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Rational Lipid Therapy on Dialysis

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KDIGO Clinical Practice Guideline for Lipid Management in Chronic Kidney Disease

http://www.kidney-international.org

contents

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Here beginneth the saga….

Chapter 1: Assessment of lipid status in adults with CKD

1.1: In adults with newly identified CKD (including those treated with chronic dialysis or kidney transplantation), we recommend evaluation with a lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). (*1C*)

1.2: In adults with CKD (including those treated with chronic dialysis or kidney transplantation), follow-up measurement of lipid levels is not required for the majority of patients. (*Not Graded*)

Now, isn't that interesting???

2.3.1: In adults with dialysis-dependent CKD, we suggest that statins or statin/ezetimibe combination not be initiated. (*2A*)

2.3.2: In patients already receiving statins or statin/ezetimibe combination at the time of dialysis initiation, we suggest that these agents be continued. (*2C*)

5.1: In adults with CKD (including those treated with chronic dialysis or kidney transplantation) and hypertriglyceridemia, we suggest that therapeutic lifestyle changes be advised. (*2D*)

The underlying rationale…..

Upon first presentation to establish the diagnosis of CKD, the nephrologist will obtain a full lipid profile as part of routine care. In case of referral and to confirm the CKD diagnosis, a full lipid profile may already be available. Results of the lipid profile should be used together with other clinical data to rule out remediable causes of secondary dyslipidemia. If excluded, the nephrologist will establish whether statin treatment is indicated (YES or NO) based on underlying cardiovascular risk. If the level of risk suggests that statin treatment is indicated, she/he will select a dose of a statin (Table 4) that is available in her/his country and has been tested for safety in people with CKD.

Contemporary practice and other clinical practice guidelines emphasize the use of targets for LDL-C (e.g., 1.8 or 2.6 mmol/l [70 or 100 mg/dl]), which require repeated measurements of LDL-C and treatment escalation with higher doses of statin or initiation of combination lipid-lowering therapy ("treat-to-target" strategy) when the LDL-C target is not met. The KDIGO Work Group does not recommend the treat-to-target strategy because it has never been proven beneficial in any clinical trial. In addition, higher doses of statins have not been proven to be safe in the setting of CKD. Therefore, the Work Group recommends a "fire-and-forget" strategy for patients with CKD (see Rationale for Recommendation 1.2). Physicians may choose to perform follow-up measurement of lipid levels in patients for whom these measurements are judged to favorably influence adherence to treatment or other processes of care.

Table 4

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Table 4 | Recommended doses (mg/d) of statins in adults with CKD

Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP	nd
Fluvastatin	GP	80[1]
Atorvastatin	GP	20[2]
Rosuvastatin	GP	10[3]
Simvastatin/Ezetmibe	GP	20/10[4]
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

