Statin Therapy Is Not Associated with Improved Vascular Access Outcomes

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Background and objectives: Neointimal hyperplasia is the major cause of vascular access failure in hemodialysis patients. Statins reduce neointimal hyperplasia in experimental models, which may reduce access failure. The study presented here evaluated whether vascular access outcomes are superior in patients receiving statin therapy than in those not on statins.

Design, setting, participants, & measurements: A prospective computerized vascular access database was retrospectively queried to determine the access outcomes of 601 patients receiving an upper-arm fistula or graft at a single large dialysis center.

Results: Primary fistula failure was observed in 37% of patients on statin therapy versus 38% not on statin therapy. Primary graft failure occurred in 20% of patients on statin therapy versus 14% not on statin therapy. A multiple variable logistic regression analysis including statin use, diabetes, coronary artery disease, peripheral artery disease, sex, and age found that only sex predicted primary fistula failure and graft failure. After excluding primary failures, cumulative fistula survival was similar for patients with or without statin therapy (hazard ratio [HR] 1.26; 95% confidence interval [CI] 0.76 to 2.16). Likewise, cumulative graft survival was similar for statin therapy versus no statin therapy (HR 0.88; 95% CI 0.59 to 1.32). Using a multivariable survival analysis model to predict cumulative fistula survival, only age predicted fistula failure (HR 1.21 per decade; 95% CI 1.02 to 1.44). None of the variables in this model predicted cumulative graft survival.

Conclusions: Statin therapy is not associated with improved fistula or graft outcomes in patients with chronic kidney disease.


H emodialysis vascular access complications are common in hemodialysis patients, accounting for approximately 20% of all hospitalizations (1–3). Arteriovenous (AV) fistulas have a much higher suitability failure (primary failure) than do AV grafts. However, once suitability for dialysis has been achieved, fistulas have a better cumulative survival as compared with AV grafts (4,5). The main cause of fistula and graft failure is aggressive neointimal hyperplasia that results in stenosis and subsequent thrombosis, most commonly in the perianastomotic region for fistulas or at the venous anastomosis for grafts (6,7).

The pathogenetic mechanisms of neointimal hyperplasia are complex and not fully understood, but inflammation plays a central role in the cascade of events leading to access stenosis (8,9). Thus, targeting neointimal hyperplasia and inflammation may be critical in improving vascular access survival. Although several drugs have been shown to inhibit neointimal hyperplasia in experimental models, current treatments to prevent or treat vascular access dysfunction in dialysis patients are minimally effective (10–14). The published literature provides conflicting evidence regarding the potential protective effects of statins on vascular access outcomes (15,16).

The aim of the study presented here was to evaluate whether fistula or graft outcomes are superior in chronic kidney disease (CKD) patients receiving statins. We assessed this research question by comparing the primary failure rate and cumulative survival of new vascular accesses in CKD patients treated or not treated with statin therapy.

Materials and Methods

We have recently reported on the vascular access outcomes of a large group of patients receiving an upper-arm fistula or graft at the University of Alabama at Birmingham between October 1, 2000 and September 30, 2006 (4). The study population included 322 patients receiving a brachiocephalic fistula and 289 patients receiving an upper-arm graft. The patients’ electronic records were reviewed to determine whether they were receiving a statin in the 3-month period preceding their access surgery and in the 6-month period after their access placement. Information about statin use was not available for ten patients. Thus, the final population for the study presented here was 601 patients, including 317 receiving a brachiocephalic fistula and 284 with an upper-arm graft.

The details of access surgery and management have been described previously (4). In brief, fistulas were cannulated 6 to 8 weeks after their placement if nurses deemed them mature. Grafts were cannulated 2 to 3 weeks after their placement. A postoperative ultrasound was performed to assess for potential remediable anatomic lesions if fistulas were clinically immature (17,18). Percutaneous and surgical interventions, including angioplasty or surgical revision for stenosis, ligation of large accessory veins, and superficialization of excessively deep fistulas, were then performed to facilitate maturation (17).
Data Analysis

An access was considered mature if it could be cannulated reproducibly for dialysis with two needles and a blood flow $>300$ ml/min for at least 1 month. A primary access failure (suitability failure) was defined as the inability to use it successfully for dialysis because of early thrombosis or failure to mature. Cumulative access survival was calculated as the time from access placement to permanent failure after excluding primary failure and regardless of the number of interventions required to maintain patency.

