

SGLT1 and SGLT2 Inhibitors: Geroprotection, Disease Amelioration and Safe Use

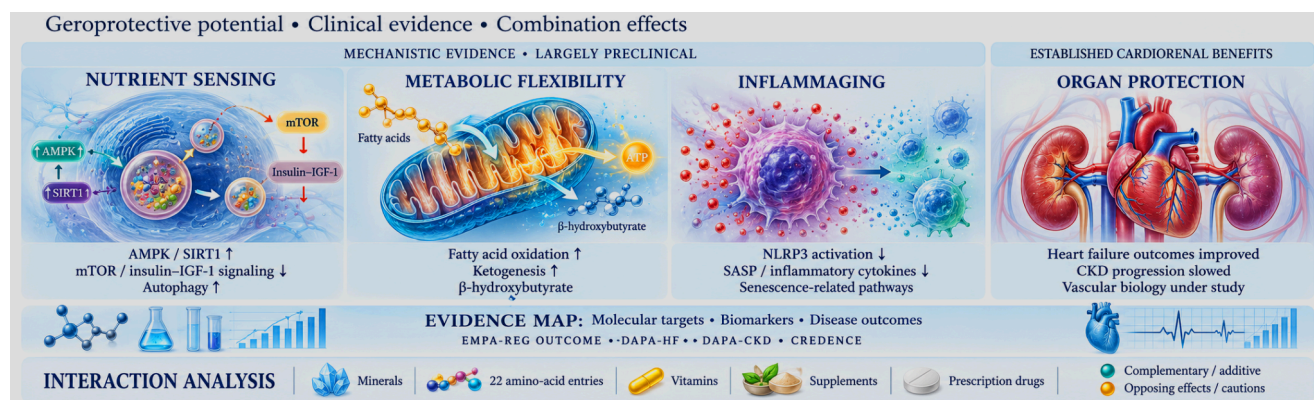
Author: Michael J Slattery

Affiliation: Age-Regression.com

Contact Email: Michael@Age-Regression.com

This document represents personal communications, not a published or reviewed manuscript.

The last revision occurred on: 10/24/2026



Abstract

Sodium–glucose cotransporter inhibitors (SGLTi) are among the most clinically substantiated candidates for pharmacological geroprotection. Large randomized trials demonstrate fewer heart-failure events, slower chronic kidney disease progression and, in relevant populations, reduced cardiovascular mortality. Cardiorenal benefits extend across heart-failure ejection fractions and to people without diabetes; dual SGLT1/2 inhibition also improves cardiovascular outcomes in selected populations. [9–11,17,83,84,86,87] A 2026 synthesis of 13 trials involving 90,413 participants reported a 12% lower hazard of all-cause mortality; five trials involving 43,027 participants showed a 10% lower hazard of first all-cause hospitalization. These broad outcomes support therapeutic effects extending beyond glucose control or a single organ. [91]

This clinical profile converges with effects on conserved aging pathways. Experimental studies link fasting-like metabolic signaling to AMPK/SIRT1 activation, mTOR suppression, enhanced autophagy and mitochondrial maintenance. Particularly compelling are reductions in inflammatory signaling, senescence-associated secretory phenotype (SASP) factors and senescent-cell burden, together with enhanced immune-mediated clearance of senescent cells in mice. [3,4,7,21,22] Human mechanistic studies demonstrate reduced NLRP3 inflammasome activity, while a randomized henagliflozin trial found increased granzyme B expression in cytotoxic T lymphocytes, providing an early human signal consistent with enhanced immune surveillance. [2,13] Lifespan extension in selected mouse models adds direct preclinical longevity evidence. [8,18]

Randomized evidence for steatohepatitis improvement and observational signals for lower dementia risk and better survival among patients with diabetes and cancer further broaden the therapeutic rationale. [12,20,92] Collectively, the convergence of clinical outcome benefits, anti-inflammatory and senescence-modulating effects, and established clinical availability makes SGLTi a leading near-term opportunity for disease amelioration and healthier aging. This review integrates that evidence with a framework for patient selection, nutritional adequacy and safe combination therapy. Their demonstrated benefits justify strong clinical prioritization in eligible older adults; dedicated trials must now determine whether these advantages translate into extended human healthspan and lifespan beyond established disease indications. See Appendix L: Candidate geroprotectors: comparative evidence between SGLT inhibitors, Metformin and Rapamycin (sirolimus)

Introduction

A useful geroprotective intervention should preserve function and reduce age-related disease while producing an acceptable overall benefit–risk balance. Lower HbA1c, body weight and blood pressure can contribute to that objective when elevated. Unwanted weight loss, hypotension or hypoglycemia can instead undermine health in a frail person. The central question is therefore whether SGLT inhibition translates biological plausibility into better clinical outcomes, and how to use it without sacrificing nutrition, physical function or safety. [9–11,17,70]

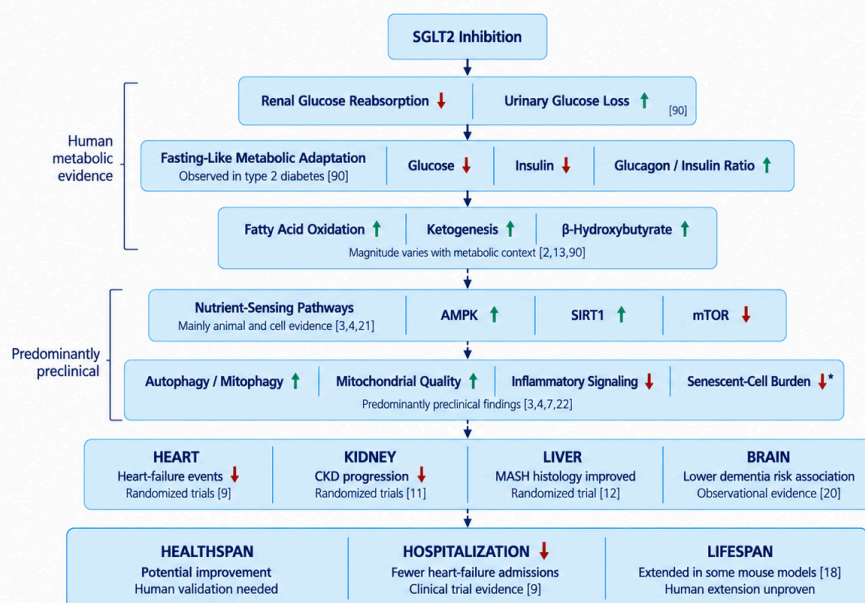
SGLT2 transports filtered glucose and sodium back into the circulation in the proximal renal tubule. Its inhibition increases urinary glucose loss and modifies renal sodium handling, contributing to glucose lowering, osmotic diuresis and changes in glomerular hemodynamics. These actions help explain why the class can affect heart and kidney disease beyond its effect on HbA1c. [61] Sotagliflozin additionally inhibits intestinal SGLT1, reducing glucose and sodium absorption; this intestinal action also helps explain its diarrhea risk. Its outcome trials assess the dual-action drug as a whole, not the independent effect of SGLT1 inhibition. [83–85]

Sections 1–5 retain the manuscript’s sequence: nutrient-deprivation signaling, metabolic flexibility, inflammaging/senescence, chronic disease protection and lifespan/mortality evidence. Section 6 translates those findings into selection, monitoring and interaction decisions. Appendix A summarizes organ outcomes; Appendix B separates molecular targets, biomarkers and diseases; Appendices C–K contain the classified interaction tables. Appendix L provides a comparison of the most prescribed and utilized Gerotherapeutics in clinical practice. Throughout, “complementary” denotes distinct useful actions, “additive” denotes an additional measured effect, and “synergistic” requires evidence of an interaction exceeding the expected combined effects. Shared pathways alone do not establish synergy.

This document was authored by myself and all ideas and subject matter were initiated by me. It was organized and formatted by ChatGPT via a dedicated SGLT related Plugin utilizing vs 6 High effort setting. The Appendix Tables A through L and images were generated by this plugin through directed prompts utilizing directed, curated published research. Searches were conducted using Google Scholar and ChatGPT SGLT Plugin. All references were managed by the Plugin.