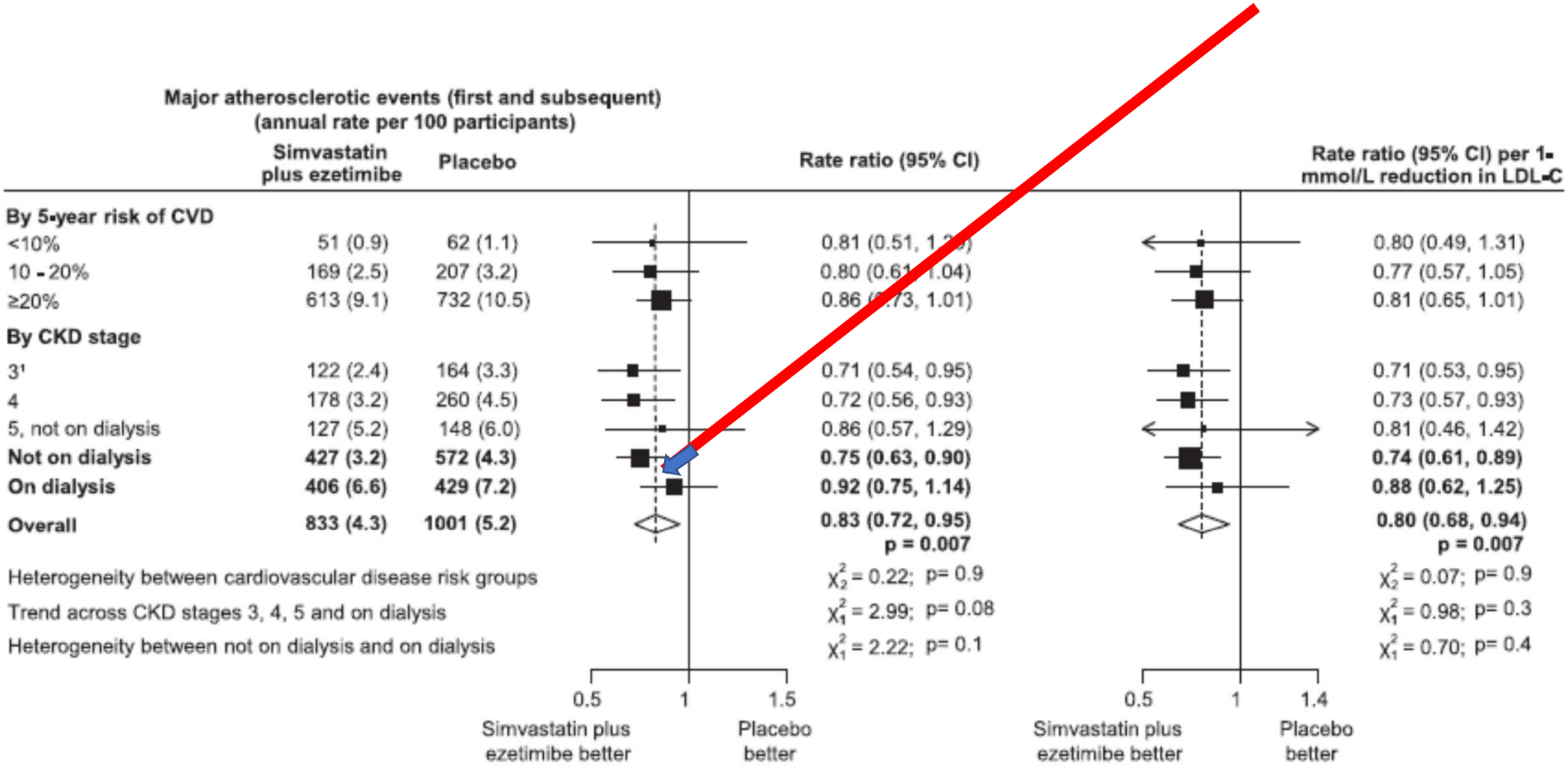
All statins may not be available in all countries. Lower doses than those used in major trials of statins in CKD populations may be appropriate in Asian countries. Note that rosuvastatin 40 mg daily is not recommended for use in CKD 1-2 non-transplant patients, as it may increase the risk of adverse renal events. Cyclosporin inhibits the metabolism of certain statins resulting in higher blood levels. Data based on [1]ALERT, [2]4D, [3]AURORA, [4]SHARP. Abbreviations: eGFR, estimated glomerular filtration rate; GP, general population; nd, not done or not studied.

In the special case of patients on dialysis…..

- 4D STUDY (2005)
  - ***Wanner C,*** Krane V, März W, Olschewski M, Mann JF, Ruf G, Ritz E; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med. 2005 Jul 21;353(3):238-48. Erratum in: N Engl J Med. 2005 Oct 13;353(15):1640.

- AURORA STUDY (2009)
  - ***Fellström BC***, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, Chae DW, Chevaile A, Cobbe SM, Grönhagen-Riska C, De Lima JJ, Lins R, Mayer G, McMahon AW, Parving HH, Remuzzi G, Samuelsson O, Sonkodi S, Sci D, Süleymanlar G, Tsakiris D, Tesar V, Todorov V, Wiecek A, Wüthrich RP, Gottlow M, Johnsson E, Zannad F; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. N Engl J Med. 2009 Apr 2;360(14):1395-407.

- SHARP-2 STUDY (2011)
  - ***Baigent C***, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, de Zeeuw D, Grönhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z, Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011 Jun 25;377(9784):2181-92.


