Preventing Cardiovascular Complications of Acute Infection
A Missed Opportunity?

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The connections between infection and cardiovascular disease have been postulated for at least 125 years, when Gilbert and Lion observed that acute infection with the typhoid bacillus resulted in atherosclerotic changes to the rabbit aorta. In the past few decades, much work has investigated the role for chronic viral and atypical bacterial infections in the progression of atherosclerosis; however, trials of antibiotics as secondary prevention for cardiovascular events have been disappointing. More recently, epidemiological studies demonstrated an association between acute infection and cardiovascular events, such as acute myocardial infarction, stroke, cardiomyopathy, or atrial fibrillation. Compared with both hospitalized patients (1.7%) and a population-based cohort (0.2%). The timeframe for increased stroke and myocardial infarction risk was mostly confined to the duration of the bacteremia hospitalization; risks declined precipitously after 30 days. Results were robust to multiple sensitivity analyses and adjustment for comorbidities.

Given that bacteremia and sepsis affected 1 million hospitalized patients in the United States in 2011, if the results of Dalager-Pedersen et al are accurate and generalizable, it is likely that 30,000 to 40,000 new strokes or myocardial infarctions occur after bacteremia each year in the United States.

What does the study by Dalager-Pedersen et al add to the literature? The authors were able to microbiologically confirm onset of bacteremia and validate temporality between infection and cardiovascular events, attenuating the effect of potential misclassification of cardiovascular events as infections. The difficulty of discerning between infection and cardiovascular disease on initial clinical evaluation is perhaps underappreciated; recent evidence suggests that 1 in 3 patients hospitalized with acute decompensated heart failure are initially treated with antibiotics. The authors linked multiple population-based databases with high levels of granularity—including access to comorbidities and medications—that allowed matching and adjustment for multiple potential founders of the association between infection and cardiovascular disease.

In addition, Dalager-Pedersen et al obtained data regarding pathogens and biomarkers of inflammation (eg, C-reactive protein, leukocyte count) to perform exploratory analyses of potential mechanisms. Supporting an “inflammation hypothesis,” the incidence of myocardial infarction and stroke appeared greater among bacteremic patients with higher leukocyte counts and C-reactive protein levels. The “dose effect” associations between markers of inflammation and cardiovascular events were not obvious when bacteremic patients were compared with hospitalized controls, who may have also had C-reactive protein and leukocyte elevations. However, the increased risk of myocardial infarction and stroke after bacteremia compared with other hospitalized patients suggests that “being sick” in general was not the only mechanism for increased risk.

The study by Dalager-Pedersen et al also has significant limitations. The study outcomes of myocardial infarction...
and stroke were identified using ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems) codes, which may be subject to misclassification bias. Previous studies showed that positive predictive values of ICD-10 codes for stroke (76% to 87%)11 and myocardial infarction (82%)12 in the Danish National Registry are fairly accurate in general. However, if differential misclassification bias occurred, in which patients with bacteremia were more likely to be recognized with stroke or myocardial infarction than the controls because of closer monitoring, then associations between bacteremia and stroke or myocardial infarction may be overestimated.

The potentially inflated classification of myocardial infarction diagnoses after bacteremia deserves additional discussion. Troponin elevations are observed in approximately half of patients with bacteremia or sepsis.13 However, an acute coronary artery thrombotic plaque rupture mechanism producing myocardial infarction (Type I Consensus definition)14 is probably the exception rather than the rule for producing troponin elevations during acute infections.15 Myocardial supply–demand mismatch (Type II Consensus definition14) is more likely to be the prevailing mechanism in patients with acute infection, although other reasons for troponin elevation during infection may include direct myocardial toxicity from endotoxin or cytokines, septic cardiomyopathy, bacterial myocarditis, or acute renal failure.15 We do not have information from Dalager-Pedersen et al as to how myocardial infarction diagnoses were determined or granular data regarding timing of the events. However, 2 factors make diagnosis of myocardial infarction solely from mild troponin elevations during bacteremia less likely. First, the incidence of “myocardial infarction” ICD-10 codes during bacteremia in the present study (1.7%) was almost 30-fold lower than the previously reported incidence of troponin elevations during bacteremia.13 Second, the incidence of myocardial infarction diagnoses did not substantially increase after introduction of the troponin assay into clinical practice. Interestingly, the risk of an acute ischemic stroke diagnosis after bacteremia was greater than the risk for a diagnosis of myocardial infarction. Concerns regarding accuracy of stroke diagnosis during infection are potentially as important as myocardial infarction diagnosis; acute delirium during infection can mimic stroke.16

Many studies have now shown increased risk for myocardial injury or stroke during, or soon after, acute infection. Future studies should now focus on investigating questions that will more specifically inform our understanding of the mechanisms linking acute infection to cardiovascular disease. For example, what proportion of patients with sepsis have ischemic electrocardiographic changes combined with elevated troponins? What is the distribution of peak troponin levels after infection? How many patients undergo diagnostic angiography for suspected acute myocardial infarction within 30 days after infection, and what are the findings? Does the timing of presentation of the cardiovascular event relative to the acute infection inform specific mechanisms of myocardial injury? Is the radiographic distribution of stroke after infection more consistent with watershed infarcts during episodes of hypotension or embolic infarcts related to atrial fibrillation?20 To what extent is risk for poor outcomes after sepsis attributable to cardiovascular complications, as opposed to cardiovascular complications being merely a marker of more severe infection?
Because of a lack of understanding of prevailing mechanisms of cardiovascular complications after acute infection, optimal treatment strategies are currently unclear. Evidence supports a strong association between influenza vaccination and cardiovascular risk reduction. Increased efforts should be made to improve suboptimal vaccination rates among patients with cardiovascular disease.\(^1\) Early, goal-directed therapy of severe sepsis has been shown to reduce sudden cardiovascular collapse, yet its adoption into practice is unclear.\(^2\) Results of recent studies also suggest that aspirin,\(^3\) β-blockers,\(^4\) or statins\(^5\) are associated with improved outcomes during sepsis. Additional mechanistic studies and large randomized trials would be required to assess whether antiplatelet, β-blocker, or statin therapies might result in lower cardiovascular complications and possibly better outcomes after acute infection. A conceptual model demonstrating how acute infection may result in cardiovascular complications and potential future directions investgating strategies that may reduce the risk of cardiovascular complications after acute infection are shown in the Figure.

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None.

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