FIGURE 1

Mechanistic Framework Linking SGLT2 Inhibition to Healthy Aging



SGLT2 inhibitors as candidate geroprotectors. Solid arrows indicate physiological links; dashed connectors indicate proposed relationships, not a validated sequential mechanism. Clinical benefits apply to studied populations. *Senescent-cell reduction is supported by mouse studies. CKD, chronic kidney disease; MASH, metabolic dysfunction-associated steatohepatitis. Reference numbers match the manuscript.

Adapted and updated from Figure 2, O’Keefe EL, O’Keefe JH, Nassif ME, Sauer AJ. SGLT Inhibitors as Geroprotectors for Age-Related Disease Prevention. OpenSource Cardiology. 2026;1(1). [91] Original article: [CC BY 4.0](#). Updated October 23, 2026.

1. Upregulation of Nutrient-Deprivation Signaling

Urinary energy loss provides a metabolic signal resembling some aspects of fasting. Human studies demonstrate reduced glucose and insulin concentrations, altered substrate use and compensatory increases in endogenous glucose production during SGLT2 treatment. The response is therefore an adaptation to glucose loss, rather than complete replication of caloric restriction. Its magnitude varies with kidney function, glycemia and food intake; a fixed daily caloric deficit should not be assumed for every patient. [90]

In animal and cellular models, SGLT2 inhibitors influence AMP-activated protein kinase (AMPK), the NAD⁺-dependent regulator SIRT1 and mechanistic target of rapamycin (mTOR). These pathways coordinate energy availability, protein synthesis and cellular maintenance. Empagliflozin experiments link AMPK/mTOR changes to autophagy and reduced inflammatory signaling; dapagliflozin protects high-glucose-exposed endothelial cells through AMPK/SIRT1-dependent signaling. Autophagy recycles cellular material, while mitophagy removes damaged mitochondria; both offer plausible routes to improved tissue resilience. These are predominantly experimental downstream effects, not proof that every SGLT inhibitor directly binds these regulators or produces equivalent pathway changes in humans. [3,4,21,22]

NAD⁺ biology requires similar precision. Empagliflozin increased skeletal-muscle NAMPT expression in normal mice, and diabetic-mouse kidney studies identified changes in NAD-related metabolites. Such observations support altered salvage capacity or metabolism, but do not establish a generalized rise in human NAD⁺ concentration. Likewise, lower insulin exposure is not evidence of uniform suppression of the entire insulin/IGF-1 system: the henagliflozin study reported increased IGF-binding protein-3. These distinctions prevent molecular findings from becoming unsupported recommendations for NAD precursors or continuous nutrient restriction. [5,6,13]

2. Metabolic Flexibility and Ketogenesis

SGLT2 inhibition can shift fuel use away from carbohydrate toward lipid oxidation. In a mechanistic study of 66 adults with type 2 diabetes, four weeks of empagliflozin increased lipid oxidation while improving measures of insulin sensitivity and beta-cell glucose responsiveness. [90] Higher β -hydroxybutyrate has also been observed in human SGLT2 studies. This ketone acts as both an energy substrate and a signaling molecule, making it a plausible connection between altered metabolism and inflammatory regulation. [2,13]

In nondiabetic pigs with heart failure, empagliflozin improved myocardial energetics alongside changes in substrate utilization. This supports a mechanistic hypothesis for cardiac benefit, but does not prove that ketones are a universally superior fuel or the necessary mediator of human trial outcomes. [19] Clinically, modest adaptive ketogenesis must be distinguished from ketoacidosis. Ketone concentrations are not a validated treatment target for longevity, and combining SGLT inhibition with a ketogenic diet, prolonged fasting or inadequate insulin can create serious risk. Section 6 addresses this boundary explicitly. [61,85]

3. Mitigation of Inflammaging and Senescence

Persistent inflammatory signaling can connect metabolic dysfunction to tissue injury. In a 30-day randomized comparison of empagliflozin and glimepiride in adults with type 2 diabetes and high cardiovascular risk, investigators found reduced NLRP3 inflammasome activation in isolated macrophages, accompanying higher ketones and lower insulin. This is human mechanistic evidence for an anti-inflammatory effect; it is not a demonstration that every inflammatory cytokine falls or that a whole-body aging process has reversed. [2]

Sensomorphic effects alter the behavior or senescence-associated secretory phenotype (SASP) of senescent cells, whereas senolysis removes those cells. Katsuomi and colleagues provided evidence for indirect senolysis in mice: canagliflozin increased an AICAR-related metabolic signal, reduced PD-L1 expression and promoted immune-mediated clearance of senescent cells. Reduced senescent-cell burden and improved pathological aging phenotypes support a connection beyond glucose lowering. However, these experiments do not establish human senolytic dosing, generalized immune rejuvenation or cancer prevention. [7]

The 26-week placebo-controlled henagliflozin trial randomized 150 adults with type 2 diabetes and reported increased leukocyte telomere length, its primary endpoint. Granzyme B expression in cytotoxic T cells increased, whereas perforin changes were not significant. These findings extend the geroscience discussion into human biomarker research, but telomere length in circulating cells does not establish rejuvenation of all tissues, and cytotoxic-cell biomarkers do not directly demonstrate clearance of human senescent cells. Larger, longer trials linking such changes to function and clinical outcomes are needed. [13]

4. Direct Protection Against Age-Related Chronic Diseases

Heart failure provides strong clinical evidence of disease amelioration. DAPA-HF randomized 4,744 patients with reduced ejection fraction: worsening heart failure or cardiovascular death occurred in 16.3% with dapagliflozin versus 21.2% with placebo over a median 18.2 months (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.65–0.85). [9] DELIVER extended this evidence to mildly reduced or preserved ejection fraction: the corresponding outcome occurred in 16.4% versus 19.5% over 2.3 years (HR 0.82, 95% CI 0.73–0.92). Benefits were observed with and without diabetes. These composite outcomes must not be described as equivalent reductions in every component or as reversal of cardiac aging. [10]

Kidney trials demonstrate slower progression to major renal outcomes. In DAPA-CKD, involving 4,304 participants, sustained $\geq 50\%$ eGFR decline, end-stage kidney disease, or renal/cardiovascular death occurred in 9.2% with dapagliflozin versus 14.5% with placebo over 2.4 years (HR 0.61, 95% CI 0.51–0.72). [11] CREDENCE established canagliflozin benefit in albuminuric diabetic kidney disease, reducing the composite of end-stage kidney disease, doubled serum creatinine, or renal/cardiovascular death by 30% (HR 0.70, 95% CI 0.59–0.82). [86] EMPA-KIDNEY broadened applicability: kidney disease progression or cardiovascular death occurred in 13.1% versus 16.9% over two years (HR 0.72, 95% CI 0.64–0.82), with consistent benefit regardless of diabetes status. These findings support preserved organ function, not restoration of lost nephrons. [87]

Dual SGLT1/2 inhibition also has outcome evidence. SCORED enrolled 10,584 adults with type 2 diabetes, chronic kidney disease and cardiovascular risk. Sotagliflozin reduced total cardiovascular deaths, heart-failure hospitalizations and urgent heart-failure visits from 7.5 to 5.6 events per 100 patient-years (HR 0.74, 95% CI 0.63–0.88). [83] In SOLOIST-WHF, 1,222 patients with diabetes and recent worsening heart failure had fewer events in the same composite (51.0 versus 76.3 per 100 patient-years; HR 0.67, 95% CI 0.52–0.85). Both trials ended early after funding loss. They support sotagliflozin in the studied settings, but neither isolates an incremental SGLT1 benefit or proves superiority to selective SGLT2 inhibition. [84]

