels of psychological stress [10], HR may be considered a surrogate marker of distress. Interestingly, elevated HR was also found to correlate with cognitive decline and poor outcome in patients after ischemic stroke [47]. Conversely, in experimental rodents, HR reduction increases brain capillary density and protects chronically stressed animals from oxidative damage [28].

One important issue still under debate is whether elevated HR is only a prognostic indicator for cardiovascular risk or if it is also a risk factor in its own right [48]. An increased HR is common in pre-existing cardiac disease and can reflect low levels of physical fitness, which makes it difficult to determine 'cause and effect'. An increased HR spells increased oxygen consumption by the myocardium along with a decrease in coronary perfusion. Other mechanisms by which elevated HR may worsen cardiovascular outcome and increase mortality include arterial stiffness, disruption of atherosclerotic plaques, and cardiac arrhythmias. Initiated in 2014, the prospective SICFAIL cohort study aims to assess the prevalence of systolic dysfunction in stroke survivors, to identify key determinants of systolic dysfunction, and to chart its course after ischemic stroke [50].

Elevated HR variability and reduced HR variability indicate an imbalance of the autonomic nervous system—they can be understood as an exaggerated sympathetic response in conjunction with a suppression of vagal tone. Autonomic imbalance may have detrimental consequences including hypertension, increased blood clotting, and electrical cardiac instability [51]. Post-stroke patients, especially those who sustained a severe stroke [52], frequently display quite profound autonomic dysregulation [53], which has serious implications for life expectancy and quality of life. Apart from stroke severity, the exact site of the stroke in the brain is also of great importance for the development of autonomic imbalance. Specifically, studies in humans as well as in rodents have demonstrated the insula's critical role in the regulation of the autonomic nervous system [54–56]. Lesions of the insular cortex, especially in the right hemisphere, are strongly associated with excess sympathetic and reduced parasympathetic tone [55], resulting in reduced HR variability, cardiac arrhythmias, and, ultimately, increased mortality [56].

There is considerable heterogeneity between stroke units in terms of the extent of cardiac monitoring. The prospective HEBRAS study [57] aims to clarify the association of

stroke localization with autonomic dysbalance and cardiac dysfunction as well as the effects of reduced HR variability on long-term clinical outcomes. In patients with stable angina, HR reduction induced by ivabradine combined with beta-blockers was correlated with improved quality of life and a reduced number of angina attacks and nitrate consumption, suggesting that selective HR reduction may also be a promising new strategy in the treatment of stroke patients [58]. As we have described above, this approach is also supported by experimental research demonstrating that heart rate reduction improves aortic compliance in apolipoprotein E-deficient mice [28, 59] and protects chronically stressed animals from cerebral ischemia by improving endothelial function [28, 59].

Psychiatric sequelae of stroke

Mood disorders and psychological distress are not only risk factors for CVD, they are also among the most common sequelae of brain ischemia (see Fig. 1). Post-stroke depression (PSD) occurs in approximately one-third of stroke survivors [60]. PSD is of enormous clinical significance as it is strongly associated with increased morbidity, mortality, and poorer functional outcome [61–63]. Far less well known is the disease entity of stroke-induced PTSD. However, a recent meta-analysis found that a staggering 23% of stroke and TIA patients show PTSD symptoms during the first year after the event [64]. Typically, patients suffering from PTSD present with symptoms of avoidance and intrusion, as well as alterations in arousal, mood, and cognition that last for at least 1 month. Similar to PSD, stroke-induced PTSD is associated with impaired functional outcome, poor medication adherence, recurrent stroke, and higher mortality [64, 65], which is why screening stroke patients for psychiatric symptoms should be an integral part of the diagnostic work-up.

Stroke is a highly disabling, potentially life-threatening illness that may provoke intense feelings of anxiety and fear. Unsurprisingly, stroke is frequently followed by long-lasting mental distress [60–62]. Moreover, ischemic damage of specific brain regions and stroke-related neuroendocrine alterations have also been causally implicated in the development of psychiatric morbidity after stroke [66]. Research conducted in experimental animals is beginning to further delineate the etiological roles of particular pathophysiological mechanisms triggered by brain ischemia such as neuroinflammation, disturbed cellular plasticity, neuroendocrine dysregulation, and neurodegeneration [66]. Recent work has especially highlighted the significance of delayed neurodegeneration [67]. In a model of mild transient brain ischemia, we found that delayed degeneration of dopaminergic neurons in the midbrain was associated with depressive-like behaviors [68]. Moreover, antidepressant treatment with a selective serotonin reuptake inhibitor (SSRI) initiated as late as 7 days after MCAo at least partly prevented degeneration of dopaminergic midbrain neurons [68]. These experimental findings dovetail with an emerging clinical literature suggesting that SSRI promote recovery after stroke [69].

Conclusion

Substantial clinical and experimental evidence has accrued to indicate that psychosocial stress and mental disorders raise the risk for CVD. High-risk behaviors, neuroendocrine alterations, inflammatory changes, and oxidative stress are some of the underlying pathophysiological pathways mediating stress-induced endothelial dysfunction. Molecular factors such as the FKBP5 gene have been identified as critical modulators of the stress response. Moreover, exciting findings from human and animal studies have firmly linked mood disorders and psychological distress with perturbations in telomere biology and, thus, with cellular senescence. However, further studies are indispensable to bridge the gap between psychiatric research into gene–environment interactions and vascular outcomes after complex events such as stroke or MI.

HR is another parameter that reflects the intertwined effects of vascular morbidity and psychological distress. HR is emerging as a valuable predictor of stroke outcome and, possibly, a target for therapeutic intervention. In this article, our aim was to review major biological interfaces between stress and stroke, placing special emphasis on the bidirectionality of the relationship between these two. Comorbid mental disorders in stroke survivors may have far-reaching effects on recovery and outcome, including quality of life, recurrent ischemic events, medication adherence, and mortality. It would, therefore, be hard to overemphasize the importance of psychosocial factors in the prevention, treatment, and follow-up of patients with vascular disease.

Compliance with ethical standards

Ethics approval and consent to participate   Not applicable.

Conflict of interest   The author(s) declare that they have no competing interests.

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