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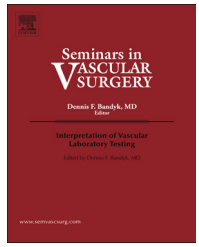

Effect of statins on survival in patients undergoing dialysis access for end-stage renal disease

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ABSTRACT

The benefit of statin therapy in patients with advanced chronic kidney disease remains uncertain. Randomized trials have questioned the efficacy of the drug in improving outcomes for on-dialysis populations, and many patients with end-stage renal disease are not currently taking statins. This study aimed to investigate the impact of statin use on survival of patients with vascular access performed at a vascular center for chronic dialysis. Consecutive end-stage renal disease patients admitted for vascular access surgery in 2006 to 2013 were reviewed. Information on therapy was retrieved and patients on statins were compared to those who were not on statins. Primary endpoint was 5-year survival. Independent predictors of mortality were assessed with Cox regression analysis adjusting for covariates (ie, age, sex, hyperlipidemia, hypertension, cardiac disease, cerebrovascular disease, chronic obstructive pulmonary disease, obesity, diabetes, and statins). Three hundred fifty-nine patients (230 males; mean age 68.9 $\pm$ 13.7 years) receiving 554 vascular accesses were analyzed: 127 (35.4%) were on statins. Use of statins was more frequent in patients with hypertension (89.8% *v* 81%; $P = .034$), hyperlipidemia (52.4% *v* 6.2%; $P < .0001$), coronary disease (54.1% *v* 42.6%; $P = .043$), diabetes (39.4% *v* 21.6%; $P = .001$), and obesity (11.6% *v* 2.0%; $P < .0001$). Mean follow-up was 35 months. Kaplan–Meier survival rates at 3 and 5 years were 84.4% and 75.9% for patients taking statins and 77.0% and 65.1% for those not taking statins ($P = .18$). Cox regression analysis selected statins therapy as the only independent negative predictor (odds ratio = 0.55; 95% confidence interval = 0.32–0.95; $P = .032$) of mortality, while age was an independent positive predictor (odds ratio = 1.05; 95% confidence interval = 1.03–1.08; $P < .0001$). Vascular access patency was comparable in statin takers and those not taking statins ($P = .60$). Use of statins might halve the risk of all-cause mortality at 5 years in adult patients with vascular access for chronic dialysis. Statins therapy should be considered in end-stage renal disease populations requiring dialysis access placement.

This was a retrospective institutional review analysis of a prospectively maintained database. The study was performed in accordance with the Institutional Ethical Committee rules and individual consent for this retrospective analysis was waived.

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1. Introduction

To date, there is little information on how to improve life expectancy in patients with chronic end-stage renal disease (ESRD), a well-known marker of poor prognostic outcomes. Studies have shown ESRD to be associated with an increased risk for atherosclerotic cardiovascular disease (CVD) [1–6] and CVD-related mortality is reported to be 5 to 30 times higher in dialysis patients than in subjects from the general population of the same age, sex, and race. Atherosclerotic heart disease may account for approximately half of all deaths in ESRD patients [5–8]. Despite the relevant burden of CVD in patients with ESRD, the use of traditional therapies to modify this risk has been called into question. Specifically, use of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (statins) therapy—a class of medications that has been shown to provide significant benefit in the general population for primary and secondary prevention of atherosclerosis and CVD events—has shown disappointing results in patients with ESRD. A benefit from statins has been suggested among individuals with moderate-stage (especially stages 1 to 3) ESRD and non-dialysis–dependent chronic kidney disease, but such positive effects were not found in most patients with ESRD [9–11]. Current renal guidelines recommend against initiation of statins in all patients undergoing hemodialysis [1,12–14]. However, the effect of statins on ESRD outcomes remains controversial; studies in ESRD patients on dialysis yielded conflicting results. In two randomized, placebo-controlled trials, statins did not reduce cardiovascular endpoints in patients receiving dialysis [15,16]. More recently, the randomized SHARP (Study of Heart and Renal Protection) study, despite its limitations (simvastatin+ezetimibe *v* placebo), showed an insignificant trend toward reducing cardiovascular events and mortality in dialysis patients [17]. Such benefit from statins in ESRD patients has also been found outside the randomized populations, according to large observational nonrandomized studies [1,3,18,19]. This study aimed to evaluate the impact of statin therapy on survival in adult population with ESRD undergoing vascular access procedures for chronic dialysis.

2. Methods

This was a retrospective institutional review analysis of a prospectively maintained database. The study was performed in accordance with the Institutional Ethical Committee rules and individual consent for this retrospective analysis was waived.

Patients referred to the Vascular Surgery Unit, Hospital S. M. Misericordia, Perugia, Italy, for vascular access surgery were managed according to a protocol with the involvement of a multidisciplinary team of vascular access specialists, including nephrologists, vascular surgeons, and interventional radiologists. The team was responsible for management of all vascular access patients during preplanning, operaion, and follow-up. According to the protocol, the primary choice for any new vascular access was autologous distal cephalic-radial arteriovenous fistula on the non-dominant arm. Redo cephalic-radial fistula in proximal position and brachial-basilic fistula with eventual autologous vein interposition were usually used for reintervention after a previous access failure. Bypass grafts (usually Omniflow II; Bio Nova Europe LTD, London UK) and accesses on the leg were used exceptionally [20].

The choice of access was based on vessel duplex ultrasound mapping to evaluate the size, patency, and availability of vessel conduits. Duplex ultrasound was also used to evaluate patency and complications after operations and during follow-up.

All patients were treated on a 1-day surgery admission unless complications required a prolonged hospital stay. After surgery, clinical outcome was recorded at regularly scheduled follow-up. Nephrologists followed all of the accesses on a regular dialysis schedule. In case of assessment of lack of functionality or doubts, the vascular surgeon was contacted for duplex evaluation of access patency and a collegial decision was made regarding any eventual treatment. For the purpose of this study, statin users were defined by their admission medication list; each statin was assumed to have an equal effect on the outcome [21,22].

To evaluate whether the effect of statins might differ across various patient groups at different cardiovascular exposure and mortality risk, subgroup analyses stratified by high-risk criteria for specified cardiovascular events were performed. The following indicators of high risk were applied for subgroup analyses in accordance with kidney guidelines: known cardiac disease, diabetes mellitus, and preoperative cerebrovascular disease [12].

2.1. *Study endpoints*

Primary endpoint of the study was all-cause mortality at 5 years. Secondary endpoints included all-cause mortality in subgroups at high-risk and vascular access patency. Patency was measured as primary patency or any “intervention-free patency” that was the patency of the access from the initial intervention to any new intervention. Outcomes data were stratified according to preoperative use of statins.

2.2. *Statistical analysis*

Continuous variables were reported as frequency, mean, standard deviation, or median and interquartile range when required. Categorical variables were summarized using number of patients and percentages. Continuous variables were compared with Student’s *t*-test or analysis of variance. For comparison of categorical data, percentages were compared by two-tailed χ^2 with a Yates correction and Fisher’s exact test, when appropriate.

Each statin was assumed to have an equal effect on outcomes; therefore, all statins were counted together as a single variable [21,22]. Unadjusted and adjusted odds ratios (ORs) with correspondent 95% confidence intervals (CIs) were used to compare statin and no-statin patients.

The rates of death and patency over time in statin and no-statin patients were estimated with the Kaplan–Meier method to compensate for patient dropout, and level of significance was calculated with log-rank test and its