Other disease signals are promising but less mature. The 154-participant DEAN trial found histological improvement of metabolic dysfunction-associated steatohepatitis without worsening fibrosis in 53% with dapagliflozin versus 30% with placebo at 48 weeks. This is a liver histology result, not evidence of reduced cirrhosis mortality. [12] Atrial-fibrillation findings derive from secondary trial analysis, dementia findings from observational comparisons, and small neuropathy trials show endpoint-specific responses rather than established nerve-disease reversal. Endothelial signaling experiments likewise do not establish clinical reversal of vascular aging. Appendix B preserves these evidence distinctions. [4,14–16,20]

5. Lifespan Extension and Mortality Reduction

The National Institute on Aging Interventions Testing Program found that canagliflozin increased median lifespan by 14% and the age at 90th-percentile survival by 9% in genetically heterogeneous male mice across three sites. Female mice did not show lifespan extension at the tested regimen, despite improvements in glucose handling. This is a particularly informative result: metabolic improvement alone did not guarantee longer life. Additional empagliflozin studies in naturally aged mice and canagliflozin experiments in premature-aging models provide convergent, but model-dependent, support. [7,8,18]

Human trials support survival benefits in selected disease populations. EMPA-REG OUTCOME enrolled 7,020 people with type 2 diabetes and established cardiovascular disease; all-cause death occurred in 5.7% with empagliflozin versus 8.3% with placebo during a median 3.1-year observation period. [17] DAPA-CKD reported

all-cause mortality of 4.7% versus 6.8% (HR 0.69, 95% CI 0.53–0.88). [11] These findings support prevention of premature death in those populations. They do not quantify additional lifetime years, establish an increase in maximum human lifespan or justify extrapolation to healthy adults. A geroprotective interpretation is biologically plausible, while the demonstrated clinical claim remains disease-specific risk reduction.

6. Optimizing Safe Use and Co-administered Agents

Optimization begins with the clinical indication and the exact drug. Benefits established for empagliflozin, dapagliflozin, canagliflozin or sotagliflozin should not automatically be assigned to every SGLT inhibitor. For example, a bexagliflozin–dapagliflozin glycemic comparison does not establish equivalent heart-failure, kidney or survival outcomes. Nor can tablet milligram strengths be used to rank clinical potency across different molecules. Use an agent and dose supported for the relevant indication; there is no validated human longevity dose. [1,61,75,76,85]

6.1 Selection, monitoring and interruption

Before treatment, assess kidney function, blood pressure, volume status, nutrition, frailty and the complete medication list. Correct volume depletion and identify insulin deficiency or previous ketoacidosis. KDIGO recommends SGLT2 therapy for appropriate CKD populations, including type 2 diabetes with CKD and eGFR ≥ 20 mL/min/1.73 m², but drug-specific labeling and indication still govern selection. An early, modest eGFR dip can reflect hemodynamic adaptation and is generally not a reason to stop treatment; progressive deterioration or symptomatic hypotension requires clinical reassessment. Follow eGFR and urine albumin-to-creatinine ratio (UACR), alongside the indication-specific outcomes. [70,88]

Provide a written plan for acute illness, poor intake, vomiting, dehydration and surgery. ADA guidance recommends withholding SGLT2 inhibitors three days before scheduled surgery, or four days for ertugliflozin; sotagliflozin labeling specifies at least three days before major surgery or procedures involving prolonged fasting. Restart only when clinically stable, oral intake has resumed and ketoacidosis risks have resolved. Avoid using prolonged fasting or ketogenic diets to intensify the drug's metabolic effects. Essential insulin must not be omitted. Nausea, abdominal pain, vomiting, malaise or rapid breathing require prompt assessment for ketoacidosis even when glucose is not markedly elevated. [85,89]

Discuss genital fungal infections and prompt evaluation of urinary infection symptoms; severe perineal pain or swelling with systemic illness needs urgent care. Review foot wounds and peripheral arterial disease, particularly when considering canagliflozin, and follow product-specific restrictions during pregnancy and breastfeeding. Routine type 1 diabetes treatment is outside the US indications reviewed here and carries substantially greater ketoacidosis risk. In older adults, follow orthostatic symptoms, falls, appetite, strength and unintended weight loss as well as laboratory values. These precautions protect the intended functional benefit; a favorable HbA1c or weight trajectory is insufficient if the person becomes volume-depleted or nutritionally compromised. [61,70,76]

6.2 Minerals — Appendix C

Magnesium replacement can be complementary when deficiency is documented; small clinical reports suggest SGLT2 treatment itself can improve refractory hypomagnesemia. This does not establish a universal need for extra magnesium. Zinc and selenium should likewise correct an identified nutritional need rather than serve as presumed pharmacological enhancers; excess exposure introduces independent toxicity. [23–25] Lithium should not be added as a speculative longevity adjunct. For patients who require prescription lithium, SGLT inhibition may increase its clearance and lower concentrations, whereas dehydration, NSAIDs or renin–angiotensin drugs can raise concentrations. Levels must therefore be monitored when treatment changes, rather than predicting the net effect from a single pathway. [26,81]

6.3 Amino acids — Appendix D

Protein adequacy and preservation of muscle take priority over attempting to suppress nutrient sensing continuously. Leucine, arginine, methionine-related signaling and glutamine can activate mTORC1, but that cellular response is not evidence that normal dietary intake cancels SGLT2 cardiorenal protection. Restricting these nutrients solely for theoretical autophagy could be counterproductive in an older person with poor intake. [30–33,70] BALLAST studied luseogliflozin in older adults receiving the same amino-acid/exercise program in both arms; it did not isolate supplementation efficacy or eliminate muscle loss. Glycine plus N-acetylcysteine has separate preliminary human redox and functional evidence, supporting a combination hypothesis rather than demonstrated SGLT2 synergy. [28,29] The appendix's 22-entry taxonomy includes pyrrolysine, a microbial amino acid, not a human supplementation requirement. [35,36]

6.4 B Vitamins — Appendix E

Use B vitamins to maintain adequacy or treat deficiency, especially vitamin B12 in a metformin-treated patient with compatible findings. Nicotinamide riboside can alter NAD-related biology, but the cited heart-failure study does not establish additional SGLT2 clinical benefit. [37–45,67] Avoid treating homocysteine reduction as a sufficient therapeutic goal: the DIVINE regimen of high-dose folic acid, B6 and B12 worsened renal decline and increased vascular events in diabetic nephropathy. Excess B6 can cause neuropathy, and pharmacological nicotinic acid can worsen glucose tolerance. These concerns apply to the relevant form, dose and population, rather than justifying avoidance of ordinary dietary vitamins or appropriate deficiency treatment. [39,41,46]

6.5 Vitamins A, C, D, E and K — Appendix F

Correct deficiency and meet nutritional requirements; routine high-dose vitamin additions have no demonstrated SGLT2 longevity advantage. Vitamin D status deserves attention when bone or mineral risk is present, because deficiency increased vulnerability to canagliflozin-associated changes in calcitriol and parathyroid hormone in a mechanistic study. This does not establish that supplementation prevents fractures or strengthens SGLT2 survival effects. [49,52] Avoid excessive preformed vitamin A, consider oxalate concerns with high-dose vitamin C in susceptible kidney patients, and review bleeding risk before high-dose vitamin E. Patients taking warfarin need consistent vitamin K intake and supervised changes, not automatic elimination of vitamin K-containing foods. [47,48,50,51]

6.6 Nutritional supplements to consider — Appendix G

The strongest rationale is a defined unmet need. Psyllium may complement glucose and cholesterol control through intestinal fiber effects, and creatine with resistance training may support muscle performance; the cited trials did not test these as SGLT2 combinations. GlyNAC remains an experimental adjunctive hypothesis. [29,55,56] A small dapagliflozin/probiotic trial reported additional glycemic and weight improvements, but its specific formulation and open-label design limit generalization. Live probiotics also require attention to infection susceptibility. [53,57] In EFFECT-II, dapagliflozin plus omega-3 carboxylic acids reduced liver fat significantly versus placebo, but superiority over dapagliflozin alone and pharmacological synergy were not established. These findings do not warrant adding generic fish oil or multiple supplements to every regimen. [54]

