Atorvastatin did not prevent cardiovascular events or death in patients with type 2 diabetes receiving hemodialysis

Wanner C, Krane V, März W, et al. **Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis.** N Engl J Med. 2005;353:238-48.

Clinical impact ratings: Hospitalists ★★★★★★☆ Endocrinology ★★★★★★☆ Nephrology ★★★★★★★

QUESTION

In patients with type 2 diabetes mellitus receiving hemodialysis, does atorvastatin reduce the composite risk for nonfatal myocardial infarction (MI), stroke, and death from cardiac causes?

METHODS

Design: Randomized placebo-controlled trial.

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: Median 4 years.

Setting: 178 centers in Germany.

Patients: 1255 patients 18 to 80 years of age (mean age 66 y, 54% men) with type 2 diabetes who had been receiving maintenance hemodialysis < 2 years. Exclusion criteria were fasting serum low-density lipoprotein (LDL) cholesterol < 80 mg/dL (2.1 mmol/L) or > 190 mg/dL (4.9 mmol/L), triglyceride levels > 1000 mg/dL (11.3 mmol/L), liver-function values > 3 times the upper limit of normal, hematopoietic disease or systemic disease unrelated to end-stage renal disease (ESRD), cardiovascular events in the previous 3 months, unsuccessful kidney transplant, or hypertension resistant to therapy.

Intervention: Atorvastatin, 20 mg (n = 619), or placebo (n = 636) once daily. The dose was reduced by half if the LDL cholesterol level fell to < 50 mg/dL (1.3 mmol/L). After the occurrence of a primary endpoint, the study drug could be replaced with an active statin.

Outcomes: Composite endpoint of death from cardiac causes, fatal or nonfatal stroke, or nonfatal MI. Secondary outcomes included death from all causes, all cardiac events, and all cerebrovascular events. The study had 90% power to detect a 27% relative reduction in the primary composite endpoint.

Patient follow-up: 100% (intention-to-treat analysis).

MAIN RESULTS

74% of patients took the study drug for ≥ 1 year and about 50% took it for ≥ 2 years. The groups did not differ for the composite endpoint, all-cause mortality, or cerebrovascular events (Table). Risk for cardiac events was lower with atorvastatin (Table). Of the 4 components of the composite endpoint, fatal stroke was the only one that differed between groups, occurring more frequently in the atorvastatin group (Table). The type and frequency of adverse events were similar in the 2 groups.

CONCLUSION

In patients with type 2 diabetes receiving hemodialysis, atorvastatin did not reduce the composite risk for cardiovascular events or death from cardiac causes more than placebo.

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*See Glossary.

Atorvastatin vs placebo in patients with type 2 diabetes on hemodialysis at median 4 years†

Outcomes	Atorvastatin	Placebo	Adjusted RRR (95% CI)‡	NNT (CI)
Composite endpoint§	37%	38%	8% (–10 to 23)	Not significant
All-cause mortality	48%	50%	7% (–8 to 21)	Not significant
All cardiac events	33%	39%	18% (1 to 32)	15 (9 to 259)
			Adjusted RRI (CI)‡	NNH (CI)
Fatal stroke	4.2%	2.1%	103% (5 to 293)	48 (17 to 981)
All cerebrovascular events	13%	11%	12% (–19 to 55)	Not significant

†Abbreviations defined in Glossary; NNT, NNH, and CI calculated from adjusted relative risk in article.
‡Adjusted for sex, age, and baseline coronary heart disease status.
§Composite endpoint = death from cardiac causes, nonfatal myocardial infarction, fatal stroke, or nonfatal stroke.

COMMENTARY

Because cardiovascular disease is the leading cause of death among patients on dialysis, cholesterol-lowering therapy might be expected to have considerable benefit. The results of the study by Wanner and colleagues are surprising; however, several reasons exist why statins may be less beneficial to patients on dialysis.

Total cholesterol levels are positively correlated with mortality in the general population, but not in patients on dialysis, possibly because of concurrent malnutrition and inflammation (1). Cardiovascular disease in patients on dialysis has been increasingly attributed to nontraditional risk factors, including vascular calcification, hyperhomocysteinemia, elevated lipoprotein(a), anemia, malnutrition, and oxidative stress. Equally important is the potential for arrhythmia. The study by Wanner and colleagues showed a 42% reduction in LDL cholesterol level in the atorvastatin group, with a nominal reduction in cardiac events but no difference in all-cause mortality. Only 21% of deaths from cardiac causes were attributed to MI, while 59% were a result of sudden death, and proportions were similar in the 2 groups. This suggests that the key pathogenic mechanisms for cardiovascular disease in this population may not be modivided with statins.

The surprising results of this study underline the need to evaluate treatments, proven to be beneficial in the general population, in patients with ESRD. Upcoming results from 2 other large trials, SHARP and AURORA, may address some of the issues discussed here (2, 3). Until then, the utility of lipid-lowering therapy with statins in patients with type 2 diabetes and ESRD is uncertain.

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References

1. **Liu Y, Coresh J, Eustace JA, et al.** Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition. JAMA. 2004;291:451-9.
2. **Baigent C, Landry M.** Study of Heart and Renal Protection (SHARP). Kidney Int Suppl. 2003;84:S207-10.
3. **Fellstrom BC, Holdaas H, Jardine AG.** Why do we need a statin trial in hemodialysis patients? Kidney Int Suppl. 2003;84:S204-6.