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2023 Update in ambulatory general internal medicine

ABSTRACT

The practice of outpatient medicine is demanding, encompasses a wide scope of practice, and leaves little time for internists to stay up to date with the current literature. This article reviews 5 studies published in 2022 and 2023 that have the potential to change the practice of outpatient medicine. Topics covered include chronic kidney disease, secondary cardiovascular disease, kidney stones, obesity, and lipid management.

KEY POINTS

- Empagliflozin slowed the progression of chronic kidney disease in patients with chronic kidney disease; the benefit was most pronounced in patients with significant albuminuria.
- A Mediterranean diet was superior to a low-fat diet for secondary prevention of major cardiovascular events.
- Hydrochlorothiazide did not decrease symptomatic or radiologic recurrence of calcium-containing kidney stones.
- Tirzepatide was effective for weight loss in patients who were obese or overweight with weight-related complications.
- Ezetimibe, added to lower-intensity statin therapy, was noninferior to high-intensity statin therapy with respect to major adverse cardiovascular events.

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Internists who practice ambulatory medicine face many challenges. The time pressure of managing a patient's acute concerns, discussing their chronic medical problems, and advising on disease prevention is excessive.[1] Often, this leaves little time for practitioners to stay current on recently published evidence.

This review identifies and critically appraises 5 studies, each covering a different topic germane to the practice of ambulatory medicine, that have the potential to change practice. Studies were identified by reviewing abstracts from high-impact journals including the *New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet*, and *Annals of Internal Medicine*. Articles addressing topics relevant to ambulatory medicine were identified and appraised, and 5 final articles were agreed upon by all authors to critique for the current review. We discuss the role of empagliflozin in preventing progression of chronic kidney disease, diet for preventing secondary cardiovascular disease, hydrochlorothiazide for preventing kidney-stone recurrence, tirzepatide for weight loss, and ezetimibe for cholesterol management.

SLOWING THE PROGRESSION OF CHRONIC KIDNEY DISEASE

A 59-year-old woman with a history of hypertension and stage 3b chronic kidney disease with an estimated glomerular filtration rate of 40 mL/min/1.73 m^2 presents for clinic follow-up. Her blood pressure is well controlled with an angiotensin II receptor blocker and a thiazide diuretic. Recent laboratory results are remarkable for a normal urine albumin-to-creatinine ratio. She asks you if there

are any other medications available that may preserve her current kidney function. What do you recommend?

SGLT-2 inhibitors and chronic kidney disease

Several large randomized trials have shown that sodium-glucose cotransporter 2 (SGLT-2) inhibitors decrease the risk of kidney-related complications for patients with or without diabetes.[2,3] For example, in a trial of patients with both type 2 diabetes and chronic kidney disease with albuminuria, the SGLT-2 inhibitor canagliflozin decreased the risk of kidney disease progression.[2] Similarly, dapagliflozin, another SGLT-2 inhibitor, decreased kidney disease progression in patients with chronic kidney disease and albuminuria, with or without diabetes.[3]

Whether SGLT-2 inhibitors slow the progression of kidney disease in patients with chronic kidney disease without albuminuria was unknown and is an important question, given that the global burden of chronic kidney disease is high[4] and most patients with it have normal urine albumin levels.[5]

Empagliflozin decreases progression of chronic kidney disease

The EMPA-KIDNEY Collaborative Group[6] examined whether empagliflozin delayed kidney disease progression in patients with established chronic kidney disease in an international, randomized, placebo-controlled trial. They enrolled 6,609 participants 18 years or older who were already receiving a renin-angiotensin system inhibitor. The participants' race-adjusted estimated glomerular filtration rate had to be either in the range of at least 20 to less than 45 mL/min/1.73 m^2, or at least 45 to less than 90 mL/min/1.73 m^2 with a urinary albumin-to-creatinine ratio of at least 200 mg/g. Exclusion criteria included a history of polycystic kidney disease, symptomatic hypotension, history of kidney transplant, or a life-limiting diagnosis.