6.7 Nutritional supplements to avoid or flag — Appendix H

Glycyrrhizin-containing licorice can raise blood pressure and promote potassium loss, opposing cardiovascular and volume-management goals. Yohimbe/yohimbine products can produce adrenergic cardiovascular adverse effects and are unsuitable elective longevity adjuncts. High-dose nicotinic acid and the harmful B-vitamin exposures discussed above merit exclusion for this purpose. These are physiological or toxicity concerns, not evidence that the substances directly block the SGLT2 binding site. Normal protein intake should not be placed in the same avoidance category merely because amino acids activate mTOR. [30–33,39,41,46,58–60]

6.8 Cardiovascular, lipid and antithrombotic medicines — Appendix I

Indicated renin–angiotensin blockade, an ARNI, evidence-based beta-blockers and mineralocorticoid antagonists can complement SGLT2 treatment in the appropriate heart-failure or kidney-disease setting. DAPA-HF background-treatment analyses support coadministration, while CONFIDENCE demonstrated additional UACR reduction from empagliflozin plus finerenone in diabetic CKD. The latter is a surrogate result, not proof of extra survival benefit; potassium and renal monitoring remain necessary. Statins and appropriate nonstatin lipid agents address residual atherosclerotic risk. [62–64]

Loop/thiazide diuretics may be necessary but can compound volume loss; adjust according to congestion, blood pressure and symptoms. Alpha-blockers and centrally acting antihypertensives warrant particular attention to orthostasis in older adults. [61,72] Anticoagulants and antiplatelets should be used for their own indications: SGLT inhibition neither replaces them nor creates a reason to start aspirin. Chronic systemic NSAIDs can impair renal perfusion and promote sodium retention, especially with dehydration, CKD or heart failure. Low-dose antiplatelet aspirin is a different exposure, although bleeding risk remains relevant and ibuprofen may interfere with aspirin's antiplatelet action. [64–66,79]

6.9 Other diabetes medicines — Appendix J

Metformin provides complementary glucose lowering; assess renal eligibility and B12 status. DURATION-8 demonstrated greater HbA1c, weight and systolic-pressure reductions with exenatide plus dapagliflozin than either alone on metformin, whereas SURPASS-3 supports tirzepatide use on metformin with or without SGLT2 therapy without establishing a specific synergistic interaction. Poor intake, gastrointestinal losses and excessive weight loss require reassessment. [67–70] Insulin and sulfonylureas may need adjustment to prevent hypoglycemia, but excessive insulin reduction can precipitate ketoacidosis. Pioglitazone-related fluid retention and the heart-failure warnings for saxagliptin/alogliptin remain relevant; SGLT treatment should not be assumed to neutralize them. [61,70,71,82]

6.10 Sleep aids and other interactions — Appendix K

Sleep medicines have no established SGLT2 geroprotective synergy. Benzodiazepines, Z-drugs and sedating antihistamines can add cognitive and fall-related harm; trazodone can cause orthostasis. An orexin antagonist may be appropriate for a separate sleep indication but still requires assessment of sedation and interactions. Combining these effects with nocturia or volume depletion creates a plausible additional fall risk, rather than a proven molecular antagonism. [72–74,77]

Drug-specific pharmacokinetics also matter. Canagliflozin and sotagliflozin can increase digoxin exposure; UGT inducers reduce exposure to selected SGLT drugs, including canagliflozin, bexagliflozin and sotagliflozin. Check the exact product's monitoring and dose instructions rather than applying a class-wide rule. [75,76,85] Necessary corticosteroids may oppose glucose, muscle or volume goals, but this calls for monitoring and management of their indication rather than abrupt withdrawal. The lithium interaction described above likewise requires concentration-guided care. [26,78,81]

7. Summary and Conclusion

SGLT inhibition has established value for disease amelioration and, in selected clinical populations, prevention of premature death. Experimental nutrient-sensing, inflammatory and senescence findings, together with male-mouse lifespan extension and emerging human biomarkers, make geroprotection a credible research direction. Evidence for dual SGLT1/2 inhibition supports sotagliflozin's clinical use in defined settings but does not establish an independent SGLT1 longevity effect. [7,9–11,13,17,18,83,84,86,87] The rational approach is to select a drug with relevant outcome evidence, preserve nutrition and function, retain beneficial indicated therapies, avoid harmful adjuncts and use explicit monitoring and interruption plans. Human age reversal, maximum-lifespan extension and a universal synergistic supplement regimen remain unestablished. The appendices support these decisions by keeping each claim attached to its drug, population, endpoint and evidence level.

Appendices

The tables below serve as the manuscript's appendices. Most interaction evidence concerns selective SGLT2 inhibitors; sotagliflozin-specific pharmacokinetic additions are identified in Appendix K. A: organ outcomes; B: biological and clinical evidence map; C: minerals; D: amino acids; E: B vitamins; F: vitamins A, C, D, E and K; G: potentially complementary nutritional supplements; H: supplements to avoid or flag; I: cardiovascular, lipid and antithrombotic medicines; J: other diabetes medicines; K: sleep aids and other interactions.

Appendix A. Organ outcomes and evidence boundaries

Organ / system	Supported finding	Evidence and limitations
Cardiovascular health	Fewer heart-failure events; survival benefit in selected high-risk populations.	DAPA-HF, DELIVER and EMPA-REG; dual inhibition: SCORED and SOLOIST-WHF. These are clinical outcomes, not proof of cardiac age reversal. [9,10,17,83,84]
Kidney function	Slower CKD progression and fewer major kidney outcomes.	CREDENCE, DAPA-CKD and EMPA-KIDNEY. Preservation of function does not demonstrate nephron regeneration. [11,86,87]
Vascular biology	Endothelial protection and senescence-related signals in experimental models.	Endothelial-cell AMPK/SIRT1 experiments and mouse aging studies support mechanisms; clinical reversal of vascular aging remains unestablished. [4,7]

Appendix B. SGLT2 inhibitors: biological and clinical evidence map

- SGLT2 inhibitors: granular evidence map across molecular mechanisms, measurable responses, and disease outcomes. Findings are drug- and population-specific; the complete profile is not established for bexagliflozin or any single agent.
- Evidence: H = human; A = animal; C = cell/ex vivo. “Emerging,” “post hoc,” “observational,” and “mechanistic” qualify human findings. ↑/↓ indicate reported direction, not universal benefit. Columns are independent lists; rows do not imply causal links. Bracketed numbers link to sources.

1. Molecular targets and biological processes	2. Biometric and laboratory measures	3. Diseases and clinical outcomes
SGLT2/SLC5A2 inhibition. Renal glucose reabsorption ↓; urinary glucose excretion ↑. Direct pharmacological target, distinct from downstream aging pathways. [H; 1]	HbA1c ↓. At 24 weeks: −1.08 percentage points with bexagliflozin 20 mg versus −1.10 with dapagliflozin 10 mg, both added to metformin. [H; 1]	Type 2 diabetes. Improved glycemic control with bexagliflozin and dapagliflozin; does not imply diabetes remission. [H; 1]
AMPK signaling ↑. Empagliflozin enhanced energy-sensing signaling in metabolic-disease models. Activation is tissue- and context-dependent. [A/C; 3,21]	Fasting plasma glucose ↓. Corresponding changes: −1.95 versus −1.87 mmol/L. [H; 1]	Heart failure with reduced ejection fraction. Dapagliflozin reduced worsening HF/cardiovascular death in DAPA-HF. Benefit included people without diabetes. [H; 9]

