Protopathic bias in observational studies on statin effectiveness

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LETTER TO THE EDITORS

Protopathic bias in observational studies on statin effectiveness

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A meta-analysis of 14 randomized controlled trials (RCT) of statins in prevention of major vascular events suggests that almost all diabetic patients benefit from statin therapy, with a 10% relative reduction in event rates for every millimole per litre reduction in low-density lipoprotein cholesterol seen in 1 year [1]. The results of the RCTs including only patients with diabetes are, however, inconclusive. For ethical reasons, long-term placebo-controlled RCTs of statins in diabetic populations are no longer possible. Therefore observational studies are an essential tool for future research [2], but they are prone to various biases. Protopathic bias occurring when the drug is preferentially prescribed to persons with early symptoms of the outcome under study is one of them [3].

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We evaluated the potential for protopathic bias in an observational study on cardiovascular benefits of statins in diabetes by examining the rates of major cardiac events (MCE) among statin initiators with diabetes, with a focus on the first year of therapy. Using a nationwide prescription-claims database maintained by the Social Insurance Institution of Finland [4], we identified 53,943 statin initiators (mean age, 62.0 years; 44.2% female) among community-dwelling patients with diabetes, aged 45–75, between January 1, 1995, and December 31, 2006. Initiators had no statin purchases in the year before the start of follow-up. MCEs included acute myocardial infarctions, subendocardial infarctions, and coronary revascularization procedures captured through the national hospital discharge register. The follow-up ended with the occurrence of an MCE, death, permanent institutionalization, or December 31, 2007, whichever came first.

During a mean of 4.0 years of follow-up, there were 6,270 hospitalizations for MCEs (2,370 for infarctions, 3,580 for revascularization procedures, 320 with both diagnoses) among patients with diabetes, corresponding to an incidence rate of 2.9 per 100 person-years. Almost half (46.4%) of the events, however, occurred within 365 days of statin initiation, resulting in an incidence rate of 5.9 per 100 person-years during the first year. Of these early MCEs, 67.1% were coronary revascularization procedures. Monthly MCE rates, especially revascularization procedure rates, declined steeply, stabilizing by the ninth month of therapy (Fig. 1). The MCE rates during the first months of therapy were higher among statin initiators in 1995–1998 (n=9,971) than among initiators in 2004–2006 (n=17,668). This probably reflects the shift in statin initiators' baseline risk, as the proportion of initiators with coronary artery disease (CAD) decreased to 10.7 from 36.3% during the same period.

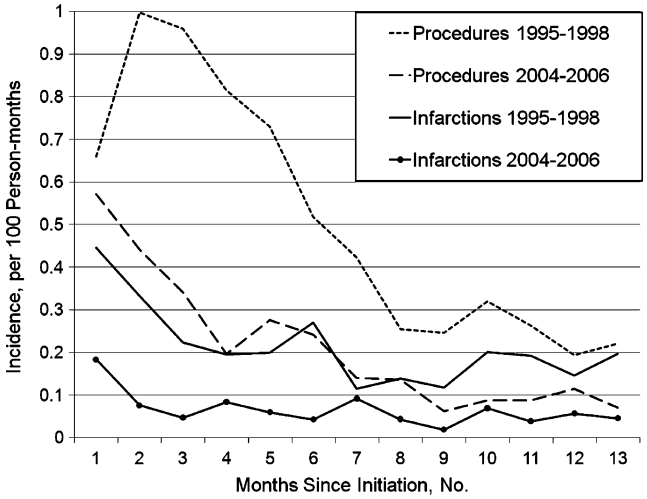

Fig. 1 Monthly incidence of hospitalizations for coronary revascularizations and infarctions among statin initiators with diabetes in Finland in 1995–1998 (n=9,971) and in 2004–2006 (n=17,668)

Our findings imply that diabetic patients may receive their first statin prescription when they present with angina and are, in some cases, scheduled for a coronary revascularization procedure at the same time. Therefore the results of observational studies on statin effectiveness in preventing MCEs among diabetic patients may be distorted by protopathic bias if the initial months of follow-up are included in the analysis. This means also that the early benefits of statins [1] may not be validly studied in observational designs.

While supporting the use of lag-time or exclusion of a specific time period of follow-up after statin initiation [3, 5], our results suggest that the optimal lag-time for avoiding protopathic bias differs over time, in the Finnish context being under 1 year. Accordingly, in a recent Canadian study comparing the risk of CAD associated with various adherence levels (≥80% versus <80%), benefits of high statin adherence appeared to emerge before 1 year [6].

Overall, our findings highlight the need to consider not only the pathophysiology of the disease and the characteristics of the population under study, but also the health-care system through which the data are generated and the changes in it over time when designing observational studies on drug effectiveness and interpreting their results.

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