Participants were randomized to receive either empagliflozin 10 mg once daily or placebo. The primary outcome of the trial was a composite of progression of kidney disease or death from cardiovascular causes. Progression of kidney disease was defined as end-stage kidney disease, a sustained decrease in the estimated glomerular filtration rate to less than 10 mL/min/1.73 m^2, a decrease in the estimated glomerular filtration rate from baseline of at least 40%, or death from cardiovascular causes.

Results. During a median follow-up of 2 years, a primary outcome event occurred in 13.1% of patients in the empagliflozin group compared with 16.9% of patients in the placebo group (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.64–0.82, $P < .001$, number needed to treat 27). The lower rate in the empagliflozin group was mostly owing to a lower rate of progression of kidney disease (HR 0.71, 95% CI 0.62–0.81); the difference in the risk of death from cardiovascular causes was not statistically significant when analyzed independently (HR 0.84, 95% CI 0.60–1.19). Serious adverse events were uncommon and did not differ between groups.

While the effect sizes in several prespecified subgroups tended to mirror those in the overall group, a differential effect was seen when the primary outcome was stratified by baseline albuminuria. Empagliflozin made no difference in the primary outcome among patients with either a baseline urine albumin-to-creatinine ratio less than 30 mg/g (HR 1.01, 95% CI 0.66–1.55) or baseline urine albumin-to-creatinine ratio of at least 30 mg/g but no higher than 300 mg/g (HR 0.91, 95% CI 0.65–1.26). Only when the baseline urine albumin-to-creatinine ratio exceeded 300 mg/g was an effect observed favoring empagliflozin (HR 0.67, 95% CI 0.58–0.78).

Should our patient get an SGLT-2 inhibitor for her chronic kidney disease?

Although the EMPA-KIDNEY trial demonstrated a reduction in the progression of kidney disease among all patients receiving empagliflozin, whether our patient, who does not have albuminuria, would stand to benefit from empagliflozin or an alternative SGLT-2 inhibitor is less clear. A discussion is warranted about the potential benefits, risks (eg, genital yeast infections,[7] diabetic ketoacidosis[8]), and cost (more than $400 per month, and an out-of-pocket expense of about $50 for Medicare patients in 1 analysis[9]) of starting an SGLT-2 inhibitor.

In clinical practice, utilization rates of SGLT-2 inhibitors are relatively low. A 2023 analysis of 105,799 patients from 130 Veterans Affairs facilities who had type 2 diabetes, heart failure, and atherosclerotic cardiovascular disease (and thus multiple indications for an SGLT-2 inhibitor) showed that only 15% were receiving an SGLT-2 inhibitor.[10] Whether healthier patients such as ours with fewer comorbidities and likely fewer baseline medications would be willing to start an SGLT-2 inhibitor to prevent chronic kidney disease progression will be an important area for future study.

DIET AS SECONDARY PREVENTION

A 63-year-old man presents for follow-up after undergoing coronary revascularization 6 months ago. He is currently adherent to medical therapy and is asking whether there are

any diets to further reduce his risk of recurrent cardiovascular disease. What would you recommend?

Diet and cardiovascular disease

Diet can be modified to reduce the incidence and recurrence of cardiovascular events.[11] Guidelines encourage everyone to limit dietary fats and to consume complex carbohydrates daily to replace saturated fats and increase fiber intake.[12,13] The Mediterranean diet—with generous portions of fruits, vegetables, legumes, cereals, nuts, and seeds, with white meat and fish as the primary sources of protein, and with olive oil as the primary source of fat—has been touted as healthy.[14,15] Estruch et al[16] demonstrated that the Mediterranean diet was more effective than a reduced-fat diet as primary prevention for patients at high risk of cardiovascular disease. However, until recently, there was little evidence on the effect of a Mediterranean diet as secondary prevention.