1. Molecular targets and biological processes	2. Biometric and laboratory measures	3. Diseases and clinical outcomes
mTOR signaling ↓. Empagliflozin attenuated nutrient-growth signaling in diabetic fatty-liver and obese-heart models. [A/C; 3,21]	Two-hour postprandial glucose ↓. Corresponding changes: -3.24 versus -3.07 mmol/L. [H; 1]	Heart failure with mildly reduced/preserved ejection fraction. Dapagliflozin reduced worsening HF/cardiovascular death in DELIVER; principally fewer worsening-HF events. [H; 10]
Macroautophagy ↑. Empagliflozin enhanced hepatic macrophage autophagy through AMPK/mTOR signaling. [A/C; 3]	Body weight ↓. Corresponding changes: -2.52 versus -2.22 kg; weight alone does not identify fat versus lean or fluid loss. [H; 1]	Chronic kidney disease progression. Dapagliflozin reduced the kidney/CV composite outcome in DAPA-CKD, with or without diabetes. [H; 11]
NLRP3 inflammasome activation ↓. Empagliflozin reduced activation in macrophages obtained from treated patients with diabetes and cardiovascular risk. [H-mechanistic; 2]	Systolic blood pressure ↓. Corresponding changes: -6.4 versus -6.3 mmHg. [H; 1]	Kidney failure. Lower risk within DAPA-CKD kidney outcomes; prevention/delay, not recovery from established end-stage disease. [H; 11]
SIRT1-dependent signaling ↑. Dapagliflozin protected high-glucose-exposed endothelial cells; AMPK or SIRT1 blockade abolished protection. This does not demonstrate a larger NAD ⁺ pool. [C; 4]	Circulating insulin ↓. Observed in the empagliflozin mechanistic study; a metabolic response, not a stand-alone aging measure. [H; 2]	Atrial fibrillation/flutter events. DECLARE post hoc analysis: dapagliflozin HR 0.81 (95% CI 0.68–0.95); fewer reported events, not proof of AF resolution. [H-post hoc; 14]
NF-κB pathway modulation. Empagliflozin altered AMPK/SIRT1/NF-κB signaling in aged mouse liver alongside reduced inflammation. [A; 8]	Serum uric acid ↓. Observed alongside inflammasome suppression in the same trial. [H; 2]	Diabetic peripheral neuropathy. DINE supports a small-fibre regeneration signal; a separate small empagliflozin trial supports selected symptoms and conduction measures. Evidence is diabetes-specific. [H-emerging; 15,16]
NAMPT expression ↑. Empagliflozin increased NAD ⁺ -salvage-enzyme transcripts in healthy mouse quadriceps; the heart did not show the same response. [A; 5]	β-Hydroxybutyrate ↑. A measured ketone/substrate shift in empagliflozin and henagliflozin trials; elevation is not inherently a health improvement. [H; 2,13]	MASH resolution. Dapagliflozin increased biopsy-defined resolution without worsening fibrosis over 48 weeks in DEAN. [H-emerging; 12]
Nicotinate/nicotinamide metabolism altered. Empagliflozin changed renal NAD ⁺ -related metabolic pathways in diabetic mice; systemic NAD ⁺ restoration was not established. [A; 6]	Macrophage IL-1β secretion ↓. Reduced release in stimulated patient-derived cell assays after treatment; distinct from a circulating cytokine measurement. [H-mechanistic; 2]	Liver fibrosis. Dapagliflozin increased histological improvement without worsening MASH; complete fibrosis reversal was not established. [H-emerging; 12]

1. Molecular targets and biological processes	2. Biometric and laboratory measures	3. Diseases and clinical outcomes
PGC-1 α expression $\uparrow$. Empagliflozin increased transcripts governing mitochondrial metabolic adaptation in healthy mouse skeletal muscle. [A; 5]	Long-term eGFR decline slowed. DAPA-CKD total slopes: -2.86 versus -3.79 mL/min/1.73 m ² /year; initial hemodynamic dip can occur. [H; 11]	Major cardiovascular events. Empagliflozin reduced the composite of CV death, nonfatal MI or nonfatal stroke in T2DM with established cardiovascular disease. Individual MI/stroke benefits were not established. [H; 17]
PD-L1 expression $\downarrow$. Canagliflozin reduced the immune-evasion signal on senescent cells in mouse experiments. [A/C; 7]	Liver inflammatory activity $\downarrow$. Dapagliflozin improved biopsy-based MASH activity over 48 weeks. [H-emerging; 12]	Cardiovascular mortality. Reduced with empagliflozin in EMPA-REG OUTCOME; applicable to the studied high-risk population. [H; 17]
Immune-mediated senescent-cell clearance $\uparrow$. Canagliflozin enhanced endogenous immunosurveillance; an indirect senolytic mechanism. [A; 7]	Liver fibrosis stage improved. Improvement without worsening MASH occurred in 45% versus 20% with placebo in DEAN. [H-emerging; 12]	All-cause mortality. Reduced in EMPA-REG OUTCOME; this is not a human lifespan-extension trial in healthy adults. [H; 17]
AICAR-related metabolic signaling $\uparrow$. Canagliflozin increased the endogenous metabolite linked to AMPK-dependent immune clearance in the senolysis study. [A; 7]	Leukocyte telomere length $\uparrow$. Henagliflozin 10 mg/day versus placebo, 26 weeks, 150 randomized participants with T2DM; primary biomarker endpoint. [H-emerging; 13]	Incident dementia. Lower incidence associated with SGLT2 inhibitors versus DPP-4 inhibitors in a large T2DM cohort; residual confounding remains possible. [H-observational; 20]
Myocardial fuel utilization shifted. Empagliflozin increased use of ketones and other oxidative substrates in nondiabetic heart-failure pigs. [A; 19]	Cytotoxic T-cell granzyme B expression $\uparrow$. Significant exploratory immune finding in the henagliflozin trial; does not directly measure senescent-cell killing. [H-emerging; 13]	Obesity-associated adipose inflammation. Canagliflozin improved inflammation and metabolic dysfunction in obese mice, including effects without weight loss. [A; 7]
Myocardial energy efficiency $\uparrow$. Empagliflozin increased cardiac ATP content and work efficiency in the same porcine model. [A; 19]	IGFBP-3 $\uparrow$. Henagliflozin increased insulin-like growth factor-binding protein-3; this is distinct from demonstrating IGF-1 reduction. [H-emerging; 13]	Age-associated liver senescence. Empagliflozin improved hepatic senescence-related changes in naturally aged mice. [A; 8]
Sestrin2 signaling restored. Empagliflozin engaged Sestrin2-associated AMPK/mTOR regulation in obesity-related cardiac dysfunction. [A/C; 21]	Renal nicotinic acid mononucleotide $\uparrow$. NAD ⁺ -pathway metabolite increased with empagliflozin in diabetic mice. [A; 6]	Premature-aging survival. Canagliflozin prolonged survival in a progeroid mouse model. [A; 7]
Nrf2 antioxidant response $\uparrow$. Empagliflozin enhanced Nrf2 signaling in obese-mouse cardiac experiments. [A/C; 21]	Renal nicotinamide $\uparrow$. NAD ⁺ -related metabolomic finding in diabetic mice; precursor changes do not establish total NAD ⁺ availability. [A; 6]	Normal-aging lifespan. Canagliflozin extended lifespan in genetically heterogeneous male mice, but not females. [A; 18]

1. Molecular targets and biological processes	2. Biometric and laboratory measures	3. Diseases and clinical outcomes
HO-1 antioxidant response ↑. Enhanced downstream heme oxygenase-1 response accompanied the Nrf2 effect. [A/C; 21]	TNF-α ↓. Reported with empagliflozin in naturally aged mice. [A; 8]	—
FUNDC1-dependent mitophagy ↑. Empagliflozin supported mitochondrial quality control through AMPKα1/ULK1/FUNDC1 in cardiac microvascular injury models. [A/C; 22]	IL-6 ↓. Reported in the same aged-mouse study; not assumed to be universal across human trials. [A; 8]	—
Oxidative injury ↓. Empagliflozin attenuated renal oxidative stress in diabetic mice; effects are model-specific. [A; 6]	CXCL9 ↓. Reported in the same aged-mouse study. [A; 8]	—
IL-17 signaling ↓. Empagliflozin suppressed IL-17-associated inflammation in experimental diabetic fatty liver. [A/C; 3]	Corneal nerve fibre density ↑. Increased within the dapagliflozin arm in DINE, a 40-participant, six-month open-label randomized study. [H-emerging; 15]	—
IL-23 signaling ↓. Empagliflozin suppressed the accompanying IL-23 inflammatory response in the same model. [A/C; 3]	Corneal nerve branch density ↑. Increased in the DINE dapagliflozin arm; no change reported in the control arm. [H-emerging; 15]	—
Endothelial apoptosis ↓. Dapagliflozin reduced high-glucose-induced cell death in endothelial cultures. [C; 4]	Corneal nerve fibre length ↑. Increased in DINE; small-study signal rather than established reversal of neuropathy. [H-emerging; 15]	—
—	Glutathione peroxidase ↑. Increased in the DINE dapagliflozin arm, supporting an antioxidant response. [H-emerging; 15]	—
—	Nerve conduction velocity improved. Reported in a 50-participant, 20-week empagliflozin randomized trial. [H-emerging; 16]	—
—	Neuropathy symptom score improved. Empagliflozin improved the MNSI questionnaire component; examination scores did not significantly differ. [H-emerging; 16]	—