Major atherosclerotic events (first and subsequent)
(annual rate per 100 participants)
Simvastatin plus ezetimibe
Placebo
Rate ratio (95% CI)
Rate ratio (95% CI) per 1-mmol/L reduction in LDL-C
By 5-year risk of CVD
<10% 51 (0.9) 62 (1.1) 0.81 (0.51, 1.29) 0.80 (0.49, 1.31)
10 - 20% 169 (2.5) 207 (3.2) 0.80 (0.61, 1.04) 0.77 (0.57, 1.05)
≥20% 613 (9.1) 732 (10.5) 0.86 (0.73, 1.01) 0.81 (0.65, 1.01)
By CKD stage
3¹ 122 (2.4) 164 (3.3) 0.71 (0.54, 0.95) 0.71 (0.53, 0.95)
4 178 (3.2) 260 (4.5) 0.72 (0.56, 0.93) 0.73 (0.57, 0.93)
5, not on dialysis 127 (5.2) 148 (6.0) 0.86 (0.57, 1.29) 0.81 (0.46, 1.42)
Not on dialysis 427 (3.2) 572 (4.3) 0.75 (0.63, 0.90) 0.74 (0.61, 0.89)
On dialysis 406 (6.6) 429 (7.2) 0.92 (0.75, 1.14) 0.88 (0.62, 1.25)
Overall 833 (4.3) 1001 (5.2) 0.83 (0.72, 0.95) p = 0.007 0.80 (0.68, 0.94) p = 0.007