A Mediterranean diet is superior to a low-fat diet for secondary prevention

Delgado-Lista et al[17] conducted the first large, long-term, randomized, controlled trial comparing the Mediterranean diet vs a low-fat diet in secondary prevention of major cardiovascular events, defined as myocardial infarction, revascularization, ischemic stroke, peripheral arterial disease, or cardiovascular death.

This single-center trial conducted in Spain enrolled 1,002 patients with established coronary heart disease; 83% were men, and the mean age was 60. Patients were excluded if they had heart failure with an ejection fraction of 35% or less or New York Heart Association class III or IV symptoms, could not follow a diet, or had severe liver, renal, pulmonary, or psychiatric disease.

No energy restriction was implemented, and no physical activity was promoted. Both groups came in for individual in-person visits every 6 months and group sessions every 3 months, and received telephone calls every 2 months. Participants in the Mediterranean-diet group received 1 L of extra-virgin olive oil per week at no charge, while the low-fat-diet group received a bag of healthy food rich in complex carbohydrates, worth about the same Euro amount as the olive oil.

Results. By the end of the 7-year study, 132 participants had abandoned their diets, 86 in the low-fat group and 46 in the Mediterranean-diet group ($P = .0002$). Baseline adherence to the Mediterranean diet was 8.78 on a scale of 0 (worst) to 14 (best). As expected, participants in the Mediterranean-diet group had increased their intake of total fat, primarily from increased intake of extra-virgin olive oil, oily fish, and nuts. In contrast, baseline adherence to the low-fat diet was 3.81 on a scale of 0 (worst) to 9 (9 best), and participants had increased their intake of carbohydrates, mainly from complex carbohydrates, and decreased their intake of total fat.

A total of 198 primary outcome events occurred, 87 in the Mediterranean-diet group (in 17.3% of this group) and 111 in the low-fat-diet group (in 22.2% of this group)—a 25% reduction in major cardiovascular events with the Mediterranean diet (unadjusted HR 0.745, 95% CI 0.563–0.986, number needed to treat 21). In men, the Mediterranean diet was even more superior, reducing the rate of major cardiovascular events by nearly 33%. The groups did not differ in their adherence with antiplatelet, antihypertensive, or lipid-lowering medications, nor in their lipid or glucose blood levels at the completion of the study.

Limitations of this study include the intense dietary interventions, the majority male population, and the study location in Spain, which has a higher acceptance of the Mediterranean diet, all of which may impact the generalizability of these results to other populations. Furthermore, the mortality rates were lower in this study than in studies in similar settings during the same time period, which might support the notion that both diets were very effective in preventing cardiovascular recurrences.

What should we tell this patient?

The patient should be told that a Mediterranean diet rich in extra-virgin olive oil, fatty fish, and nuts lowers the risk of recurrent major cardiovascular events by roughly 25% compared with a low-fat diet. A referral to a nutritionist may lead to better adherence to the Mediterranean diet.

PREVENTING RECURRENT KIDNEY STONES

A 62-year-old man presents for a routine physical. You note a history of kidney stones. His last stone event was 1 year ago, and the stone passed spontaneously. The stone was mostly composed of calcium oxalate. Laboratory testing shows a normal serum calcium level and a high 24-hour level of urine calcium excretion. Do you recommend hydrochlorothiazide to try to prevent recurrent stones?