1. Molecular targets and biological processes	2. Biometric and laboratory measures	3. Diseases and clinical outcomes
—	Senescence-associated β -galactosidase $\downarrow$. Canagliflozin reduced this tissue marker in mouse senolysis experiments. [A; 7]	—
—	p21/Cdkn1a expression $\downarrow$. Reduced in adipose tissue in the same mouse study. [A; 7]	—
—	p16/Cdkn2a expression $\downarrow$. Reduced in adipose tissue in the same mouse study. [A; 7]	—

Appendix C. Minerals

- Continuation of the evidence table. Classifications describe interactions alongside SGLT2 treatment; “neutral/undetermined” means no established enhancing or opposing effect, not proof of no interaction. None of these combinations has established human anti-aging synergy. Shared mechanisms alone do not demonstrate an effect greater than expected from the individual agents.

Mineral	Interaction classification	Evidence and interpretation
Zinc	Neutral/undetermined; potentially complementary if deficient	Deficiency correction supports immune function and metabolism. Added zinc has no established SGLT2-specific enhancing effect in zinc-replete people; geroprotective synergy is unproven. Excess supplementation can cause copper deficiency. [23]
Magnesium	Potentially complementary, particularly with hypomagnesemia	SGLT2 inhibitors can increase serum magnesium. In three patients with diabetes and refractory hypomagnesemia, treatment improved magnesium status and sometimes reduced replacement requirements. This supports a favorable physiological relationship, not demonstrated synergy from adding magnesium or additional longevity benefit. [24]
Selenium	Neutral/undetermined when selenium status is adequate	Selenium supports glutathione peroxidases and thioredoxin reductases. Correcting deficiency is mechanistically complementary; extra supplementation has not consistently improved cardiometabolic outcomes in replete populations. SGLT2-specific synergy is unproven. Excess selenium is toxic. [25]
Lithium	SGLTi Potentially antagonistic to lithium exposure	SGLT2 inhibitors may increase renal lithium excretion and lower serum concentrations, potentially reducing lithium’s therapeutic effect. This is a pharmacokinetic interaction, not evidence that lithium blocks SGLT2 benefits. Prescription lithium requires closer level monitoring when SGLT2 treatment starts or changes. Significance for low-dose supplemental lithium is uncertain; geroprotective synergy is unproven. [26]

● Appendix D. Amino acids: 22-entry evaluation

- Scope: the 20 standard proteinogenic amino acids plus selenocysteine and pyrrolysine; humans use selenocysteine, whereas pyrrolysine belongs to certain microorganisms. Taurine, citrulline and ornithine are outside this defined set. [35,36]
- Interpretation: neutral/undetermined means insufficient combination evidence, not proven neutrality. “Potentially complementary” is a hypothesis, not demonstrated synergy. No reviewed combination establishes human age reversal. Nutrient-sensing opposition is endpoint-specific and does not establish loss of SGLT2 cardiorenal protection. Metabolomics studies measured amino-acid responses, not supplementation efficacy; ATIRMA involved 40 young adults with type 1 diabetes and does not establish routine treatment guidance. [27]

Amino acid	Interaction classification	Evidence and interpretation
Alanine	Neutral/ undetermined	Plasma alanine increased after empagliflozin in ATIRMA. This is a substrate-response observation, not evidence that alanine supplementation enhances treatment. [27]
Arginine	Context-dependent; theoretical pathway opposition	Arginine activates mTORC1 through CASTOR1. This could oppose an autophagy-focused objective, but clinical antagonism to SGLT2 benefits is unproven. Nitric-oxide biology alone does not establish synergy. [31]
Asparagine	Neutral/ undetermined	No isolated supplementation–SGLT2 interaction demonstrated in the reviewed evidence. Measuring circulating asparagine does not establish supplementation benefit.
Aspartate (aspartic acid)	Neutral/ undetermined	Relevant to nitrogen and energy metabolism. Pathway associations provide no demonstrated benefit from adding aspartate to SGLT2 therapy.
Cysteine	Potentially complementary; indirect evidence	Glutathione precursor. GlyNAC improved redox and functional measures in a small older-adult trial; the cysteine source was N-acetylcysteine, not free cysteine. SGLT2 combination benefit was not tested. [29]
Glutamate (glutamic acid)	Neutral/ undetermined	Participates in nitrogen transfer and glutathione synthesis. Neither endogenous pathway involvement nor GlyNAC results establish benefit from oral glutamate with SGLT2 inhibitors. [29]
Glutamine	Context-dependent; theoretical pathway opposition	Glutamine can activate mTORC1 through an Arf1-dependent route in cells. Possible opposition to autophagy-focused signaling is mechanistic inference; clinical SGLT2 antagonism or synergy is unestablished. [33]
Glycine	Potentially complementary; indirect human evidence	GlyNAC improved glutathione status, oxidative stress and selected physical-function measures in older adults. Results concern a two-agent intervention, not glycine alone or an SGLT2 combination. [29]
Histidine	Neutral/ undetermined; human metabolic signal	Empagliflozin increased plasma histidine in a 58-patient, 12-week randomized open-label T2D trial. Increased endogenous availability does not prove benefit from supplementation. [34]

Amino acid	Interaction classification	Evidence and interpretation
Isoleucine	Neutral/ undetermined; nutritional complement possible	Essential branched-chain amino acid. Adequate intake supports protein nutrition; altered BCAA metabolism does not establish an isolated isoleucine–SGLT2 interaction.
Leucine	Potentially complementary for muscle; context-dependent signaling	BALLAST tested luseogliflozin with leucine-enriched amino acids and exercise; both arms received these co-interventions. Strength remained stable, but muscle loss was not eliminated. Leucine activates Sestrin2–mTORC1 signaling; muscle support and autophagy objectives may differ. Neither synergy nor clinical antagonism was established. [28,30]
Lysine	Neutral/ undetermined	Essential protein substrate. Changes in acetyl-lysine in metabolomics must not be interpreted as lysine deficiency or evidence for lysine supplementation. [27]
Methionine	Context-dependent; theoretical pathway opposition	Methionine supplies S-adenosylmethionine, sensed by SAMTOR to regulate mTORC1. Excess supplementation could oppose a nutrient-restriction objective; this does not demonstrate antagonism to SGLT2 clinical benefits or justify deficiency. [32]
Phenylalanine	Neutral/ undetermined	An empagliflozin-associated increase under hyperglycemic clamp was reported. This does not establish supplementation benefit or a favorable aging effect. [27]
Proline	Neutral/ undetermined	No direct combination efficacy established. Participation in arginine/proline metabolism is not evidence of synergy from supplemental proline.
Serine	Neutral/ undetermined	An amino-acid and one-carbon-metabolism substrate. Current SGLT2 metabolomics does not establish that serine supplementation improves clinical outcomes or rejuvenation.
Threonine	Neutral/ undetermined	Essential protein substrate. No isolated threonine–SGLT2 supplementation benefit demonstrated; metabolite measurements are not intervention evidence.
Tryptophan	Neutral/ undetermined	Empagliflozin-associated changes in tryptophan and kynurenine depended on experimental conditions. Neither proves enhanced NAD ⁺ synthesis or benefit from supplementation. [27]
Tyrosine	Neutral/ undetermined	No direct supplementation synergy or antagonism established. Aromatic-amino-acid pathway findings do not determine the effect of adding tyrosine.
Valine	Neutral/ undetermined; nutritional complement possible	Essential branched-chain amino acid. Metabolic associations cannot determine whether isolated valine supplementation improves or impairs SGLT2 treatment.
Selenocysteine	Not established as a supplementation strategy	Human selenoproteins incorporate selenocysteine synthesized on specialized tRNA. Dietary selenium adequacy and direct selenocysteine supplementation are different interventions; SGLT2 combination benefit is unproven. [25,35]

