Correspondence

Aspirin Use in Infective Endocarditis

To the Editor—Chan et al. [1], are to be congratulated for their prospective interventional study of aspirin use in patients with infective endocarditis (IE). Their study did not find that aspirin reduced the frequency of major embolic events and showed a trend towards an increase in the number of major bleeding episodes in the intervention group. As acknowledged in their recent article [2], the initial study may have underestimated the benefit of aspirin, because the intervention was started relatively late after symptomatic onset of IE. Thus, they carried out a post-hoc analysis of observational data comparing patients taking long-term aspirin (in various doses) prior to the onset of IE, who continued using aspirin after the diagnosis, versus “placebo-control” patients with IE who did not receive aspirin before or after the diagnosis of IE. Data from this most recent study appear to support the authors’ prior contentions that aspirin use in IE does not reduce embolic complications, although it potentially increases the risk of major hemorrhage. Importantly, these data are in contradistinction to a recent, well-conducted, retrospective study from the Mayo Clinic that showed significantly reduced rates of emboli in patients with IE who had been taking aspirin prior to the diagnosis [3]. Moreover, many of the limitations extant in the initial article [1] are perpetuated in this follow-up investigation and serve to substantially confound the authors’ conclusions.

Firstly, the animal studies cited showing the benefit of aspirin in improving IE outcomes are specific for IE caused by Staphylococcus aureus [4–6]. This paradigm was recently underscored by a prospective investigation [7] showing significant reduction in the frequency of S. aureus (but not streptococcal or enterococcal) bacteremia in patients with indwelling hemodialysis catheters who had been taking long-term aspirin. Thus, a major shortcoming in the clinical data reported in both papers by Chan and colleagues is the relatively small number of S. aureus IE cases. This small sample size prevents a valid statistical analysis of potential salutary impacts of aspirin on IE complications.

Secondly, initial studies by Kupferwasser et al. [4] were careful to point out that the antimicrobial and anti-embolic impacts of aspirin in animals with established S. aureus IE depended on the dose. Thus, there appears to be a prominent “Goldilocks effect,” in which too little or too much aspirin may cause paradoxically diminished impacts on outcome metrics in IE. This speaks to the need to carefully monitor and correlate aspirin blood levels with outcome events in IE in future trials to achieve a likely “sweet spot” within which the maximal benefit of aspirin will be observed.

Finally, a trend to an increased rate of hemorrhage was the basis for the authors’ cautionary statements regarding aspirin’s use in IE [1, 2]. Although it may be argued that a P value <.05 is an arbitrary indicator of statistical significance this, and 95% confidence intervals that do not cross unity are widely accepted markers of differences in study populations. Neither of these yardsticks were satisfied in Chan and colleague’s comparison of bleeding risk relating to aspirin, further reducing the impact of their conclusions.

We suggest that future prospective studies should investigate potential benefit of aspirin either in preventing S. aureus IE or in ameliorating embolic events in established disease. We submit that the issue of potential increases of major bleeding episodes due to aspirin use in IE patients is not proven by the current [2] or the previous study [1] by Chan and colleagues and, as such, should not preclude future prospective studies.

Acknowledgments

Potential conflict of interest. A.S.B. has received funding from the National Institutes of Health, Titan Pharmaceuticals, Cubera Pharmaceuticals, Seresta Pharmaceuticals, and Targanta Therapeutics; has been a consultant for Pfizer Anti-infectives and Inhibitex; has received honoraria from Cubist and Johnson & Johnson; and has ownership interest in Inhibitex. D.P.E.: no conflicts

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References

Determination of the Incidence of Tuberculosis in Low-Income Countries

To the Editor—We read with interest the report by The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration on tuberculosis (TB) after initiation of antiretroviral therapy in low-income and high-income countries [1]. The authors do not mention the number of patients who were already receiving treatment for TB when the antiretroviral therapy was started (were the data not available?). However, they do mention that programs in lower-income countries routinely screened patients for TB before they commenced HAART. It is unclear to us whether patients being given treatment for TB at the start of HAART were included in the analysis. We propose that they should have been excluded from the study population if the aim of the study was to determine the incidence of TB and to compare the incidence rate ratios for new TB infections. Indeed, in contrast to in high-income countries, in low-income countries, TB is one of the main reasons to initiate HAART. In Malawi, for example, from July through September 2005, 12% of the patients who started HAART did so because of TB [2]. During treatment for TB, by definition these patients cannot develop a new TB infection. We suppose that, if this approach were taken, the conclusions of the report would remain the same, but the calculations may change slightly. If the number of patients not receiving treatment for TB who started HAART is used as the denominator, the real incidence of TB in low-income countries will be even higher, particularly soon after the initiation of HAART.

Acknowledgments

Potential conflict of interest. R.C. and S.C.: no conflicts

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References


Reply to Colebunders and Caluwaerts

To the Editor—We thank Colebunders and Caluwaerts [1] for their interest in the recent analysis by The Antiretroviral Therapy in Low-Income Countries Collaboration of the International epidemiological Databases to Evaluate AIDS (IeDEA) and The ART Cohort Collaboration [2]. In this collaborative study, we compared the incidence rates of tuberculosis (TB) among patients receiving HAART in low-income and high-income countries. Colebunders and Caluwaerts ask whether the analysis included patients who were receiving treatment for TB at the start of HAART and argue that, if so, this might have biased the incidence rates of TB downward in low-income countries and might have distorted the incidence-rate ratios during the first year of HAART.

As Caluwaerts and Colebunders [1] suspected, data on treatment for TB at the time of initiation of HAART were not available for all the cohorts from low-income countries. But note that, as we pointed out in our report [2], the main objective of the analysis was not to estimate absolute rates but was to compare relative changes in rates of TB during the first year of HAART in low-income and high-income settings. The incidence rates obtained in such an analysis of data from 15 different sites were a weighted average of site-specific rates, influence by variation in background rates and diagnostic procedures, and are not applicable to any specific setting.

We repeated analyses for 9 low-income cohorts with data on previous treatment for TB, including 2050 patients who were not receiving treatment when HAART was started. Among these patients, the incidence of TB in the first year of HAART was 8.8 cases per 100 person-years (95% CI, 7.5–10.3 cases per 100 person-years), which is slightly higher than the 7.4 cases per 100 person-years (95% CI, 6.6–8.4 cases per 100 person-years) reported in the previously published analysis [2]. As predicted by Caluwaerts and Colebunders [1], this difference was more pronounced during the first 3 months of treatment: 13.9 cases per 100 person-years (95% CI, 11.0–17.6 cases per 100 person-years) in this analysis, compared with 10.7 cases per 100 person-years (95% CI, 8.9–12.9 cases per 100 person-years) in the original analysis. The decrease in the incidence rate during the first year of HAART was, however, similar for the 2 analyses. Compared with the rate for months 1–3, the rate ratio was 0.65 (95% CI, 0.44–0.96) for months 4–6 and was 0.39 (95% CI, 0.27–0.58) for months 7–12. The corresponding ratios from the original analysis were 0.70 (95% CI, 0.52–0.94) and 0.48 (95% CI, 0.36–0.64), respectively. Interestingly, the inci-