Data on preventing recurrent calcium stones are sparse

Roughly 80% of kidney stones contain calcium, most commonly in the form of calcium oxalate.[18] Small studies have suggested that dietary modifications such as taking in more potassium and calcium and less animal protein and sodium can reduce the likelihood of

recurrent calcium stones.[19–22] One randomized controlled trial showed that increasing water intake to achieve urine volume of more than 2 L per day significantly reduced the risk of recurrent stones compared with standard water intake.[23]

Thiazide diuretics reduce urine calcium excretion.[24] One meta-analysis found moderate-strength evidence that thiazides decrease the risk of stone recurrence but not the risk of *symptomatic* recurrence, and the included studies were small and had methodologic limitations.[25]

Hydrochlorothiazide to prevent recurrent calcium stones

Dhayat et al[26] recently performed the largest study to date examining whether thiazide diuretics prevent recurrent stones. Patients were enrolled from 12 centers in Switzerland; eligibility criteria included age greater than 18, at least 2 kidney-stone episodes in the past 10 years, and any stone containing at least 50% calcium oxalate or calcium phosphate. Those with secondary causes of stones or who were taking medications that could interfere with stone formation were excluded. Of 1,335 patients who were screened, 416 were assigned to treatment. The median age was 49, 80% were men, and 63% had baseline hypercalciuria.

Patients were randomized in 4 equal groups to receive hydrochlorothiazide 12.5 mg, 25 mg, or 50 mg daily or placebo. They were followed for a maximum of 3 years for both radiographic and symptomatic recurrence of stones.

Results. There were no differences in the rate of the primary outcome between any of the groups, and no relation between hydrochlorothiazide dose and occurrence of a primary end-point event. Higher doses of hydrochlorothiazide (25 and 50 mg) were associated with a reduced risk of radiographic recurrence, a secondary study end point. Patients assigned to hydrochlorothiazide had lower urine calcium excretion, but urine relative supersaturation ratios were not different from those in patients assigned to placebo. Patients taking hydrochlorothiazide had higher rates of hypokalemia, gout, new-onset diabetes, skin allergy, and acute kidney injury.

Limitations of the trial included nonadherence to assigned treatment in 15% to 26% of patients, underrepresentation of women in the trial, and relatively short trial duration.

What should we recommend for our patient?

The results of this trial would not support a recommendation to use hydrochlorothiazide to reduce the likelihood of recurrent stones. Our patient should be told to increase his water intake to achieve a urine output of at least 2 L per day. Based on limited available evidence, other measures to consider would be use of citrates and allopurinol, dietary changes including more dietary calcium and potassium, and reduction in intake of soft drinks, animal protein, and sodium.

LOSING WEIGHT

A 46-year-old woman with obesity (body mass index 34 kg/m^2), prediabetes, and hypertension presents to clinic for follow-up. She takes olmesartan 20 mg daily for hypertension. She has made several unsuccessful attempts to lose weight with changes in diet and exercise. What additional pharmacotherapy might you recommend next?

The obesity epidemic and its treatments

Obesity is a global epidemic. Its prevalence has been increasing worldwide for several decades, and it is associated with poor health outcomes including cardiovascular disease, diabetes mellitus, malignancy, and musculoskeletal diseases.[27] For people who are obese, losing as little as 5% to 10% of body weight helps to improve cardiovascular risk factors, and losing more has even greater benefit.[28] Major guidelines continue to recommend low-calorie diets, exercise, and comprehensive lifestyle management plans as cornerstones of obesity management.[29,30]

However, the human body seems to have a set point for weight, with metabolic and homeostatic adaptations that make it difficult to lose weight or maintain weight loss.[31] Therefore, many patients regain weight after participating in lifestyle modification programs.[32] As a result, pharmacotherapy is an important consideration for achieving weight-loss goals. Newer drugs such as semaglutide have shown promising outcomes for weight loss and maintenance.[33,34]

Tirzepatide once weekly promotes weight loss in patients without diabetes

Jastreboff et al[35] examined whether tirzepatide, a once-weekly subcutaneous injection drug with agonist activity at glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors, was safe and effective for weight loss in people with obesity. In a double-blind, industry-sponsored, randomized clinical trial conducted in 19 countries, participants were randomized in a 1:1:1:1 ratio to receive tirzepatide 5 mg, 10 mg, or 15 mg or placebo injections for 72 weeks. All groups received dietary and physical activity intervention.

