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EDITORIAL

The hostile heart: anger as a trigger for acute cardiovascular events

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This editorial refers to 'Outbursts of anger as a trigger of acute cardiovascular events: a systematic review andmeta-analysis*†, by E. Mostofsky *et al.*, on page 1404

The link between anger and adverse cardiovascular events is well ingrained in both patients' and clinicians' minds. Mediated through increases in circulating catecholamines, increased myocardial oxygen demand, coronary vasospasm, and increased platelet aggregability, anger can cause transient ischaemia, disruption of vulnerable plaques, and increased thrombotic potential. These changes can then result in myocardial or cerebral ischaemia or malignant arrhythmias.[1] Multiple studies have shown that acute mental stress (in a laboratory setting) can provoke ischaemia of similar or greater severity and extent to exercise in 40–70% of patients with coronary artery disease,[2,3] and this ischaemia increases the long-term risk of fatal and non-fatal cardiac events.[4,5] In addition, T-wave alternans induced by mental stress in a laboratory has been shown to predict future ventricular arrhythmias in patients with implantable defibrillators.[6]

While the long-term link between chronic mental stress, anxiety, depression, and hostility with adverse cardiovascular events has been well established, it has been more difficult to determine the short-term risk of an acute outburst of anger. Ideally, understanding this risk would require large, prospective epidemiological studies that track outbursts of anger and incidence and timing of cardiovascular events. Alternatively, studies have tried to account for this by performing case-crossover designs, which use each patient as his or her own control and track the episodes of anger over a defined period of time and the temporal association of the episodes with the cardiovascular event. In general, these studies have consistently found an increased risk of acute coronary syndrome, stroke, and malignant arrhythmia after an acute anger episode. While many of these studies have been rather small, involving ~200–300 patients, a recent study of nearly 4000 patients with myocardial infarction (MI) demonstrated a 2.4-fold increased risk of MI within 2 h of an outburst of anger, with a stronger effect with increasing anger intensities.[7]

Mostofsky and colleagues now further this work by performing a meta-analysis of case-crossover studies to try to summarize the available evidence regarding the short-term risk of anger and estimate this risk in regard to various adverse cardiovascular events.[8] After an extensive literature review, including meeting abstracts and contacting investigators for unpublished data, the authors identified just nine studies that looked at the effect of anger on four outcomes: MI, ischaemic stroke, ruptured aneurysm, and ventricular arrhythmias. They found consistent and significant associations between anger and increased cardiovascular events within 2 h of the outburst.

There are several limitations to the analyses that the authors acknowledge. The small number of available studies to include in the meta-analysis and their significant heterogeneity speaks to a paucity of overall evidence in this area and substantially complicates the interpretation of their pooled estimates. In addition, given the relatively consistent findings across studies and the difficulty in combining their results using meta-analytic techniques, it is unclear whether combining studies that used such disparate methods provides incrementally more additional information than the individual studies alone. For example, only in the setting of acute myocardial ischaemia were there >2 studies to examine. As such, this manuscript functions far more effectively as a systematic review, as opposed to providing reliable pooled estimates of risk.

Those limitations aside, as a systematic review, the manuscript highlights important, consistent findings of an increased risk of diverse cardiovascular events after an acute outburst of anger. Given the known physiological effects of acute (and chronic) anger, these results are not surprising. The remaining question in all of these studies, however, is how to prevent these dangerous anger episodes. While the authors suggest that the use of 'beta-blockers to break the link between anger outbursts and cardiovascular events' may be reasonable, a recent analysis from the multinational REACH registry demonstrated no effect of beta-blockers on cardiovascular death, non-fatal MI, or non-fatal stroke among either patients with stable coronary artery disease or those at high-risk for developing MI.[9] Of course, the REACH study was unable to assess the

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prevalence of anger prior to the observed cardiovascular events, and thus the benefit of targeting beta-blockers to patients at risk for anger outbursts remains untested and uncertain. Other suggested treatments that might also target mental stress, such as selective serotonin release inhibitors, have also had disappointing results in reducing cardiovascular mortality after MI.[10,11]

So what might be the next steps to explore in this area? The natural extension of a study such as this is to test an intervention that specifically targets the factor that is associated with the adverse outcome. However, in the setting of psychological distress and its effect on cardiovascular outcomes, this may not be the best strategy. For example, despite overwhelming evidence of depressive symptoms after MI being associated with increased cardiovascular mortality[12] and worse health status,[13] screening for and treating depressive symptoms after an MI has failed to reduce this excess risk.[10,11] One possibility for the divergence between 'risk factor' treatment and improved outcomes could be the great degree of overlap between a multitude of psychological stressors (e.g. anger, anxiety,[14] depression,[12] or chronic stress[15]) that have been shown to be associated with increased adverse cardiovascular events, often independently of each other. In addition, these psychological stressors are often associated with hazardous behaviours, such as smoking, lack of exercise, obesity, and medication non-adherence, which are often not addressed with narrowly targeted treatment strategies.

As such, patients with any of these identified psychological risk factors may benefit from a multimodal psychological evaluation and intervention. Expanding psychosocial interventions to address factors such as anger management, coping skills, chronic stress, anxiety, and other psychosocial impairments in a comprehensive manner may improve cardiovascular outcomes in vulnerable patients. For example, in a study of 237 Swedish women with coronary disease, patients randomized to a group-based psychosocial intervention designed to improve coping skills, reduce stress, and improve social support had significantly reduced mortality as compared with patients who received usual care.[16] While such interventions are not nearly as simple to implement as a beta-blocker or other medication, the impact on outcomes may be more profound.

Based on the multiple prior studies and the current one from Mostofsky *et al.*, the impact of psychological distress, whether in the form of chronic stress[15] and anxiety[16] or acute outbursts of anger,[8] on the risk of adverse cardiovascular events is substantial. However, how to move forward in reducing the burden of these risk factors in patients and, hopefully, its impact on cardiovascular health is still in question. Given the lessons we have learned from trying to treat depression after MI, treating anger in isolation is unlikely to be impactful. Instead, a broader and more comprehensive approach to treating acute and chronic mental stress, and its associated psychological stressors, is likely to be needed to heal a hostile heart.

Conflict of interest: none declared.

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