Intensity-Dependent Benefit of Statins in Survival Among Prospective Kidney Transplant Patients

Michael Lawrenz F. Co, MD, MSc[a,b,*], Arianne Clare Agdamag, MD[a], Mita Zahra Co, MD[c,d], Martin Hertl, MD, PhD[e], and Burhan Mohamedali, MD[c]

Statin use in patients listed for in kidney transplant is believed to be beneficial. However, the optimum statin dose for improved survival in this high-risk population is unknown. Our study aimed to determine the impact of prekidney transplant statin dosage on survival postkidney transplant. In this retrospective cohort study, we enrolled patients who underwent kidney transplant from January 2005 to September 2015 at Rush University Medical. Data on the statin use and intensity used before kidney transplant were obtained. The patient population was stratified into 2 groups based on prekidney transplant use of statins. Patients using any form of statin, without regard to the type and dose, were placed in the statin groups, whereas the rest were categorized as the no statin group. The statin group was further classified into low-intensity, moderate-intensity, and high-intensity statin subgroups based on the present atherosclerotic cardiovascular disease definition of statin intensity. The primary outcome was patient survival after kidney transplant. A total of 687 patients had data on statin use before kidney transplant were followed. Median follow-up time was 3.4 years (interquartile range 1.2 to 5.6 years). Multivariate analysis showed that the use of statins prekidney transplant was associated with improved survival postkidney transplant compared with prestatin group (Hazard ratio 0.56, confidence intervals 0.32 to 1.00, p = 0.05). When patients on statins were stratified by statin intensity, Kaplan-Meier survival analysis revealed a significant dose-dependent improvement in survival. Multivariate analysis showed that the relation between statin intensity and survival was maintained even after adjusting for confounder (hazard ratio 0.30, confidence intervals 0.18 to 0.51, p < 0.001). In conclusion, our data indicate statistically significant survival benefit in patients receiving high-intensity statin before kidney transplant. **(Am J Cardiol 2019;123:254−259)**

Patients with chronic kidney disease (kidney transplant) are at an increased risk of cardiovascular disease (CVD) events.[1] Compared with the general population, patients with end stage renal disease (ESRD) are 20 to 30 times more likely to die from CVD.[1,2] The increased risk is believed to be due to higher prevalence of traditional CVD risk factors such as older age, hypertension, dyslipidemia, diabetes, and smoking in this population.[3] Statins have been shown in multiple studies to be effective in primary and secondary prevention of CVD.[4−11] Unfortunately, majority of these studies largely excluded patients with kidney dysfunction hence the results cannot be extrapolated to kidney transplant patients. The use of statins to reduce mortality in the hemodialysis population has revealed mixed results. The benefit of statins on kidney transplant recipients was previously investigated by the Assessment of Lescol in Renal Transplant (ALERT trial). Initial findings demonstrated no significant risk reduction with fluvastatin; however, the extension study which involved a longer follow-up and a higher dose of fluvastatin demonstrated a reduced risk of major adverse cardiac events and a 29% reduction in cardiac death or definite nonfatal myocardial infarction.[12,13] However, the optimal statin intensity to improve survival in this high-risk population is not known. In this study, we aimed to determine whether the use of prekidney transplant statins conferred a survival benefit in patients who underwent kidney transplant and also examined the survival outcomes of patients on different statin intensities.

Methods

In this retrospective cohort study, patients who underwent kidney transplant at Rush University Medical Center from January 2005 to September 2015 were enrolled. The study population was first divided into 2 groups called the "statin group" who consisted of patient on statins before kidney transplant and the "no statin" group who comprised of patients who were not on preoperative statins. In a second analysis, the statin group was further divided into 3 subgroups: low-intensity statin; moderate-intensity statin; and high-intensity statin as per 2013 American College of Cardiology (ACC) and American Heart Association (AHA) ACC/AHA Blood Cholesterol Guideline definition.[14]

[a]Department of Internal Medicine, Rush University Medical Center, Chicago, Illinois; [b]Department of Cardiology, Loma Linda University Medical Center, Loma Linda, California; [c]Division of Cardiology, Rush University Medical Center, Chicago, Illinois; [d]Department of Internal Medicine, Presence Saint Joseph Hospital, Chicago, Illinois; and [e]Department of Surgery, Rush University Medical Center, Chicago, Illinois. Manuscript received May 27, 2018; revised manuscript received and accepted September 25, 2018.