The patients’ clinical characteristics were compared using paired $t$ tests. Multiple variable logistic regression analysis was used to evaluate which factors were associated with primary access failure. Survival analysis techniques were used to model access survival time. Odds ratios (ORs) and their 95% confidence intervals (CIs) were computed. Multivariable survival analysis was used to model the association between the clinical variables and access survival. A $P$ value $<0.05$ was considered statistically significant. All analyses were performed using the Statistical Analysis Software (SAS) version 9.0.

Results

Patient Population

The study population was comprised of 601 subjects receiving a new upper-arm vascular access with known information about statin use before access surgery. They included 317 patients with a brachiocephalic fistula and 284 patients with an upper-arm graft. Statins were being used by 28% of the patients at the time of the access placement, including 31% of those receiving fistula and 25% of those with a graft. The baseline characteristics of the study population are summarized in Tables 1 and 2. Statin use was significantly associated with older age, female sex, and diabetes. Peripheral artery disease was associated with statin use in patients receiving an upper-arm vascular access. The patients treated with a statin had similar primary access failure (fistula or graft) as compared with those not on statin therapy. Likewise, cumulative fistula and graft survival (after excluding primary access failure) was also similar between subjects with and without statin therapy. The overall burden of primary fistula and AV graft failures was substantial and comparable to that described in the literature (4,5,11,16).

Primary Access Failure

Primary fistula failure (access never usable for dialysis) was observed in 37% of patients on statin therapy versus 38% not on statin therapy (OR $= 0.97$; 95% CI 0.59 to 1.58; $P = 0.90$). Primary graft failure occurred in 20% of patients on statin therapy versus 14% not on statin therapy (OR $= 1.53$; 95% CI 0.76 to 3.09; $P = 0.23$). Using a multiple logistic model to predict primary access failure, with statin use, diabetes, coronary artery disease, peripheral artery disease, sex, and age being in the model, only female sex predicted primary fistula failure (OR $= 1.68$; 95% CI 1.06 to 2.63; $P = 0.03$) and primary graft failure (OR $= 2.42$; 95% CI 1.16 to 5.00; $P = 0.02$).

Cumulative Access Survival

After excluding primary failures, the cumulative fistula survival (from fistula creation to permanent failure) was not significantly associated with statin therapy (hazard ratio [HR] $= 1.26$; 95% CI, 0.76 to 2.16; $P = 0.35$) (Figure 1). Using a multivariable survival analysis model to predict cumulative fistula survival, with statin use, diabetes, coronary artery disease, peripheral vascular disease, sex, and age being in the model, only age predicted cumulative fistula survival (HR $= 1.21$ per decade; 95% CI, 1.02 to 1.44; $P = 0.02$).

Similarly, after excluding primary failures, there was no significant association between statin use and cumulative graft survival (HR $= 0.88$; 95% CI, 0.59 to 1.32; $P = 0.54$) (Figure 2). Using a multivariable survival analysis model to predict cumulative fistula survival, with statin use, diabetes, coronary artery disease, peripheral vascular disease, sex, and age being in the model, none of the variables predicted cumulative graft survival.

Discussion

Vascular access dysfunction is a major contributor to morbidity and health care costs in hemodialysis patients (1,2). Any treatment that prolongs vascular access survival may significantly improve the patients’ quality of life and reduce costs. The study presented here evaluated the association between statin use and hemodialysis vascular access outcomes in CKD patients receiving an upper-arm vascular access. The patients treated with a statin had similar primary access failure (fistula or graft) as compared with those not on statin therapy. Likewise, cumulative fistula and graft survival (after excluding primary access failure) was also similar between subjects with and without statin therapy. The overall burden of primary fistula and AV graft failures was substantial and comparable to that described in the literature (4,5,11,16).