Heterogeneity between cardiovascular disease risk groups χ^2_2 = 0.22; p= 0.9 χ^2_2 = 0.07; p= 0.9
Trend across CKD stages 3, 4, 5 and on dialysis χ^2_1 = 2.99; p= 0.08 χ^2_1 = 0.98; p= 0.3
Heterogeneity between not on dialysis and on dialysis χ^2_1 = 2.22; p= 0.1 χ^2_1 = 0.70; p= 0.4
0.5
1
1.5
Simvastatin plus ezetimibe better
Placebo better
0.5
1
1.4
Simvastatin plus ezetimibe better
Placebo better

Meta-analyses…..

34. Palmer SC, Craig JC, Navaneethan SD *et al.* Benefits and harms of statin therapy for persons With chronic kidney disease: A systematic review and meta-analysis. *Ann Intern Med* 2012; **157**: 263–275.

46. Hou W, Lv J, Perkovic V *et al.* Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J* 2013; **34**: 1807–1817.

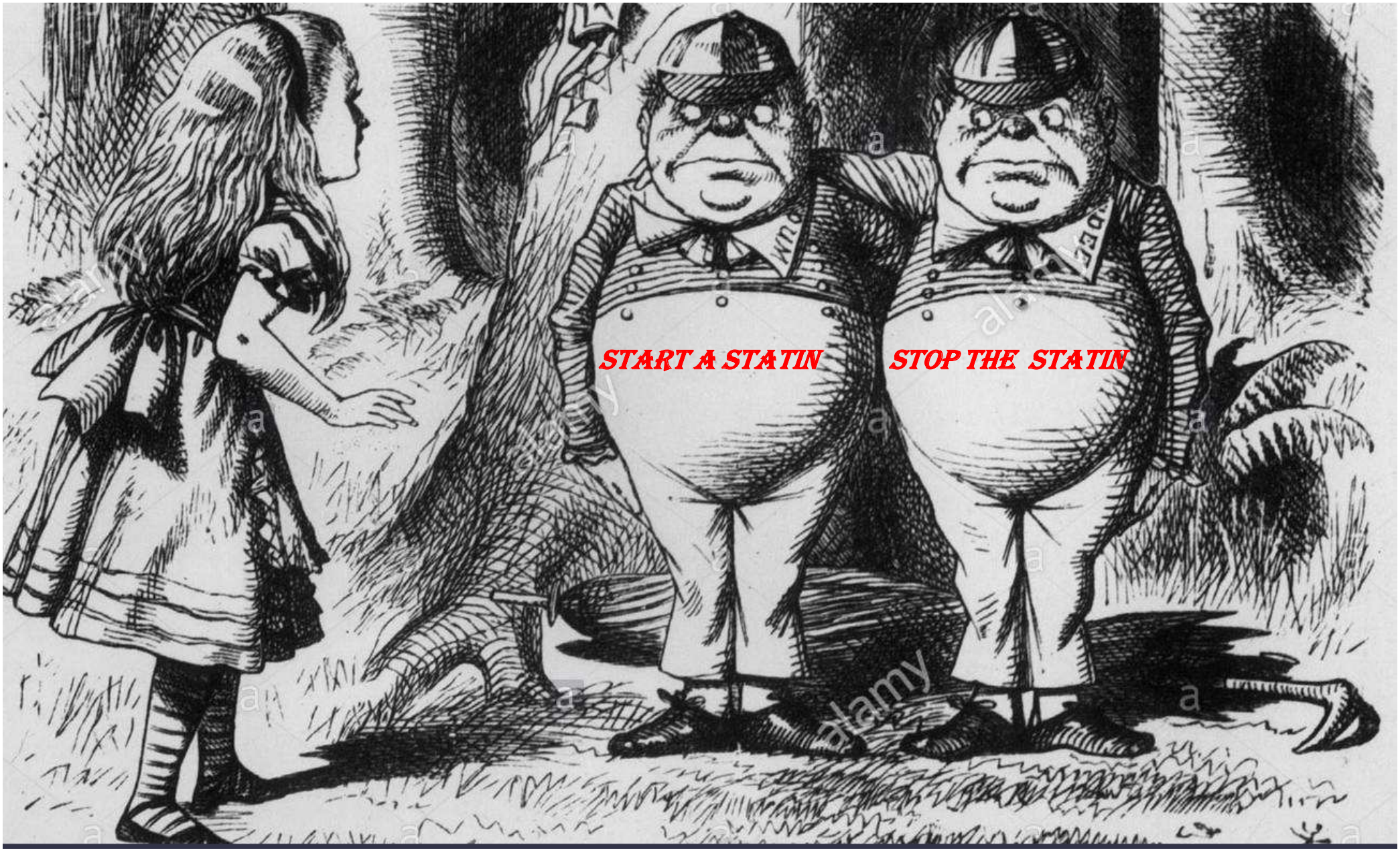
Taking the results from all three of the studies …..