*Corresponding author: Tel: 201-844-3453.

E-mail address: michaellawrenzco@gmail.com (M.L.F. Co).

0002-9149/
https://doi.org/10.1016/j.amjcard.2018.09.037

Prekidney transplant factors including age at transplant, gender, weight, height, body mass index (BMI), race, presence of co-morbidities, cardiac medications profiles (including statins), vital signs, laboratory data (within 3 months before transplant), and survival data were obtained from the institution's medical records and kidney transplant database. The study was approved by the Institutional Review Board of Rush University Medical Center.

The primary outcome measured in the study was all-cause mortality. Our secondary analysis examined effect of statin intensity on survival outcomes. Continuous variables were presented as mean ± standard deviation or median (interquartile range). Categorical variables were displayed as frequencies and percentages. Baseline data in groups were compared using the chi-square test for categorical and *t* test for continuous variables. Chi-square and Fischer's exact tests were used to compare mortality rates in groups. Kaplan-Meier curves were obtained for survival and log-rank tests were performed to compare these curves. Cox survival analyses were done to control for possible confounders. Data were analyzed using SPSS 22 Premium. (IBM, Chicago).

Results

A total of 705 patients underwent kidney transplant at our institution in the study period of which only 687 patients had complete data on preoperative statin use. Of these 687 patients, 265 patients (38.6%) were on statins. The baseline demographics data are shown in Tables 1a and 1b. The overall mortality rate of in our population was 101 of 687 (14.7%). The median follow-up duration for the entire kidney transplant population was 3.4 years (interquartile range 1.2 to 5.6 years).

Baseline demographic differences between the "statin group" and the "no statin group" are summarized in Table 1a. Patients on a statin tended to be older, obese and had higher prevalence of hypertension, diabetes, coronary artery disease, obstructive sleep apnea, and cerebrovascular accident compared with those of the no statin group. They also tended to use aspirin, clopidogrel, β blockers more frequently.

The mortality rate of the statin group was 15.8% whereas that of the no statin group was 14.0%. Univariate analysis showed that statin use was not associated with an effect on survival However, when multivariate analysis incorporating age at transplant, BMI, coronary artery disease, hypertension, diabetes, and cerebrovascular accident as covariates was done, patients using statins were shown to have an improved survival compared with the no statin group (hazard ratio 0.56, confidence interval 0.32 to 1.00, $p = 0.05$). There were no differences in lipid profiles between the statin and no statin group (Table 1a).

The low-, moderate- and high-intensity statin groups had 81 (30.6%), 136 (51.3%), and 48 (18.1%) patients, respectively. Apart from age at transplant and blood urea nitrogen (BUN) before transplantation, the 3 statin intensity groups were similar in baseline characteristics except for age at transplant, BMI and serum chloride, and BUN. The mean age of low-, moderate-, and high-intensity statins were 51, 57, and 56 years, respectively ($p < 0.001$). The mean BMI were 29.8, 28.0, and 30 kg/m^2, respectively ($p = 0.009$). The mean BUN were 44, 44, and 52 mg/dl, respectively ($p = 0.04$). Lipid profiles based on statin groups were also analyzed and are shown in Table 2. Kruskal-Wallis Test showed that only low-density lipoprotein (LDL) distribution was different in the 3 groups: 86.6 ± 16 mg/dl in low-intensity group, 105 ± 12 mg/dl in moderate-intensity group, 80 ± 41 mg/dl in high-intensity group ($p = 0.035$) with the high-intensity statin group having the lowest LDL. Dose-dependent decrease in LDL was not seen (Table 2).