Participants were age 18 and older, had a body mass index of at least 30 kg/m^2, or had a body mass index of at

least 27 kg/m^2 with at least 1 weight-related complication, defined as hypertension, hyperlipidemia, obstructive sleep apnea, or cardiovascular disease. Exclusion criteria included diabetes, treatment with other weight-loss medications within 90 days before screening, and planned weight-loss surgery. The coprimary outcomes were change in body weight from baseline to week 72 and weight reduction of at least 5%.

Results. A total of 2,539 participants were randomized, of whom 68% were women, 71% were White, and 48% were Hispanic or Latino. All of the active-treatment groups lost a significant amount of weight, and the higher the dose the more they lost: The mean change in body weight was –15% with tirzepatide 5 mg, –19.5% with tirzepatide 10 mg, –20.9% with tirzepatide 15 mg, and –3.1% with placebo. More than 85% of participants in the tirzepatide groups lost more than 5% of their body weight, compared with 35% of those in the placebo group.

Nausea, vomiting, and diarrhea were more common in patients receiving tirzepatide than in patients receiving placebo, but these adverse effects infrequently led to drug discontinuation and were clustered around drug initiation or dose increases. A higher risk of cholecystitis was seen in patients receiving tirzepatide, but the incidence was less than 0.6%.

Should we prescribe tirzepatide for our 46-year-old patient without diabetes?

In addition to ongoing diet, exercise, and lifestyle counseling, consideration of pharmacotherapy is a reasonable option. Both tirzepatide and semaglutide are approved by the US Food and Drug Administration for weight loss, but the high cost and varying insurance coverage for each of these medications render them unobtainable for many patients.[36] Before patients start weight-loss therapy, clinicians and patients should discuss its possible benefits, risks, cost, availability, and duration (which is unknown at this point but may need to be lifelong to prevent weight regain).

LOWERING LDL-C

A 60-year-old man presents to his primary care physician with concerns about his cardiovascular health. He had a myocardial infarction at age 57 for which he received a coronary artery stent. He has been taking aspirin 81 mg, irbesartan 150 mg, metoprolol succinate 50 mg, and rosuvastatin 20 mg daily with good adherence, but endorses mild, intermittent myalgias, which he attributes to his rosuvastatin. His current low-density lipoprotein cholesterol (LDL-C) level is 85 mg/dL. What changes to his medications might you advise?

Lower LDL-C is associated with reduced risk of major cardiovascular events

Current clinical guidelines for blood cholesterol management in people with atherosclerotic cardiovascular disease recommend starting with statin monotherapy and titrating up to the highest tolerated dose before considering additional nonstatin therapy.[12] This is in part based on the low cost, wide availability, and efficacy of statins with respect to lowering LDL-C and reducing major cardiovascular events compared with other lipid-lowering therapy.[37,38] However, adherence to high-intensity statins remains relatively low, even in high-risk groups.[39]

Ezetimibe has been shown to decrease the risk of major cardiovascular events when added to statin therapy in patients recently hospitalized with acute coronary syndrome.[40] Whether a lower-intensity statin combined with ezetimibe would provide clinical benefit similar to that of high-intensity statin monotherapy had not been previously evaluated prospectively.

High-intensity statin monotherapy vs lower-dose statin therapy combined with ezetimibe

Kim et al[41] conducted a pharma-sponsored, randomized, open-label, noninferiority trial in South Korea comparing the long-term clinical outcomes of high-intensity statin monotherapy vs lower-intensity statin therapy combined with ezetimibe.

Patients were included if they were over age 18 and had a history of atherosclerotic cardiovascular disease. Exclusion criteria included active liver disease, persistent unexplained elevation of aspartate aminotransferase or alanine aminotransferase twice the upper limit of normal, and prior allergy or hypersensitivity to any statin or ezetimibe. The mean age was 64, and 75% of the patients were men.

