formidable question to answer, and it requires a rigorous investigative approach.

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DISCLOSURES

None.

REFERENCES

1. Schell C, Huber TB: New players in the pathogenesis of focal segmental glomerulosclerosis. *Nephrol Dial Transplant* 27: 3406–3412, 2012
2. D'Agati VD, Kaskel FJ, Falk RJ: Focal segmental glomerulosclerosis. *N Engl J Med* 365: 2398–2411, 2011
3. Fukuda A, Chowdhury MA, Venkatareddy MP, Wang SQ, Nishizono R, Suzuki T, Wickman LT, Wiggins JE, Muchayi T, Fingar D, Shedden KA, Inoki K, Wiggins RC: Growth-dependent podocyte failure causes glomerulosclerosis. *J Am Soc Nephrol* 23: 1351–1363, 2012
4. Kriz W: Glomerular diseases: Podocyte hypertrophy mismatch and glomerular disease. *Nat Rev Nephrol* 8: 618–619, 2012
5. Ichikawa I, Ma J, Motojima M, Matsusaka T: Podocyte damage damages podocytes: Autonomous vicious cycle that drives local spread of glomerular sclerosis. *Curr Opin Nephrol Hypertens* 14: 205–210, 2005
6. Fukuda A, Wickman LT, Venkatareddy MP, Sato Y, Chowdhury MA, Wang SQ, Shedden KA, Dysko RC, Wiggins JE, Wiggins RC: Angiotensin II-dependent persistent podocyte loss from destabilized glomeruli causes progression of end stage kidney disease. *Kidney Int* 81: 40–55, 2012
7. Schiffer M, Bitzer M, Roberts IS, Kopp JB, ten Dijke P, Mundel P, Böttinger EP: Apoptosis in podocytes induced by TGF-beta and Smad7. *J Clin Invest* 108: 807–816, 2001
8. Hartleben B, Gödel M, Meyer-Schwesinger C, Liu S, Ulrich T, Köbler S, Wiech T, Grahammer F, Arnold SJ, Lindenmeyer MT, Cohen CD, Pavenstädt H, Kerjaschki D, Mizushima N, Shaw AS, Walz G, Huber TB: Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice. *J Clin Invest* 120: 1084–1096, 2010
9. Hartleben B, Wanner N, Huber TB: Autophagy in glomerular health and disease. *Semin Nephrol* 34: 42–52, 2014
10. Kume S, Yamahara K, Yasuda M, Maegawa H, Koya D: Autophagy: Emerging therapeutic target for diabetic nephropathy. *Semin Nephrol* 34: 9–16, 2014
11. Inoki K, Mori H, Wang J, Suzuki T, Hong S, Yoshida S, Blattner SM, Ikenoue T, Rüegg MA, Hall MN, Kwiatkowski DJ, Rastaldi MP, Huber TB, Kretzler M, Holzman LB, Wiggins RC, Guan KL: mTORC1 activation in podocytes is a critical step in the development of diabetic nephropathy in mice. *J Clin Invest* 121: 2181–2196, 2011
12. Gödel M, Hartleben B, Herbach N, Liu S, Zschiedrich S, Lu S, Debreczeni-Mór A, Lindenmeyer MT, Rastaldi MP, Hartleben G, Wiech T, Fornoni A, Nelson RG, Kretzler M, Wanke R, Pavenstädt H, Kerjaschki D, Cohen CD, Hall MN, Rüegg MA, Inoki K, Walz G, Huber TB: Role of mTOR in podocyte function and diabetic nephropathy in humans and mice. *J Clin Invest* 121: 2197–2209, 2011
13. Wan G, Zhaorigetu S, Liu Z, Kaini R, Jiang Z, Hu CA: Apolipoprotein L1, a novel Bcl-2 homology domain 3-only lipid-binding protein, induces autophagic cell death. *J Biol Chem* 283: 21540–21549, 2008
14. Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR: APOL1 localization in normal kidney and nondiabetic kidney disease. *J Am Soc Nephrol* 22: 2119–2128, 2011
15. Yaddanapudi S, Altintas MM, Kistler AD, Fernandez I, Möller CC, Wei C, Peev V, Flesche JB, Forst AL, Li J, Patrakka J, Xiao Z, Grahammer F, Schiffer M, Lohmüller T, Reinheckel T, Gu C, Huber TB, Ju W, Bitzer M, Rastaldi MP, Ruiz P, Tryggvason K, Shaw AS, Faul C, Sever S, Reiser J: CD2AP in mouse and human podocytes controls a proteolytic program that regulates cytoskeletal structure and cellular survival. *J Clin Invest* 121: 3965–3980, 2011
16. Faul C, Donnelly M, Merscher-Gomez S, Chang YH, Franz S, Delfgaauw J, Chang JM, Choi HY, Campbell KN, Kim K, Reiser J, Mundel P: The actin cytoskeleton of kidney podocytes is a direct target of the antiproteinuric effect of cyclosporine A. *Nat Med* 14: 931–938, 2008
17. Kawakami T, Gomez IG, Ren S, Hudkins K, Roach A, Alpers CE, Shankland SJ, D'Agati VD, Duffield JS: Deficient autophagy results in mitochondrial dysfunction and FSGS. *J Am Soc Nephrol* 26: 1040–1052, 2015