A systematic review pooling data from all available randomized trials done in CKD populations reported significant heterogeneity between dialysis and non-dialysis patients for the benefit of statins on major cardiovascular events (HR for dialysis 0.96; 95% CI 0.88–1.03; HR for non-dialysis 0.76; 95% CI 0.72–0.79; p for heterogeneity <0.001).[34] When findings from SHARP, 4D and AURORA are considered together, the clinical benefit of statins (alone or in combination with ezetimibe) in prevalent dialysis patients is uncertain. Another meta-analysis in essence confirmed the results, although the data were analyzed in a different manner.[45] Even if statins truly do prevent cardiovascular events in prevalent dialysis patients, it is clear that the magnitude of any relative reduction in risk is substantially smaller than in earlier stages of CKD.[34] However, if this speculative benefit among dialysis patients is confirmed in future studies, the absolute benefit might be comparable to that in people with less severe CKD, due to the higher event rate among dialysis patients.[46]

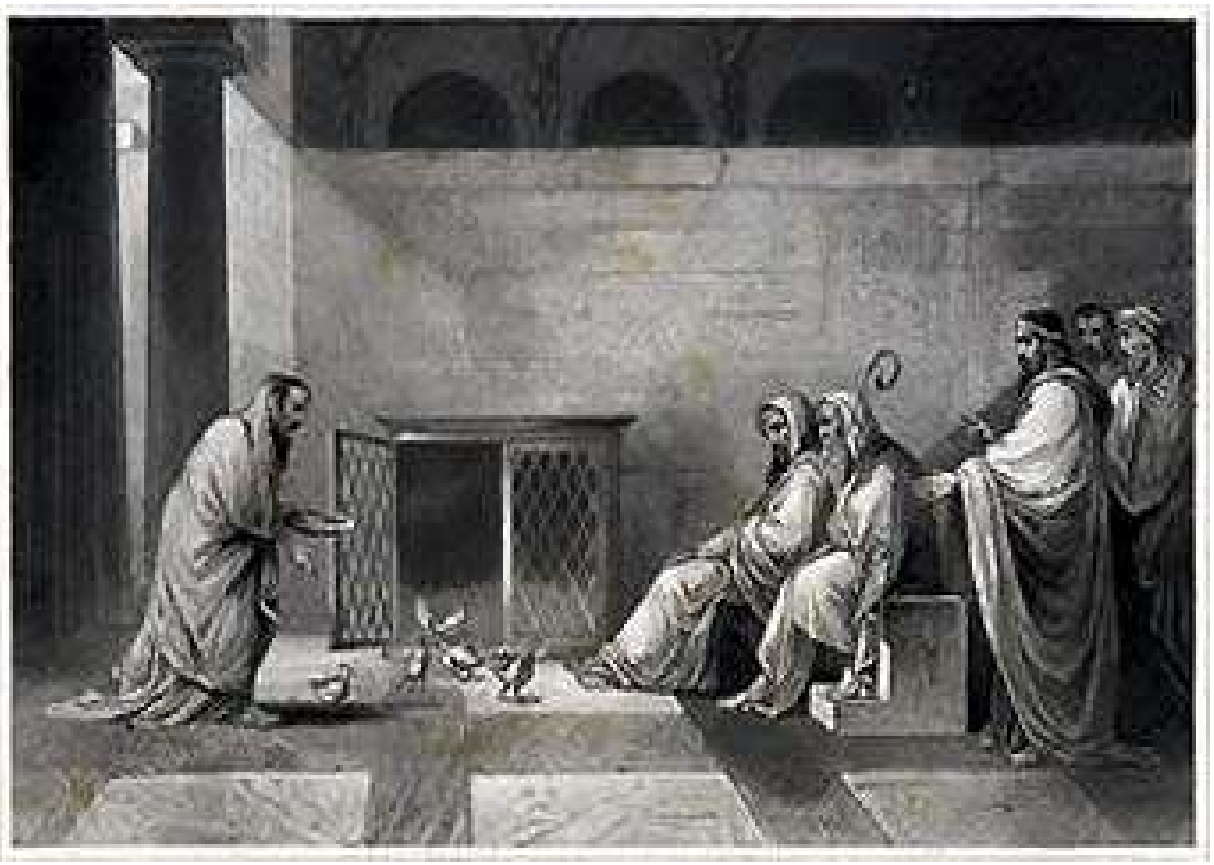
A perfect storm?

- Patients with dialysis-dependent CKD should not be initiated on statin or statin/ezetimibe treatment, given the lack of evidence that such treatment is beneficial. However, statin or statin/ezetimibe treatment should not necessarily be discontinued among existing users when dialysis treatment is initiated.

- But there are no obvious or known safety concerns specific to dialysis patients on statins


START A STATIN
STOP THE STATIN

Divination – by haruspication, or by augury



So, it comes down to…..

- Think about it…
- Think about it maybe some more…
- Ask the patient for their views…
- Toss a coin… ask a spiritualist…

- If a patient is ON a statin, on dialysis, then LEAVE THEM BE and continue the statin treatment
- If a patient is NOT on a statin, on dialysis, DO NOT routinely start one, though maybe be “guided” by innate / underlying CV risk