Patients were randomly assigned in a 1:1 ratio to monotherapy with rosuvastatin 20 mg or combination therapy with both rosuvastatin 10 mg and ezetimibe 10 mg. The primary end point was a composite outcome of cardiovascular death, major cardiovascular events, and nonfatal stroke within 3 years, with a noninferiority margin of 2%.

Results. Combination therapy was noninferior to high-intensity statin monotherapy for the 3-year composite outcome, which occurred in 9.1% of the combination-therapy group vs 9.9% of the high-intensity statin group (absolute difference –0.78%, 90% CI –2.39 to 0.83). Additionally, the combination-therapy group had a significantly lower mean LDL-C at 3 years than the high-intensity-statin monotherapy group (58 mg/dL vs 66 mg/dL),

and more patients in the combination-therapy group achieved a target LDL-C concentration of less than 70 mg/dL (72% vs 58%).

Subjective adverse effects such as muscle pain were reported more frequently with high-intensity statin monotherapy than with combination therapy (1.9% vs 1.1%, respectively), and more patients in the high-intensity-statin monotherapy group had to discontinue or take a lower dose of the study medications than in the combination therapy group (8.2% vs 4.8%, respectively, $P < .0001$).

Limitations of the study include its open-label design, lower-than-expected event rates, and lack of a study arm receiving moderate-intensity statin monotherapy (rosuvastatin 10 mg), which would have afforded a better comparison of the potential benefit of adding ezetimibe to rosuvastatin.

Overall, the study suggests that combination therapy using a moderate-intensity statin and ezetimibe is an effective and safe alternative to high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease. Given that lipid-lowering therapy is not intense enough in the real world,[42] these findings could help usher in a shift in strategy in lipid management toward combination therapy, similar to the current standard of care in hypertension management.[43] Will this strategy be an acceptable alternative to statin monotherapy in real-world practice? Will it contribute to polypharmacy? These are important topics for future study.

What should we advise our patient?

Given the patient's history of myalgias on his current high-intensity rosuvastatin dose, reducing his rosuvastatin dose to 10 mg and adding ezetimibe 10 mg daily is a reasonable option to consider to reduce his risk of future cardiovascular events and improve long-term adherence, and may carry less risk of myalgia than continuing his current rosuvastatin dose.

