The aim of this article is to provide an overview on depression as a risk factor for the onset and follow-up of cardiovascular disease (CVD). In brief, the current state of psychobiological mechanisms bridging the gap between affective states and somatic consequences are presented. Four meta-analyses dealing with depression as a CVD risk factor in apparently healthy populations with >100,000 participants included, extracted an adjusted effect estimator of 1.60-1.90. Depressed subjects present with an unhealthier lifestyle (nutrition, smoking, physical activity). Three major psychobiological pathways directly acting on the circulatory system are under discussion: (1) hyperregulation of the autonomic nervous system (e.g., increased mean heart rate, increased heart rate responses, impaired heart rate variability), (2) overshooting stress responses of the endocrine system with impaired feedback mechanisms (e.g., for cortisol release), and (3) the immune system with dysregulated release of acute phase proteins and proinflammatory cytokines, all involved in a bidirectional crosstalk with the patient's affective state and leading to platelet activation and flow mediated endothelial (dys-)function. Nonadherence and adverse side effects of medications also contribute to the lethal properties of depression in CVD.