The mortality rate of the whole statin group was 42 of 265 (15.8%). Mortality rate in the low-, moderate- and high-intensity groups was 27.2%, 14.7%, and 0%, respectively ($p \leq 0.001$). Kaplan-Meier analysis (Figure 1) confirmed that there was improved survival as the statin intensity increased (log-rank $p = 0.001$). The mean survival of low- and moderate-intensity statins was 2,649 ± 188 and 3,207 ± 147 days, respectively. Cox regression analysis showed that after adjusting for differences in baseline age at transplant, CAD and DM the relation between statin intensity and survival was preserved (hazard ratio 0.30, confidence interval 0.18 to 0.51, $p < 0.001$).

Discussion

Our knowledge on the impact of statins on patients with kidney transplant and ESRD is limited. Latest guidelines from prominent cardiology and nephrology societies have a paucity of recommendations regarding the use of statins on patients with kidney transplant. The 2013 guidelines from the ACC and the AHA on cholesterol management do not have specific recommendations for this population group.[14] The Kidney Disease: Improving Global Outcomes 2013 guidelines recommend initiating statins in kidney transplant recipients, continuing them in ESRD patients already on statins and not starting them at all in patients on dialysis.[15] There is no specific recommendation in regards to the statin or statin intensity to be used in this population groups.

In this study, we attempted to compare survival of patients on statins versus no statins. Unfortunately, the 2 population groups were very heterogeneous. As expected based on indications for use, patients on statins had more co-morbidities. When multivariate analysis incorporating possible confounders was performed, patients on statins had a statistically significant survival advantage compared with the no statin group. The results of this analysis were consistent with the findings from the ALERT trial that showed improved outcomes with statins.

Our subgroup analysis showed a dose-dependent benefit of preoperative statin use on survival after kidney transplant. Mortality consistently decreased as the intensity of statin used increased, with no deaths being recorded in the high-intensity statin group. Our findings are similar to previous studies in other patient population groups, like the HPS, TNT, LIPID, CARE, 4S PROVE IT-TIMI 22, and JUPITER trials.[4–11] These findings build on to the body of knowledge derived from the Aurora, 4D, and ALERT trials. The Aurora and 4D trials found no benefit in statin use in hemodialysis patients whereas the ALERT trial, as previously mentioned, showed benefit among kidney transplant patients. All 3 of these studies used moderate intensity

Table 1a
Baseline demographics and co-morbidities prekidney transplant (no statin vs statin groups)