See related article, "Deficient Autophagy Results in Mitochondrial Dysfunction and FSGS," on pages 1040–1052.

We Don't Prescribe Statins to Lower Cholesterol: We Prescribe Statins to Reduce Vascular Risk

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Statins are an important method for reducing the global burden of noncommunicable chronic diseases (NCDs) such as, vascular disease, hypertension, and diabetes. Statins are one of the most intensively studied medications, with >200,000 patients enrolled in randomized trials. Although statins are not "magic bullets," they have important clinical benefits when used appropriately—including reductions in the risk of death, stroke, and myocardial infarction.

Because higher levels of LDL cholesterol (LDL-C) are associated with excess vascular risk in the general population, it is logical to assume that statins should be prescribed to treat hypercholesterolemia, which in turn reduces the risk of vaslar events. This assumption has served patients well,

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because it was the basis for most of the landmark trials that established the evidence base in favor of statin use. However, it is now time to discard the corollary of this assumption: that statins should not be used in people without hypercholesterolemia.

Data now clearly show that the relative reduction in the risk of vascular events associated with a 1-mmol/L lowering in LDL-C is consistently 20%–25%, even for patients with blood cholesterol levels below the normal range.[1] Thus, the primary determinant of benefit from statins is baseline risk rather than baseline LDL-C, and so normal or even low LDL-C should not preclude the use of statins in people at high vascular risk. Instead, the goal should be to identify patients whose clinical characteristics (including LDL-C) place them at higher vascular risk, and increase the use of statins and other beneficial therapies in this population.

A risk-based approach is more rational for all patients, but especially so for the care of CKD patients, in whom LDL-C levels are less reliable predictors of vascular risk than in the general population[2] and who may be at exceedingly high vascular risk despite normal or low cholesterol levels. In fact, the risk of future myocardial infarction is higher among people with CKD than in those with diabetes,[3] who are already considered to be in the highest risk category for vascular events.

In response to the evolving evidence, guideline producers around the world have adjusted their primary criterion for statin prescription accordingly, with most recommendations now appropriately based on overall risk and not LDL-C alone. Two recently published guidelines that take this approach are those from the international Kidney Disease Improving Global Outcomes (KDIGO) organization (which apply only to people with CKD)[4] and those from the American College of Cardiology/American Heart Association (ACC/AHA)[5] (which apply to all adults). Although both guidelines use overall risk as the key criterion for statin prescription, the KDIGO guidelines are simpler to apply, because risk is estimated chiefly by age and the presence/absence of prior vascular events and diabetes (Table 1).