Amino acid	Interaction classification	Evidence and interpretation
Pyrrolysine	Not applicable to human protein supplementation	The 22nd genetically encoded amino acid occurs in certain microorganisms, not normal human protein synthesis. No established human nutritional requirement or SGLT2 adjunct role. [36]

• **Appendix E. The eight B vitamins**

- Scope: B1, B2, B3, B5, B6, B7, B9 and B12. Classification concerns supplementation alongside SGLT2 treatment. Deficiency correction is complementary care, not demonstrated pharmacological synergy. No reviewed combination establishes human age reversal; unproven interactions remain undetermined rather than proven neutral.

B vitamin / forms	Interaction classification	Evidence and interpretation
B1 — Thiamine	Complementary when deficient ; otherwise undetermined	Thiamine-dependent enzymes support energy metabolism and nerve function. Deficiency correction is beneficial; extra thiamine has no established SGLT2 synergy. Benfotiamine is a thiamine derivative, not an additional B vitamin; its pharmacology cannot establish a class-wide combination benefit. [37]
B2 — Riboflavin	Complementary when deficient ; otherwise undetermined	Supplies FMN/FAD cofactors for mitochondrial oxidation and redox reactions. This creates mechanistic compatibility with SGLT2-associated metabolic adaptation, not demonstrated supplementation synergy in vitamin-replete people. [38]
B3 — Niacin / nicotinamide; related NAD ⁺ precursors	Form-dependent: possible complementarity or opposing glycemic effect	NAD ⁺ /NADP ⁺ precursor biology provides a rationale for complementarity. High-dose nicotinic acid can worsen insulin resistance and glucose control; this is not SGLT2 blockade. Nicotinamide is not interchangeable with nicotinic acid. NR increased blood NAD ⁺ in a small heart-failure trial, but NR/NMN–SGLT2 synergy and rejuvenation remain unestablished. [39,45]
B5 — Pantothenic acid	Complementary when deficient ; otherwise undetermined	Precursor for coenzyme A and acyl-carrier protein, supporting fatty-acid and energy metabolism. Adequacy is necessary; surplus supplementation has no established SGLT2-enhancing effect. Pantethine results cannot automatically be attributed to pantothenic acid. [40]
B6 — Pyridoxine / PLP	Complementary when deficient ; excess can oppose neuropathy goals	PLP supports amino-acid metabolism and neurotransmitter synthesis. Chronic excess supplemental B6, particularly pyridoxine, can cause sensory neuropathy. This is dose-related toxicity, not a demonstrated SGLT2 interaction. PLP/P5P labeling does not establish combination benefit or justify unrestricted dosing. [41]
B7 — Biotin	Complementary when deficient ; otherwise undetermined	Cofactor for carboxylases involved in intermediary metabolism. No established SGLT2 supplementation synergy. Supplemental biotin can interfere with some troponin, thyroid and other immunoassays, confounding clinical assessment rather than directly opposing SGLT2 action. [42]

B vitamin / forms	Interaction classification	Evidence and interpretation
B9 — Folate / folic acid / 5-MTHF	Complementary when deficient ; high-dose benefit cannot be assumed	Supports one-carbon metabolism and nucleotide synthesis. Homocysteine reduction does not establish additional cardiorenal protection. Folate can correct B12-deficiency anemia without treating neurological injury; 5-MTHF has no established SGLT2-specific advantage. [43]
B12 — Cobalamins	Complementary when deficient , especially with neuropathy; otherwise undetermined	Correction treats deficiency-related hematological and neurological dysfunction. Concurrent metformin can impair B12 status; that established effect should not be attributed to SGLT2 inhibitors. Methylcobalamin, cyanocobalamin and other forms have no demonstrated differential SGLT2 synergy. [44]

Combination evidence boundary: in DIVINE, high-dose folic acid/B6/B12 lowered homocysteine but worsened renal-function decline and increased vascular events in diabetic nephropathy. This was not an SGLT2-combination trial and does not argue against treating a documented deficiency. [46]

• **Appendix F. Vitamins A, C, D, E and K**

- Together with the preceding eight B vitamins, this section covers all 13 recognized vitamins. Common forms are grouped by vitamin. Choline, inositol, CoQ10 and compounds marketed under obsolete vitamin labels are not additional recognized vitamins. Classifications concern use alongside SGLT2 inhibitors; nutritional adequacy, mechanistic complementarity and demonstrated combination benefit remain distinct.

Vitamin / common forms	Interaction classification	Evidence and interpretation
A — Retinol / retinyl esters; beta-carotene	Complementary when deficient ; otherwise undetermined	Supports epithelial integrity, vision and immune function. No established SGLT2 supplementation synergy. Excess preformed vitamin A can cause toxicity; beta-carotene is not interchangeable with retinol, and high-dose beta-carotene increased lung-cancer risk in smokers. These are supplement effects, not demonstrated SGLT2 antagonism. [47]
C — Ascorbic acid / mineral ascorbates	Potentially complementary; combination benefit unproven	Supports collagen synthesis and antioxidant defenses. Correcting deficiency is beneficial; antioxidant overlap does not prove additional SGLT2 efficacy or rejuvenation. High intake can increase urinary oxalate, particularly relevant with renal disease. Buffered/mineral or liposomal formulations have no established SGLT2-specific advantage. [48]
D — D2 / D3	Complementary when deficient , direct human biomarker evidence	In 11 initially vitamin-D-deficient adults, D3 repletion reduced the canagliflozin-associated fall in active vitamin D from approximately 31% to 9%, and the PTH rise from 36% to 10%. This small sequential challenge study did not establish fracture prevention, class-wide benefit or longevity synergy. D2/D3 are distinct from prescription calcitriol; excess vitamin D can cause hypercalcemia. [49,52]

Vitamin / common forms	Interaction classification	Evidence and interpretation
E — Alpha-tocopherol / mixed tocopherols / tocotrienols	Complementary when deficient ; otherwise undetermined	Membrane antioxidant activity provides mechanistic compatibility, but no established SGLT2 combination benefit. Results for alpha-tocopherol cannot automatically be generalized to mixed tocopherols or tocotrienols. High-dose supplementation can increase bleeding risk, especially with anticoagulants or antiplatelets; this is not direct SGLT2 antagonism. [50]
K — K1; K2 (MK-4 / MK-7)	Complementary when deficient ; otherwise undetermined	Supports vitamin-K-dependent protein carboxylation in coagulation and bone/mineral biology. K2 has no established SGLT2-specific vascular, skeletal or longevity synergy. Vitamin K can oppose warfarin's anticoagulant effect; that interaction is with warfarin, not SGLT2 inhibition. MK-4 and MK-7 are distinct forms, not additional vitamins. [51]

● **Appendix G. Nutritional supplements: potential complementary effects**

- Included entries have direct combination evidence or a human-supported complementary rationale. “Likely” identifies an inference, not demonstrated synergy. Benefits must match the endpoint and population; none establishes human age reversal. Neutral or unsupported candidates are omitted. Earlier vitamin/mineral entries qualify only under their stated conditions, particularly correction of deficiency.