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REFERENCES

1. **Porter J, Boyd C, Skandari MR, Laiteerapong N.** Revisiting the time needed to provide adult primary care. J Gen Intern Med 2023; 38(1):147–155. doi:10.1007/s11606-022-07707-x
2. **Perkovic V, Jardine MJ, Neal B, et al.** Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019; 380(24):2295–2306. doi:10.1056/NEJMoa1811744
3. **Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.** Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383(15):1436–1446. doi:10.1056/NEJMoa2024816
4. **GBD Chronic Kidney Disease Collaboration.** Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020; 395(10225):709–733. doi:10.1016/S0140-6736(20)30045-3
5. **Levey AS, Coresh J.** Chronic kidney disease. Lancet 2012; 379(9811):165–180. doi:10.1016/S0140-6736(11)60178-5
6. **The EMPA-KIDNEY Collaborative Group; Herrington WG, Staplin N, Wanner C, et al.** Empagliflozin in patients with chronic kidney disease. N Engl J Med 2023; 388:117–127. doi:10.1056/NEJMoa2204233
7. **Alexander JT, Staab EM, Wan W, et al.** Longer-term benefits and risks of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes: a systematic review and meta-analysis. J Gen Intern Med 2022; 37(2):439–448. doi:10.1007/s11606-021-07227-0
8. **Fralick M, Schneeweiss S, Patorno E.** Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. N Engl J Med 2017; 376(23):2300–2302. doi:10.1056/NEJMc1701990
9. **Aggarwal R, Vaduganathan M, Chiu N, Bhatt DL.** Out-of-pocket costs for SGLT-2 (sodium-glucose transport protein-2) inhibitors in the United States. Circ Heart Fail 2022; 15(3):e009099. doi:10.1161/CIRCHEARTFAILURE.121.009099
10. **Hussain A, Ramsey D, Lee M, et al.** Utilization rates of SGLT2 inhibitors among patients with type 2 diabetes, heart failure, and atherosclerotic cardiovascular disease: insights from the Department of Veterans Affairs. JACC Heart Fail 2023; 11(8 pt 1):933–942. doi:10.1016/j.jchf.2023.03.024
11. **Ge L, Sadeghirad B, Ball GDC, et al.** Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials [published correction appears in BMJ 2020; 370:m3095]. BMJ 2020; 369:m696. doi:10.1136/bmj.m696
12. **Grundy SM, Stone NJ, Bailey AL, et al.** 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in Circulation 2019; 139(25):e1182–e1186] [published correction appears in Circulation 2023; 148(7):e5]. Circulation 2019; 139(25):e1082–e1143. doi:10.1161/CIR.0000000000000625
13. **Eckel RH, Jakicic JM, Ard JD, et al.** 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in Circulation 2014; 129(25 suppl 2):S100–S101] [published correction appears in Circulation 2015; 131(4):e326]. Circulation 2014; 129(25 suppl 2):S76–S99. doi:10.1161/01.cir.0000437740.48606.d1
14. **Widmer RJ, Flammer AJ, Lerman LO, Lerman A.** The Mediterranean diet, its components, and cardiovascular disease. Am J Med 2015; 128(3):229–238. doi:10.1016/j.amjmed.2014.10.014
15. **Martínez-González MA, Gea A, Ruiz-Canela M.** The Mediterranean diet and cardiovascular health. Circ Res 2019; 124(5):779–798. doi:10.1161/CIRCRESAHA.118.313348
16. **Estruch R, Ros E, Salas-Salvadó J, et al.** Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018; 378(25):e34. doi:10.1056/NEJMoa1800389
17. **Delgado-Lista J, Alcala-Diaz JF, Torres-Peña JD, et al.** Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet (CORDIOPREV): a randomised controlled trial. Lancet 2022; 399(10338):1876–1885. doi:10.1016/S0140-6736(22)00122-2
18. **Alelign T, Petros B.** Kidney stone disease: an update on current concepts. Adv Urol 2018; 2018:3068365. doi:10.1155/2018/3068365