Variable	Statin therapy		p value
	No (n = 422)	Yes (n = 265)	
Age at transplant (years)	49 ± 14	56 ± 12	<0.001*
Men	269 (63.7%)	183 (64.7%)	0.43
Body mass index (kg/m^2)	27.4 ± 5.5	28.9 ± 4.7	<0.001*
Black	191 (46.4%)	112 (42.9%)	0.01*
White	109 (26.5%)	76 (29.1%)	
Hispanic	102 (24.8%)	54 (20.7%)	
Others	10 (2.4%)	19 (7.3%)	
Hypertension	346 (88.3%)	243 (92.4%)	0.05*
Diabetes mellitus	94 (23.8%)	148 (56.3%)	<0.001*
Coronary artery Disease	27 (6.9%)	85 (32.3%)	<0.001*
Atrial fibrillation	5 (1.3%)	9 (3.4%)	0.06
Ventricular tachycardia	1 (0.3%)	1 (0.4%)	0.64
Chronic obstructive pulmonary disease	9 (2.3%)	5 (1.9%)	0.48
Obstructive sleep apnea	7 (1.8%)	18 (6.%)	0.001*
Peripheral arterial disease	9 (2.3%)	7 (2.7%)	0.48
Cerebrovascular accident	16 (4.1%)	30 (11.4%)	<0.001*
Aspirin use	86 (25.6%)	128 (52.9%)	<0.001*
Clopidogrel use	8 (2.4%)	27 (11.1%)	<0.001*
angiotensin converting enzyme inhibitor/angiotensin I receptor blocker use	103 (30.7%)	88 (36.2%)	0.09
Beta-blocker use	172 (51.7%)	160 (65.8%)	<0.001*
Calcium-channel blocker use	139 (41.4%)	107 (44.0%)	0.29
Hydralazine use	40 (11.9%)	40 (16.5%)	0.09
Ejection Fraction (%)	60 ± 8	60 ± 8	0.08
Systolic blood pressure (mm Hg)	140 ± 24	144 ± 23	0.89
Diastolic blood pressure (mm Hg)	82 ± 15	79 ± 13	0.007*
Mean arterial pressure (mm Hg)	101 ± 17	100 ± 14	0.41
Heart rate (bpm)	83 ± 15	80 ± 13	0.04*
Sodium (mmol/L)	139 ± 4	139 ± 3	0.79
Potassium (mmol/L)	4.5 ± 0.8	4.5 ± 0.7	0.73
Chloride (mmol/L)	101 ± 6	101 ± 5	0.96
Bicarbonate (mmol/L)	25 ± 5	25 ± 5	0.62
Blood urea nitrogen (mg/dl)	44 ± 20	46 ± 20	0.28
Creatinine (mg/dl)	8.4 ± 3.7	8.0 ± 3.2	0.09
Total protein (g/dl)	7.1 ± 1.1	8.0 ± 10.1	0.17
Albumin (g/dl)	3.6 ± 0.7	3.6 ± 0.6	0.74
Calcium (mg/dl)	9.3 ± 1.0	9.3 ± 1.0	0.73
Total bilirubin (mg/dl)	1.3 ± 5.3	0.6 ± 0.2	0.005*
Alkaline phosphatase (U/L)	136 ± 222	101 ± 49	0.003*
Aspartate aminotransferase (U/L)	50 ± 223	21 ± 13	0.012*
Alanine aminotransferase (U/L)	27 ± 58	20 ± 17	0.03*
Hemoglobin	11.5 ± 1.8	11.5 ± 1.7	0.83
Triglyceride (mg/dl)	173 ± 125	164 ± 126	0.61
High-density lipoprotein (mg/dl)	44 ± 16	45 ± 13	0.60
Low-density lipoprotein (mg/dl)	96 ± 39	93 ± 38	0.91

* $p < 0.05$.

statins (atorvastatin 20 mg, rosuvastatin 10 mg, and fluvastatin 40 to 80 mg daily, respectively). Before our study, we have no data on the use of high-intensity statins.

Proposed mechanisms for the dose-dependent benefit of statins include a more intense lipid lowering effect, decreased oxidative stress, and improved in endothelial dysfunction with higher statin doses seen in previous studies.[16,17] Aggressive statin therapy can also lead to better anti-inflammatory and cholesterol-independent effects. The marked endothelial improvement leads to a decreased vascular response to angiotensin II, which may be the possible explanation for its benefit in coronary artery disease.[18,19] More pronounced C-reactive protein reduction has also been associated with slowing of the atherosclerotic process.[19] It has also been postulated that higher statin intensity can lead to better antithrombotic effect by reduction of fibrin formation and inhibition of matrix metalloproteinases.[19]

Although the findings from our study are preliminary and are hypothesis generating only, they do indicate the potential benefit of high dose statin on ESRD patients listed for kidney transplantation. Our study suggests that simply placing an ESRD on a low or moderate statins for their pleiotropic effects may not be sufficient. This was

Table 1b
Baseline demographics and co-morbidities prekidney transplant (low- vs moderate- vs high-intensity statin)

