Diabetes mellitus and insulin therapy in infective endocarditis

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This editorial refers to 'Diabetes mellitus and infective endocarditis: the insulin factor in patient morbidity and mortality' by X. Duval et al., on page 59

Infective endocarditis (IE) is an uncommon disease but is associated with substantial morbidity and mortality. In the contemporary era, despite advancements in diagnosis and both antimicrobial and surgical therapies, IE is associated with an in-hospital mortality rate of nearly 20%.1,2 Given this high mortality, numerous studies have investigated clinical characteristics of IE that are associated with poor outcome. On the basis of such observational studies, current consensus guidelines for the evaluation and treatment of IE3,4 outline complications of IE that are indications for cardiac surgery in active IE.

In addition to describing prognostic complications of IE, observational studies have identified demographic, echocardiographic, and microbiologic characteristics associated with poorer outcome.1,2,5 The role of diabetes mellitus (DM) in the outcome of IE has been previously investigated. In a study of 267 patients with possible or definite IE including 88 (33%) with DM, Chu et al.1 found that DM was a strong, independent early predictor of in-hospital mortality. Recently, an analysis of the large, multicentre International Collaboration on Endocarditis (ICE) Merged Database found that DM patients with IE had an in-hospital mortality rate of 30.3% compared with 18.6% for non-DM patients, and confirmed that DM was independently associated with in-hospital mortality.2 However, no statistically significant differences in non-fatal complications of IE were noted between DM and non-DM patients.

The present study by Duval et al.6 evaluated the effect of therapy utilized for DM on outcome of IE in a prospective, population-based, observational study in France. Among 559 patients with definite IE by Duke criteria between 1998–2000, 75 (13%) of the cohort had DM based on the patients’ medical history, including 22 patients requiring insulin therapy and 53 patients receiving oral agents for the DM management. Patients receiving insulin therapy at the time of admission were found to have significantly higher in-hospital mortality (50%) than patients treated with oral DM medications (19%) or non-DM patients (15%). In multivariate analysis, insulin therapy for DM was the strongest predictor of mortality (OR 4.69, 95% CI 1.77–12.44).

The finding that a specific therapy—in this case, insulin therapy—is associated with an outcome in an observational study challenges one to consider whether the therapy itself was associated with the endpoint or whether it acted as a surrogate for other characteristics associated with outcome. It is very unlikely that insulin therapy itself caused the higher mortality rate in IE. Since the landmark Diabetes Control and Complications Trial (DCCT) in 1993,7 intensive glycemic control with insulin therapy has been recognized and well accepted as beneficial for reducing end-organ, including cardiovascular, complications of DM. In addition, insulin therapy has been studied in two recent, randomized trials of patients predominantly undergoing cardiac surgery and has been found to significantly reduce infectious complications compared with conventional therapy. Van den Berghe et al.8 randomized 1548 patients in intensive care settings, including only 13% with a history of DM and 4% previously treated with insulin, to insulin infusion or conventional therapy. Insulin therapy reduced mortality during intensive care from 8.0 to 4.6%, with the major survival benefit among patients with a proven septic focus.8 Furthermore, the incidence of sepsicaemia was significantly reduced by insulin treatment from 7.8 to 4.2%.8 Lazar et al.9 randomized 141 DM patients undergoing coronary artery bypass surgery to insulin infusion (as a part of glucose–insulin–potassium, or GIK solution) or conventional subcutaneous insulin therapy. The majority of these patients were treated with oral medications for DM before surgery. Although no patients died during the 30-day peri-operative period, GIK therapy was associated with lower rates of post-operative infection (0 vs. 13%, P = 0.010) and lower rates of recurrent ischaemia and mortality in 2-year follow-up.9 As a result of this latter study, intensive insulin therapy is now widely utilized in the treatment of cardiac surgery patients with DM.

Rather than the cause of higher mortality in IE, insulin treatment of DM appears to be a host factor associated with worse outcome. The higher prevalence of end-organ complications of DM (coronary artery disease, heart failure, and renal failure) in the insulin therapy group was significant co-morbid illnesses and unfavourable prognostic
factors prior to the diagnosis of IE. The adverse effect of co-morbid conditions on 6-month mortality in IE has been recently reported.\(^5\) Similarly, these co-morbid conditions may reflect more advanced acute physiology at presentation that has been found to be independently associated with mortality in IE.\(^1\) Insulin-treated DM was also associated with a higher prevalence of S. aureus infection, and each of these variables was predictive of mortality in multivariable analysis. Complications of IE, including cardiac abscess, valvular regurgitation, advanced heart failure, and embolic events, as well as the rate of cardiac surgery, were statistically similar across the three sub-groups of patients, but a trend towards septic shock occurring more commonly in the insulin-treated DM patients was noted.

Based on these results, should patients with DM and IE or other serious infection be treated more aggressively? And if so, what other intervention should be used? The greater prevalence of end-organ complications in the insulin-treated group suggests that long-term glycaemic control was worse in these patients. One important limitation of the present study is the lack of information regarding glycaemic control before or during the hospitalization for IE, yet the previous studies mentioned herein\(^8,9\) suggest a potential benefit of strict glycaemic control at the time of an acute illness or intervention. Other large, observational databases or registries may be able to offer insight regarding a possible relationship between glycaemic control during treatment of IE and outcome. The current study’s finding of similar mortality rates of DM patients treated with oral medications and non-diabetic patients suggests that the diagnosis of DM alone may not be the specific marker of higher risk. Rather, intensive glycaemic control of all patients with IE may be a broader but more meaningful therapeutic intervention, and would reduce potential biases in the diagnosis and treatment of DM before the onset of IE. In light of the unchanged and high mortality of IE, randomized, controlled studies to evaluate interventions, such as the effect of intensive glycaemic control, are necessary and multicentre collaborations such as the Association pour l’Etude et la Prévention de l’Endocardite Infectieuse (AEPEI) and the ICE offer foundations for future investigations.

Conflict of interest: none declared.

References