19. **Curhan GC, Willett WC, Rimm EB, Stampfer MJ.** A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. N Engl J Med 1993; 328(12):833–838. doi:10.1056/NEJM199303253281203
20. **Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ.** Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Ann Intern Med 1997; 126(7):497–504. doi:10.7326/0003-4819-126-7-199704010-00001
21. **Curhan GC, Willett WC, Knight EL, Stampfer MJ.** Dietary factors and the risk of incident kidney stones in younger women: Nurses' Health Study II. Arch Intern Med 2004; 164(8):885–891. doi:10.1001/archinte.164.8.885
22. **Borghi L, Schianchi T, Meschi T, et al.** Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med 2002; 346(2):77–84. doi:10.1056/NEJMoa010369
23. **Borghi L, Meschi T, Amato F, Briganti A, Novarini A, Giannini A.** Urinary volume, water and recurrences in idiopathic calcium nephrolithiasis: a 5-year randomized prospective study. J Urol 1996; 155(3):839–843. pmid:8583588
24. **Nijenhuis T, Hoenderop JG, Loffing J, van der Kemp AW, van Os CH, Bindels RJ.** Thiazide-induced hypocalciuria is accompanied by a decreased expression of Ca2+ transport proteins in kidney. Kidney Int 2003; 64(2):555–564. doi:10.1046/j.1523-1755.2003.00128.x
25. **Fink HA, Wilt TJ, Eidman KE, et al.** Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians clinical guideline [published correction appears in Ann Intern Med 2013; 159(3):230–232]. Ann Intern Med 2013; 158(7):535–543. doi:10.7326/0003-4819-158-7-201304020-00005
26. **Dhayat NA, Bonny O, Roth B, et al.** Hydrochlorothiazide and prevention of kidney-stone recurrence. N Engl J Med 2023; 388(9): 781–791. doi:10.1056/NEJMoa2209275
27. **Boutari C, Mantzoros CS.** A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 2022; 133:155217. doi:10.1016/j.metabol.2022.155217
28. **Wing RR, Lang W, Wadden TA, et al.** Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. Diabetes Care 2011; 34(7):1481–1486. doi:10.2337/dc10-2415
29. **Garvey WT, Mechanick JI, Brett EM, et al.** American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016; 22(suppl 3):1–203. doi:10.4158/EP161365.GL
30. **Jensen MD, Ryan DH, Apovian CM, et al.** 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [published correction appears in Circulation 2014; 129(25 suppl 2):S139–S140]. Circulation 2014; 129(25 suppl 2):S102–S138. doi:10.1161/01.cir.0000437739.71477.ee
31. **Martínez-Gómez MG, Roberts BM.** Metabolic adaptations to weight loss: a brief review. J Strength Cond Res 2022; 36(10):2970–2981. doi:10.1519/JSC.0000000000003991
32. **Wadden TA, Tronieri JS, Butryn ML.** Lifestyle modification approaches for the treatment of obesity in adults. Am Psychol 2020; 75(2):235–251. doi:10.1037/amp0000517
33. **Garvey WT, Batterham RL, Bhatta M, et al.** Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med 2022; 28(10):2083–2091. doi:10.1038/s41591-022-02026-4
34. **Bergmann NC, Davies MJ, Lingvay I, Knop FK.** Semaglutide for the treatment of overweight and obesity: a review. Diabetes Obes Metab 2023; 25(1):18–35. doi:10.1111/dom.14863
35. **Jastreboff AM, Aronne LJ, Ahmad NN, et al.** Tirzepatide once weekly for the treatment of obesity. N Engl J Med 2022; 387(3):205–216. doi:10.1056/NEJMoa2206038
36. **Chakhtoura M, Haber R, Ghezzawi M, Rhayem C, Tcheroyan R, Mantzoros CS.** Pharmacotherapy of obesity: an update on the available medications and drugs under investigation. EClinicalMedicine 2023; 58:101882. doi:10.1016/j.eclinm.2023.101882
37. **Wilkins JT, Lloyd-Jones DM.** Novel lipid-lowering therapies to reduce cardiovascular risk [published correction appears in JAMA 2021; 326(16):1637]. JAMA 2021; 326(3):266–267. doi:10.1001/jama.2021.2244
38. **Navarese EP, Robinson JG, Kowalewski M, et al.** Association between baseline LDL-C level and total and cardiovascular mortality after LDL-C lowering: a systematic review and meta-analysis [published correction appears in JAMA 2018; 320(13):1387]. JAMA 2018; 319(15):1566–1579. doi:10.1001/jama.2018.2525
39. **Colantonio LD, Huang L, Monda KL, et al.** Adherence to high-intensity statins following a myocardial infarction hospitalization among Medicare beneficiaries. JAMA Cardiol 2017; 2(8):890–895. doi:10.1001/jamacardio.2017.0911
40. **Cannon CP, Blazing MA, Giugliano RP, et al.** Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372(25):2387–2397. doi:10.1056/NEJMoa1410489
41. **Kim BK, Hong SJ, Lee YJ, et al.** Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial. Lancet 2022; 400(10349):380–390. doi:10.1016/S0140-6736(22)00916-3
42. **Cannon CP, de Lemos JA, Rosenson RS, et al.** Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. JAMA Cardiol 2021; 6(9):1–9. doi:10.1001/jamacardio.2021.1810
43. **Whelton PK, Carey RM, Aronow WS, et al.** 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018; 138(17):e426–e483. doi:10.1161/CIR.0000000000000597

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