In this issue of *JASN*, Colantonio and colleagues report an interesting analysis that compares the performance of the KDIGO and ACC/AHA guidelines in a large national cohort of US adults (the Reasons for Geographic and Racial Differences in Stroke [REGARDS] study).[6] The REGARDS study included white and black adults from across the United States; the current analysis focused on those who were aged 50–79.9 years and had CKD (eGFR<60 ml/min per 1.73 m^2 or albuminuria>30 mg/g) but were not treated with dialysis.

Colantonio and colleagues used the clinical characteristics of the 4726 participants with CKD to identify those who would be recommended statins by the two sets of guidelines, to assess who actually received statins in clinical practice, and to ascertain the occurrence of vascular events (fatal/nonfatal stroke, myocardial infarction, and death from coronary disease) over 5 years of follow-up. This simple but rigorously done analysis yielded the following key findings.

First, despite their very high vascular risk (average 10-year risk of vascular events of 14.1%), only 50% of CKD patients were taking statins. The underuse of statins in high-risk CKD populations has been repeatedly reported for more than a decade,[7] and is a key quality gap that clinicians should address. There is strong evidence that statin-based regimens safely reduce the risk of vascular events in people with nondialysis-dependent CKD, and that the absolute risk reduction is especially favorable in this population due to their high baseline risk. Although there is no evidence that statins improve outcomes in dialysis patients, neither of the two guidelines recommend initiation of statins in this population.

Second, although the KDIGO and ACC/AHA guidelines use very different methods for estimating future vascular risk (and were developed independently by separate groups of experts), concordance between the two is extremely high. In fact, Colantonio and colleagues found that 92% of CKD patients in whom statins were recommended by KDIGO were also recommended for statin treatment by the ACC/AHA. This suggests that among people with CKD who are aged 50–80 years, the differences between the guidelines are unlikely to cause

Table 1. Comparison of the KDIGO and ACC/AHA guidelines: Criteria for statin prescription in people with nondialysis-dependent CKD (any stage)

Aged ≥50 yr		Aged <50 yr	
KDIGO	**ACC/AHA**	**KDIGO**	**ACC/AHA**
All	Known vascular disease[a]	Known vascular disease[a]	Known vascular disease[a]
	LDL-C>190 mg/dl		LDL-C>190 mg/dl
	Diabetes+age 40–79 yr+LDL-C 70–189 mg/dl	Diabetes	Diabetes+age 40–79 yr+LDL-C 70–189 mg/dl
	10-yr predicted risk for vascular event[b] >7.5% using the pooled cohort risk equations	10-yr predicted risk for vascular event[b] >10%	10-yr predicted risk for vascular event[b] >7.5% using the pooled cohort risk equations

Nondialysis-dependent CKD is defined by eGFR<60 ml/min per 1.73 m^2 or albuminuria>30 mg/g.

[a]Known vascular disease was defined by KDIGO as myocardial infarction, stroke, or coronary revascularization and was defined by ACC/AHA as myocardial infarction, stroke, coronary revascularization, peripheral revascularization, or aortic aneurysm repair.

[b]Future vascular events were defined by KDIGO as cardiovascular death or nonfatal myocardial infarction and were defined by ACC/AHA as fatal/nonfatal stroke, myocardial infarction, and death from coronary disease.

much confusion for clinicians about who should receive statin treatment.

Third, although the two guidelines reach very similar conclusions when applied to individual patients, the KDIGO guideline is substantially less complex to use. For the population studied by Colantonio and colleagues, KDIGO recommends that all should be treated, whereas the ACC/AHA guideline requires clinicians to assess whether the patient has coronary disease or diabetes, to measure LDL-C, and to use a risk calculator before deciding who to treat or not. More complex guidelines are less likely to be used in practice,[8] meaning that more complicated recommendations are less likely to increase the low prevalence of statin use in CKD populations. For this reason, the KDIGO Lipid Guideline Development Work Group placed a high priority on drafting simple recommendations that would be easy for clinicians to use.