17
25
2
21
4
19
15
32
0

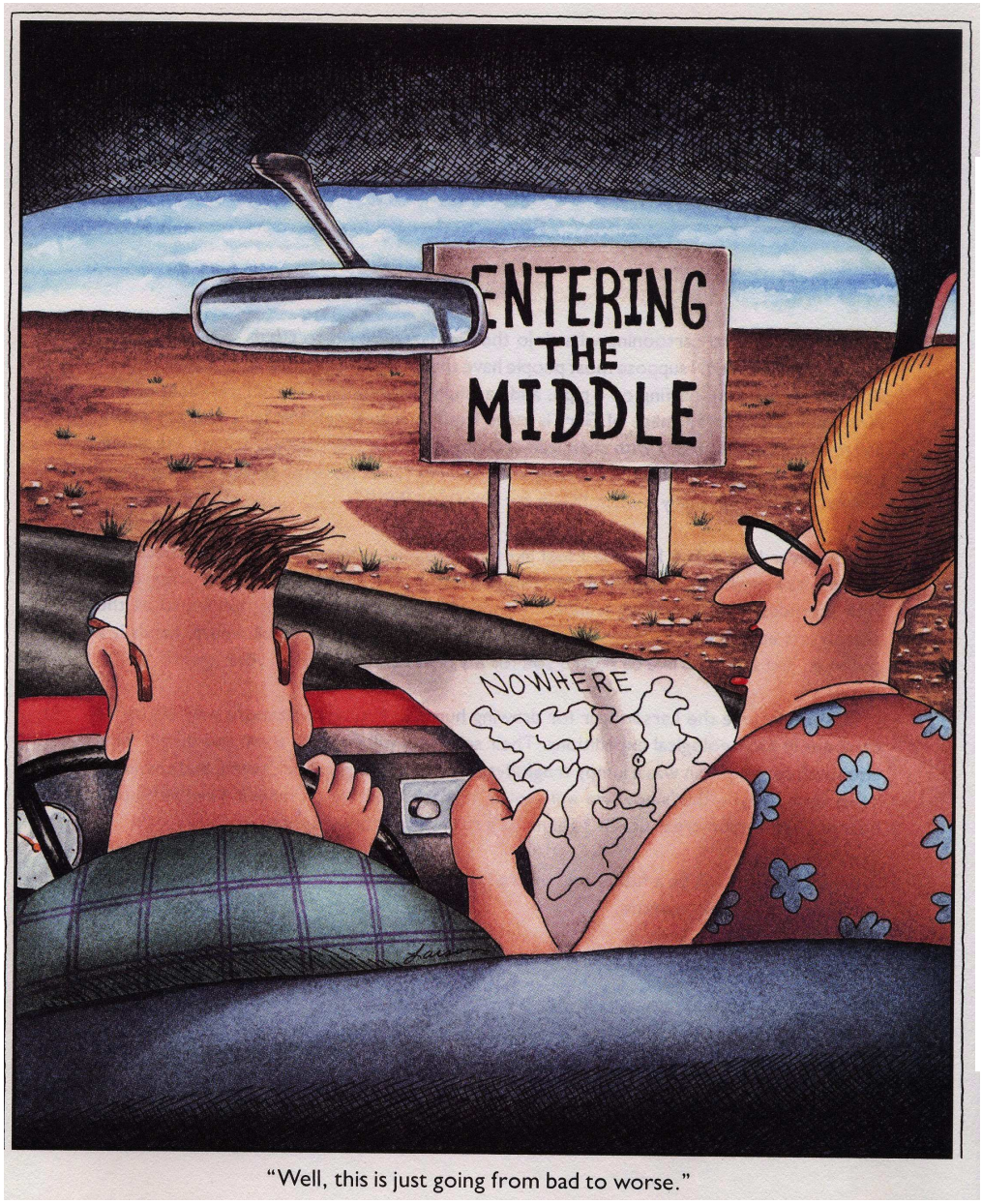
Cost-effectiveness of Simvastatin plus Ezetimibe for Cardiovascular Prevention in CKD: Results of the Study of Heart and Renal Protection (SHARP)
https://doi.org/10.1053/j.ajkd.2015.09.020

- In SHARP, the proportional reductions per 1 mmol/L of low-density lipoprotein (LDL) cholesterol reduction with simvastatin plus ezetimibe in all major atherosclerotic events of 20% (95% CI, 6%-32%) and in the costs of vascular hospital episodes of 17% (95% CI, 4%-28%) were similar across participant categories by cardiovascular risk and CKD stage.
- The 5-year reduction in major atherosclerotic events per 1,000 participants ranged from 10 in low-risk to 58 in high-risk patients and from 28 in CKD stage 3 to 36 in patients on dialysis therapy.
- The net cost per major atherosclerotic event avoided with simvastatin plus ezetimibe compared to no LDL-lowering regimen ranged from £157,060 in patients at low risk to £15,230 in those at high risk (£30,500-£39,600 per QALY); and from £47,280 in CKD stage 3 to £28,180 in patients on dialysis therapy (£13,000-£43,300 per QALY).
- In scenario analyses, generic high-intensity statin regimens were estimated to yield similar benefits at substantially lower cost.

Do YOU think this constitutes rational lipid therapy in dialysis patients?

What else?

- Consider age, diabetes, and pre-existing overt CVD as important modifiers
- Consider pro-active statin Rx where patients on a renal transplant list
- Consider using statins for their anti-inflammatory effect as well as any measurable impact on lipid profiles
- Consider maximising calorie/protein/lipid intake in dialysis patients, to try to mitigate MIA type scenarios (and statins might remove concerns about resultant hypercholesterolaemia)
- PSK9 inhibitors, LDL-apheresis
- More trials (but of what, and, how conducted? All comers, or targeted? By cholesterol, by modality, incident versus prevalent???)



"Well, this is just going from bad to worse."

BREXIT