Variable	Statin intensity			p value
	Low(n = 81)	Moderate(n = 136)	High(n = 48)	
Age at transplant (years)	51 ± 13	57 ± 11	56 ± 9	< 0.001*
Gender (men)	50 (61.7%)	92 (67.6%)	30 (62.5%)	0.628
BMI (kg/m^2)	29.8 ± 5.0	28.0 ± 4.7	30.0 ± 3.3	0.009*
Black	38 (48.1%)	52 (38.8%)	22 (45.8%)	0.63
White	22 (27.8%)	38 (28.4%)	16 (33.3%)	
Hispanic	13 (16.5%)	33 (24.6%)	8 (16.7%)	
Others	6 (7.6%)	11 (8.2%)	2 (4.2%)	
Hypertension	74 (92.5%)	126 (93.3%)	43 (89.6%)	0.70
Diabetes mellitus	42 (52.5%)	77 (57%)	29 (60.4%)	0.66
Coronary artery disease	21 (26.3%)	45 (33.3%)	19 (39.6%)	0.28
Atrial fibrillation	3 (3.8%)	5 (3.7%)	1 (2.1%)	0.86
Ventricular tachycardia	1 (1.3%)	0	0	0.32
Chronic obstructive pulmonary disease	0	4 (3%)	1 (2.1%)	0.30
Obstructive sleep apnea	5 (6.3%)	9 (6.7%)	4 (8.3%)	0.90
Peripheral arterial disease	3 (3.8%)	3 (2.2%)	1 (2.1%)	0.77
Cerebrovascular accident	7 (8.8%)	17 (12.6%)	6 (12.5%)	0.67
Aspirin use	33 (47.8%)	66 (52.0%)	29 (63.0%)	0.27
Clopidogrel use	9 (12.9%)	11 (8.7%)	7 (15.2%)	0.41
Angiotensin converting enzyme inhibitor/angiotensin II receptor blocker use	26 (37.1%)	44 (34.6%)	18 (39.1%)	0.85
Beta-blocker use	49 (70.0%)	85 (66.9%)	26 (56.5%)	0.30
Calcium channel blocker use	33 (47.1%)	54 (42.5%)	20 (43.5%)	0.82
Hydralazine use	12 (17.1%)	18 (14.2%)	10 (21.7%)	0.49
Ejection fraction (%)	60.2 ± 7.8	59.2 ± 7.5	59.8 ± 10.1	0.69
Systolic blood pressure (mm Hg)	143.1 ± 24.8	142.3 ± 20.9	148.7 ± 23.8	0.26
Diastolic blood pressure (mm Hg)	79.0 ± 12.7	77.0 ± 13.2	81.7 ± 14.5	0.12
Mean arterial pressure (mm Hg)	100.4 ± 14.7	98.8 ± 13.0	104.0 ± 15.5	0.10
Heart rate (bpm)	79 ± 11	82 ± 13	79 ± 14	0.41
Sodium (mmol/L)	139 ± 4	139 ± 3	140 ± 3	0.14
Potassium (mmol/L)	4.5 ± 0.8	4.5 ± 0.7	4.7 ± 0.8	0.27
Chloride (mmol/L)	100 ± 4	100 ± 5	102 ± 6	0.05
Bicarbonate (mmol/L)	25 ± 5	25 ± 5	24 ± 5	0.10
Blood urea nitrogen (mg/dl)	44 ± 20	44 ± 19	52 ± 22	0.04*
Creatinine (mg/dl)	8.22 ± 3.31	7.69 ± 3.22	8.31 ± 3.18	0.36
Total protein (g/dl)	7.1 ± 1.2	8.9 ± 13.9	7.1 ± 0.9	0.41
Albumin (g/dl)	3.4 ± 0.6	3.6 ± 0.6	3.5 ± 0.5	0.09
Calcium (mg/dl)	9.2 ± 1.0	9.3 ± 0.3	9.3 ± 1.0	0.87
Total bilirubin (mg/dl)	0.6 ± 0.2	0.6 ± 0.3	0.5 ± 0.2	0.70
Alkaline phosphatase (U/L)	104 ± 46	99 ± 44	100 ± 65	0.81
Aspartate aminotransferase (U/L)	21 ± 12	21 ± 12	25 ± 18	0.15
Alanine aminotransferase (U/L)	18 ± 12	20 ± 17	23 ± 22	0.32
Triglyceride (mg/dl)	181 ± 159	144 ± 81	200 ± 174	0.22
High-density lipoprotein (mg/dl)	48 ± 16	46 ± 12	41 ± 13	0.30
Low-density lipoprotein (mg/dl)	86 ± 30	105 ± 42	80 ± 30	0.02*

* $p < 0.05$.

demonstrated by our survival analysis, where the survival of patients who were not on statin, despite having a better co-morbidity profiles than patients on moderate and low-intensity statin were comparable. Patients on high-intensity statin did have the best LDL profiles, but whether the survival advantage was conferred by the lower LDL or other confounders will need to be further studied.