Fourth, Colantonio and colleagues did not study CKD patients aged <50 years, so the consequences of applying the KDIGO versus the ACC/AHA guidelines for this population are unknown. KDIGO recommendations for nondialysis CKD patients aged <50 years are more complex than for those aged ≥50 years (Table 1) but still less complex than the ACC/AHA recommendations. In essence, KDIGO recommends statin therapy for all such patients with prior vascular events, diabetes, or a functioning kidney transplant, in whom the 10-year risk of vascular events is very high. For the smaller number of CKD patients aged <50 years who do not meet these criteria, the KDIGO guideline suggests the use of a risk calculator, with statins advised for those in whom 10-year risk is >10%. By contrast, the ACC/AHA guideline again requires LDL-C measurement and use of a risk calculator, with treatment recommended for those in whom 10-year risk is >7.5%.

These considerations suggest that for those aged <50 years, the ACC/AHA guideline will recommend for statin treatment in a larger proportion of CKD patients than the KDIGO guideline, and that most of the additional statin recipients will have 10-year risks between 7.5% and 10%. Because thresholds of >7.5% and >10% are both arbitrary, this difference does not imply that one guideline is superior. However, the added complexity of the ACC/AHA guideline seems unnecessary for CKD patients, and remains a potential barrier to uptake.

The negative findings of statin trials in hemodialysis patients should not distract clinicians or policymakers from the critical objective of improving care for the much larger population of people with milder CKD, in whom statins are clearly effective. In both rich and poor countries, CKD and other NCDs collectively represent the major health threat of our time.[9] Population-based, risk-driven strategies aimed at preventing vascular events will be a key method for reducing death and disability, but only if they are simple enough for clinicians to rapidly apply at the bedside. The findings of Colantonio and colleagues suggest that the KDIGO guideline is more likely to achieve this goal for CKD patients than the ACC/AHA guideline. The next step is to increase the dissemination and uptake of population-based strategies for NCD control, including statins but also interruption of the renin/angiotensin system, healthy diet and exercise, smoking cessation, and control of BP, blood sugar, and body weight.

DISCLOSURES

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REFERENCES

1. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R; Cholesterol Treatment Trialists' (CTT) Collaboration: Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 376: 1670–1681, 2010
2. Tonelli M, Muntner P, Lloyd A, Manns B, Klarenbach S, Pannu N, James M, Hemmelgarn B; Alberta Kidney Disease Network: Association between LDL-C and risk of myocardial infarction in CKD. *J Am Soc Nephrol* 24: 979–986, 2013
3. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, James MT, Hemmelgarn BR; Alberta Kidney Disease Network: Risk of coronary events in people with chronic kidney disease compared with those with diabetes: A population-level cohort study. *Lancet* 380: 807–814, 2012
4. Tonelli M, Wanner C; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members: Lipid management in chronic kidney disease: Synopsis of the Kidney Disease: Improving Global Outcomes 2013 clinical practice guideline. *Ann Intern Med* 160: 182, 2014
5. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 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* 129[Suppl 2]: S1–S45, 2014
6. Colantonio LD, Baber U, Banach M, Tanner RM, Warnock DG, Gutiérrez OM, Safford MM, Christoph W, Howard G, Muntner P: Contrasting cholesterol management guidelines for adults with CKD. *J Am Soc Nephrol* 26: 1173–1180, 2015
7. Tonelli M, Bohm C, Pandeya S, Gill J, Levin A, Kiberd BA: Cardiac risk factors and the use of cardioprotective medications in patients with chronic renal insufficiency. *Am J Kidney Dis* 37: 484–489, 2001
8. Cabana MD, Rand CS, Powe NR, Wu AW, Wilson MH, Abboud PA, Rubin HR: Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 282: 1458–1465, 1999
9. Murray CJ, Lopez AD: Measuring the global burden of disease. *N Engl J Med* 369: 448–457, 2013

See related article, "Contrasting Cholesterol Management Guidelines for Adults with CKD," on pages 1173–1180.