HIV and Cardiovascular Disease

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(See the article by Bedimo et al., on pages 84–91.)

Over the past decade, there has been great interest in the relationships around the human immunodeficiency virus (HIV) and cardiovascular disease. Indeed, a recent major subject heading search in PubMed using the search terms “HIV Infections” and (“Cardiovascular Diseases” or “Cerebrovascular Disorders”) yielded nearly 3000 articles. A review of this vast and often confusing literature is beyond the scope of this piece, but summaries are available [1]. Some things are relatively clear. Cardiovascular disease is an increasingly important cause of death in patients with HIV as rates of HIV-related opportunistic infections and cancers decrease, but the absolute rate of myocardial infarction within age cohorts does not seem to be rising. Those infected with HIV have an elevated risk of vascular disease that manifests in a number of ways, the most clinically prominent being a high rate of myocardial infarction and probably stroke. The mechanisms for this include both direct effects of HIV infection and conventional risk factors such as hyperlipidemia, some of which may be exacerbated by HIV infection and its treatment. The role of treatment is complex, with most studies suggesting a modest relationship between duration of protease inhibitors in particular and risk of myocardial infarction at the same time that strong data suggest that treatment reduces overall risk of disease. The situation is more complex with abacavir, where some observational studies show an increased risk from short-term but not long-term use. Such findings in the setting of multiple hypothesis testing should be interpreted with caution, especially as pooled randomized trials do not show this effect.

The paper by Bedimo and colleagues in this issue of Clinical Infectious Diseases is one of several outcome-based cohort studies published from the Veterans Affairs Health Care System [2]. The authors have elected to concentrate on myocardial infarction per se and stroke. The strengths of this work relative to other cohort studies include the large patient population and the availability of laboratory data while the weaknesses include the need to rely on administrative data for diagnoses of endpoints and certain risk factors (eg, smoking) as well as a relatively short median follow-up period.

In the survival analysis, the hazard ratio for both myocardial infarction and stroke was significantly higher for patients receiving less effective mono and dual antiretroviral therapy (ART) regimens, nonsignificantly higher for patients undergoing highly active antiretroviral therapy (HAART) including abacavir, and not elevated for persons on other HAART regimens. The addition of covariates had only a small effect on these hazard ratios, suggesting little confounding, but the large hazard ratios for these conventional risk factors reinforce their importance. The analysis of current therapy showed that, compared with current use of tenofovir, current use of abacavir was associated with a higher rate of myocardial infarction and stroke as well as with chronic kidney disease. Though chronic kidney disease was also strongly associated with myocardial infarction and stroke, adjustment for this factor again made little difference to effect sizes. However, the hazard ratios were of interest. Regimens containing abacavir had the highest hazard ratios for myocardial infarction and stroke, regimens containing tenofovir had the lowest hazard ratios, and regimens containing both had intermediate hazard ratios. However, all the hazard ratios were significantly lower compared with the group receiving no therapy or regimens containing neither abacavir nor tenofovir. It is perhaps unfortunate that neither direct comparisons of abacavir vs tenofovir–containing regimens...
nor fully adjusted models using a no-therapy control were presented.

This combination of findings supports the viewpoint that the immediate effect of therapy is to reduce risk but that risk increases with longer term therapy, even though colinearity between duration of therapy and simple aging likely magnifies the latter putative effect. Moreover, the trends tend to support the controversial notion of a differential effect of abacavir, as it was found in, for this study, what was an a priori hypothesis.

Mechanistic studies are now probably the highest research priority. Further clinical epidemiology could be useful but must be carefully done. Outcomes should be expanded to include revascularization and perhaps, if it can be adequately operationalized, unstable angina. Both cumulative and current therapy should be analyzed with particular attention to effects during transitions in therapy. Survival analysis should be preferred to analyses of counts of events, and there should be attempts to break up the colinearity between aging and cumulative dosing—especially during longer term follow-up [3]. Selection bias, also known as channeling, should be approached by emphasizing secondary analyses of randomized trials, by limiting observation to periods before a possible effect was widely known, or by mathematical means (as we recently attempted) [4]. Perhaps most important, exploratory and a priori analyses should be differentiated, and the number and extent of the former described.

The main clinical messages from this body of work remain the same. Cardiovascular and cerebrovascular disease are of special concern in patients with HIV, control of conventional risk factors is paramount, and the risk-benefit ratio of ART is, of course, overwhelmingly favorable. It is reasonable to consider effects on risk factors (eg, lipids) when selecting initial therapy. Many clinicians would now hesitate to initiate abacavir in patients with known vascular disease or even risk factors for vascular disease. Though this may represent an over-abundance of caution given the current state of knowledge, it is not unreasonable. Some clinicians, particularly in Europe, would now also switch regimens based on cardiovascular risks. Others, including myself, think it imprudent to jeopardize an effective therapeutic program for a possible small increased risk of an adverse outcome, particularly one that can be easily counterbalanced by behavioral or other intervention (eg, low-dose statins, which may have other benefits.)

Acknowledgments

Potential conflicts of interest. Author certifies no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

References