Table 1. Baseline characteristics of the fistula population with or without statins

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statin</th>
<th>No Statin</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Percent</td>
<td></td>
</tr>
<tr>
<td>Patients ($n = 317$)</td>
<td>99</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>58 ± 13</td>
<td>55 ± 15</td>
<td>0.05</td>
</tr>
<tr>
<td>Gender, female</td>
<td>60</td>
<td>55</td>
<td>0.04</td>
</tr>
<tr>
<td>Race, African-American</td>
<td>77</td>
<td>78</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes</td>
<td>74</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>97</td>
<td>96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>34</td>
<td>35</td>
<td>0.98</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>16</td>
<td>16</td>
<td>0.50</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>11</td>
<td>19</td>
<td>0.50</td>
</tr>
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</table>
Our findings are similar to those reported from the Dialysis Outcomes and Practice Patterns Study (DOPPS) (16). In this prospective, longitudinal, observational study of adult hemodialysis patients, statin treatment was not associated with improved primary (unassisted) or secondary (assisted) survival of fistulas or grafts. However, unlike our study, DOPPS did not evaluate the association between statin therapy and primary access failure. In addition, African Americans were more common in our study than in DOPPS (80% versus 38%). In contrast, a recent retrospective analysis from an Italian single-center study reported a lower vascular access failure rate in hemodialysis patients receiving statin therapy as compared with those without statins (33% versus 56%) (15). The small sample size or difference in racial background of the patients enrolled may account for the positive findings in the latter study.

Experimental studies have demonstrated endothelial protective effects of statins that are distinct from their lipid-lowering ability. Beneficial effects of statins in those reports include increased fibrinolysis, mobilization of endothelial progenitor cells from the bone marrow, and inhibition of neointimal hyperplasia (19–21). Statins reduce neointimal hyperplasia in experimental models (22,23). They also decrease the levels of C-reactive protein, an independent predictor of vascular access thrombosis in dialysis patients (24). These lines of evidence suggest that treatment with statins may improve vascular access outcomes. However, these benefits do not appear to translate into improved vascular access outcomes in the study presented here or in DOPPS. The discrepancy between the lack of clinical benefit of statins in dialysis patients and their inhibition of neointimal hyperplasia in animal models may be due to differences in drug doses, species differences, or the effect of uremia.

The study presented here has some limitations. First, it was a retrospective study. However, all of the access events were recorded prospectively in the computerized access database, providing a high level of confidence that all access events had been captured. Large observational studies such as the current one are useful in generating hypotheses about the potential value of an intervention, which can be tested subsequently in a randomized clinical trial. The lack of association between statin use and vascular access outcomes in this study and in DOPPS would dampen the enthusiasm for pursuing a randomized study. Second, our study represented the outcomes of a single dialysis center that might not be generalized to all centers. Third, our study enrolled only patients receiving an upper-arm fistula and may not generalize to patients receiving a forearm fistula. Finally, because of the retrospective study design, we were not able to ascertain the indications for statin use, serum cholesterol or C-reactive protein levels, or the patients’ compliance with their statin prescription.

In summary, the study presented here suggests that statin ther-

### Table 2. Baseline characteristics of the graft population with or without statins

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Statin</th>
<th>No Statin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n = 284)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>70 ± 12</td>
<td>54 ± 15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, female</td>
<td>54</td>
<td>112</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race, African-American</td>
<td>57</td>
<td>179</td>
<td>0.67</td>
</tr>
<tr>
<td>Diabetes</td>
<td>49</td>
<td>93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>67</td>
<td>188</td>
<td>0.06</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>25</td>
<td>54</td>
<td>0.09</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>20</td>
<td>35</td>
<td>0.03</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>10</td>
<td>20</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Figure 1. Cumulative fistula survival (excluding primary failures) in patients with or without statin therapy (P = 0.35).

Figure 2. Cumulative graft survival (excluding primary failures) in patients with or without statin therapy (P = 0.54).
apy is not associated with prolonged vascular access survival in patients with CKD, despite its known beneficial effects on endothelial function and inflammation. Future studies should focus on alternative drugs for the prevention of vascular access failure.

Acknowledgments

Part of this material was presented in abstract form at the 2009 annual meeting of the American Society of Nephrology; October 27 through November 1, 2009; San Diego, CA.

Disclosures

None.

References


Access to UpToDate on-line is available for additional clinical information at http://www.cjasn.org/