Table 2
Lipid level distribution based on statin intensity

Statin intensity	Number	LDL	HDL	Triglyceride
None (mg/dl)	422 (61%)	85 ± 30	44 ± 16	172 ± 125
Low (mg/dl)	81 (12%)	86 ± 30	48 ± 16	181 ± 159
Moderate (mg/dl)	136 (20%)	105 ± 42	46 ± 12	144 ± 81
High (mg/dl)	48 (7%)	80 ± 30	41 ± 13	200 ± 174

This study carries the major intrinsic limitation of being a retrospective cohort study. Information was obtained from chart review. A potential patient selection bias in terms of which patients received kidney transplant in our institution may be present. Labs were obtained as deemed necessary by the treatment care team at the time of presentation. Duration of statin used was not available, and it was not ascertained whether there was significant crossover after kidney transplant. Our study was male predominant (64% men). Many patients followed up on a different

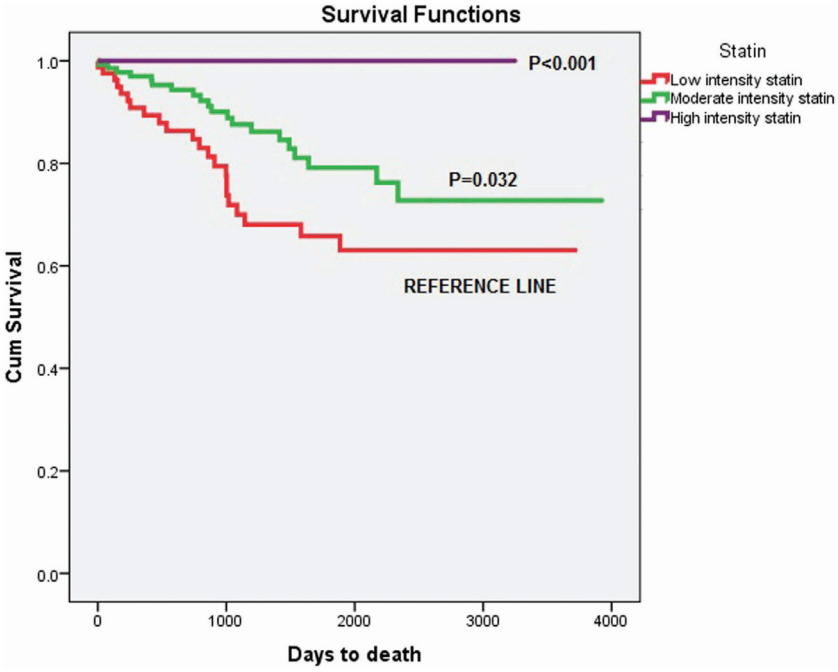

Figure 1. Kaplan-Meier curve comparing survival of different statin intensity groups.

institution after kidney transplant so follow-up data may be incomplete in many patients. However, accurate mortality data were obtained from the kidney transplant program that actively tracks survival data ensuring that the quality of the primary end point analysis was robust. Despite our limitations, this is a first large sample cohort examining the effect of statin intensity on kidney transplant outcomes.

Our long-term follow-up retrospective study involving 687 patients showed that in ESRD patients who eventually underwent kidney transplant, a statistically significant survival benefit is associated using statins and increasing statin intensities confer higher survival benefit.

Declarations of interest

None.

1. Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. *Heart Asia* 2016;8:5–61. https://doi.org/10.1136/heartasia-2016-010809.
2. Neale J. Cardiovascular risk factors following renal transplant. *World J Transplant* 2015;5:183. https://doi.org/10.5500/wjt.v5.i4.183.
3. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Hypertens* 2003;42:1050–1065. https://doi.org/10.1161/01.HYP.0000102971.85504.7c.
4. Pedersen TR, Kjheksus J, Berg K, Haghfelt T, Faergeman O, Faergeman G, Pyorala K, Miettinen T, Wilhemsen L, Olsson AG, Wedel H. Randomized trial of cholesterol-lowering in 444 patients with coronary-heart-disease - the scandinavian simvastatin survival study (4S). *Lancet* 1994;344:1383–1389.
5. Shepherd J, Cobbe SM, Ford I, Isless CG, Lorimer AR, MacFarlane PW, McKillop JH, Packard CJ. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301–1308. https://doi.org/10.1056/NEJM199511163332001.
6. Group TL-TI with P in ID (LIPID) S. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349–1357. https://doi.org/10.1056/NEJM199811053391902.
7. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–1504. https://doi.org/10.1056/NEJMoa040583.
8. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–1435. https://doi.org/10.1056/NEJMoa050461.
9. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto A.M. Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepher J, Willerson JT, Glynn RJ. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. *N Engl J Med* 2008;359:2195–2207. https://doi.org/10.1056/NEJMoa0807646.
10. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The Effect of Pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001–1009. https://doi.org/10.1056/NEJM199610033351401.
11. Heart protection Study Collaborative group. MRC/BHF Heart protection study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22. https://doi.org/10.1016/S0140-6736(02)09327-3.
12. Fellström B, Holdaas H, Jardine AG, Holme I, Nyberg G, Fauchald P, Gronhagen-Riska C, Madsen S, Neumayer H, Cole E, Maes B, Ambuhl P, Olsson AG, Hartmann A, Logan JO, Pedersen TR. Effect of fluvastatin on renal end points in the assessment of lescol in renal transplant (ALERT) trial. *Kidney Int* 2004;66:1549–1555. https://doi.org/10.1111/j.1523-1755.2004.00919.x.
13. Holdaas H, Fellström B, Cole E, Nyberg G, Olsson AG, Pedersen TR, Madsen S, Gronhagen-Riska C, Neumayer HH, Maes B, Ambuhl P, Hartmann A, Staffler B, Jardine AG. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the ALERT extension study. *Am J Transplant* 2005;5:2929–2936. https://doi.org/10.1111/j.1600-6143.2005.01105.x.

14. Stone NJ, Robinson JG, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. *Circulation* 2014;129(25 SUPPL. 1). https://doi.org/10.1161/01.cir.0000437738.63853.7a.
15. Kdigo. Clinical practice guideline for lipid management in chronic kidney disease. *Kidney Int* 2013;3:182–189. https://doi.org/10.7326/M13-2453.
16. Wissing KM, Unger P, Ghisdal L, Broeders N, Berkenboom G, Carpentier Y, Abramowicz D. Effect of atorvastatin therapy and conversion to tacrolimus on hypercholesterolemia and endothelial dysfunction after renal transplantation. *Transplantation* 2006;82:771–778. https://doi.org/10.1097/01.tp.0000235446.50715.ef.
17. Ivanovski O, Szumilak D, Nguyen-Khoa T, Nikolov IG, Joki N, Mothu N, Maizel J, Westenfeld R, Ketteler M, Lacour B, Drueke TB, Massy ZA. Effect of simvastatin in apolipoprotein E deficient mice with surgically induced chronic renal failure. *J Urol* 2008;179:1631–1636. https://doi.org/10.1016/j.juro.2007.11.042.
18. van der Harst P, Wagenaar LJ, Buikema H, Voors AA, Thijs Plokker HW, Morshuis WJ, Six AJ, Boonstra PW, Nickenig G, Wassmann S, van Veldhuisen DJ, van Gilst WH. Effect of intensive versus moderate lipid lowering on endothelial function and vascular responsiveness to angiotensin II in stable coronary artery disease. *Am J Cardiol* 2005;96:1361–1364. https://doi.org/10.1016/j.amjcard.2005.07.052.
19. Gupta S. Does aggressive statin therapy offer improved cholesterol-independent benefits compared to conventional statin treatment? *Int J Cardiol* 2004;96:131–139 https://doi.org/10.1016/j.ijcard.2003.10.013.