Nutritional supplement	Classification	Evidence, complementary activity and limits
Specific triple-strain probiotic	Add-on benefit demonstrated; synergy unproven	A 24-week randomized study (120 adults with overweight/obesity and T2D) compared dapagliflozin alone with added <i>B. longum</i> , <i>L. acidophilus</i> and <i>E. faecalis</i> tablets. HbA1c fell 1.8 versus 0.8 percentage points; weight fell 5.2 versus 3.1 kg. Microbiota changes accompanied benefit; causality was not established. Single-center, open-label evidence requires replication and does not generalize to other probiotics. Live products require individualized infection-risk assessment in immunocompromised patients. [53,57]
Omega-3 EPA/DHA preparation	Likely complementary; direct combination evidence, mixed endpoints	EFFECT-II (84 participants, 12 weeks) tested dapagliflozin and 4 g/day omega-3 carboxylic acids. Liver fat fell 21% with combination versus 13% with dapagliflozin; only combination differed significantly from placebo. This does not establish superiority over dapagliflozin or synergy. Liver-injury markers improved with dapagliflozin alone, not combination. Evidence is formulation- and liver-fat-specific; generic fish oil and extra cardiorenal protection cannot be assumed. [54]

Nutritional supplement	Classification	Evidence, complementary activity and limits
Psyllium husk	Likely complementary for postprandial glycemia and cholesterol	Viscous intestinal fiber provides a mechanism distinct from renal glucose excretion. A placebo-controlled T2D trial found lower postprandial glucose and total cholesterol; LDL reduction did not reach significance in that trial. No direct SGLT2 combination efficacy trial is cited. Use requires adequate fluid and attention to product instructions concerning oral-medication separation. This is targeted metabolic complementarity, not demonstrated longevity synergy. [55]
Creatine monohydrate with resistance exercise	Likely complementary for muscle preservation	Phosphocreatine supports rapid ATP buffering. A 24-week randomized trial in 60 older women found greater appendicular lean-mass and bench-press gains with creatine plus training than training alone; incremental leg-press benefit was not significant. No direct SGLT2 combination evidence or proof of preventing SGLT2-associated lean-mass loss. Renal disease warrants individualized assessment; supplementation can complicate creatinine-based monitoring. [56]
GlyNAC (glycine plus N-acetylcysteine)	Likely mechanistic complement; early human evidence	Provides substrates for glutathione synthesis. A small randomized older-adult trial reported improvements in redox status, mitochondrial measures and physical function. These independently observed effects align with SGLT2-associated metabolic and inflammatory pathways, supporting a combination hypothesis. Direct combination efficacy, optimal joint dosing and human age reversal remain untested. [29]
Leucine-enriched amino-acid supplementation with exercise	Conditional complement for muscle goals	BALLAST tested luseogliflozin in older adults receiving the same amino-acid/exercise program in both arms. It supports coadministration, not an isolated supplement effect; muscle-mass loss was not eliminated. Inclusion is conditional on nutritional adequacy and muscle-preservation needs. Leucine-driven mTORC1 activation can support muscle anabolism while opposing an autophagy-focused cellular objective; it is not a general SGLT2 contraindication. [28,30]

● **Appendix H. Nutritional supplements: avoid or flag**

- Avoidance below applies to the specified exposure and purpose. Clinical harm, physiological opposition and molecular pathway opposition are different claims. Amino-acid activation of mTORC1 through leucine/Sestrin2, arginine/CASTOR, methionine/SAMTOR or glutamine warrants a context-specific flag when sustained autophagy is the objective, not blanket amino-acid restriction in older adults. No evidence here shows that these nutrients abolish established SGLT2 cardiorenal benefit. [30,31,32,33]

Supplement / exposure	Disposition	Opposing activity and evidence boundary
Glycyrrhizin-containing licorice	Avoid as an elective SGLT2 adjunct	Mineralocorticoid-like effects promote sodium retention, hypertension and potassium loss, opposing volume/BP treatment goals. A randomized crossover trial detected BP effects at 100 mg/day glycyrrhizic acid. Cardiac/renal disease increases concern. This is physiological opposition, not proven blockade of SGLT2 binding. Deglycyrrhizinated licorice is a different exposure. [58,60]
Yohimbe / yohimbine supplements	Avoid as an elective metabolic or longevity adjunct	Adrenergic stimulation can produce BP disturbances, tachycardia and arrhythmia, opposing hemodynamic goals and adding cardiovascular risk. Product content is variable. Evidence supports avoidance on safety/physiological grounds, not a demonstrated pharmacokinetic interaction with SGLT2 drugs. [59]
High-dose nicotinic acid	Avoid routine addition for this purpose	Pharmacological nicotinic acid can worsen glucose tolerance and insulin resistance, opposing glycemic goals. This concern does not apply equivalently to nutritional B3 intake or establish the same interaction for nicotinamide, NR or NMN. A separate clinical indication requires its own benefit–risk assessment. [39]
High-dose B-vitamin regimens in diabetic nephropathy; excessive B6	Avoid the harmful regimen/exposure	DIVINE found faster renal decline and more vascular events with folic acid 2.5 mg, B6 25 mg and B12 1 mg daily in diabetic nephropathy. Separately, excessive B6 can cause sensory neuropathy. These oppose renal/neurologic objectives through observed harm, not demonstrated SGLT2 receptor antagonism; deficiency treatment is a different indication. [41,46]

● **Appendix I. Cardiovascular, lipid and antithrombotic medicines**

- Classification applies to the stated indication and patient population. Complementary means distinct useful actions; additive means extra measured benefit or effect; synergy requires more than shared pathways. Most listed combinations are not contraindicated solely because an SGLT2 inhibitor is present. Disease-specific contraindications and additive toxicity are identified separately. Evidence for empagliflozin/dapagliflozin outcomes must not automatically be transferred to bexagliflozin. This is a class-level review, not an individualized medication-change order.

Drug class / examples	Classification	Evidence, interaction and practical implication
ACE inhibitors / ARBs Lisinopril, ramipril; losartan, valsartan	Established complementary cardiorenal therapy	Renin–angiotensin blockade and SGLT2 inhibition address different renal/hemodynamic mechanisms. DAPA-CKD and DAPA-HF support SGLT2 benefit on this background. Monitor BP, creatinine/eGFR and potassium. A small initial eGFR dip does not by itself establish harmful antagonism. Use an ACE inhibitor OR ARB, not routine dual blockade. [11,62,64]
ARNI Sacubitril/valsartan	Complementary in HFrEF	Dapagliflozin benefit persisted in DAPA-HF participants taking sacubitril/valsartan. This supports combined clinical use, not a formal synergy claim. Monitor symptomatic hypotension and volume status; the ARNI replaces ACE-inhibitor/ARB therapy rather than being added to it. [62,64]

Drug class / examples	Classification	Evidence, interaction and practical implication
Evidence-based beta-blockers Carvedilol, metoprolol succinate, bisoprolol	Complementary in HFrEF	SGLT2 benefit was maintained on beta-blocker background therapy in DAPA-HF. Adrenergic blockade and SGLT2 inhibition target distinct components of HF. Monitor BP and heart rate; SGLT2 therapy does not replace indicated beta-blockade. [62]
Steroidal mineralocorticoid antagonists Spironolactone, eplerenone	Complementary in HFrEF; potassium monitoring	DAPA-HF supports SGLT2 benefit with background MRA treatment. Hyperkalemia risk from the MRA remains relevant, especially with CKD and renin–angiotensin blockade. Check potassium and renal function; do not assume SGLT2 treatment eliminates that risk. [62,64]
Finerenone	Demonstrated additional albuminuria reduction	CONFIDENCE randomized 800 adults with T2D, CKD and albuminuria on renin–angiotensin blockade. At 180 days, combination with empagliflozin reduced UACR more than either alone; this is a surrogate endpoint, not proof of additional survival benefit. A 2026 secondary analysis found greater SBP reduction when baseline SBP was ≥ 130 mmHg. Monitor potassium/eGFR; these findings do not justify combining finerenone with spironolactone. [63,80]
Loop / thiazide diuretics Furosemide, torsemide; hydrochlorothiazide, chlorthalidone	Additive fluid/BP effects; excess-effect risk	SGLT2-related osmotic diuresis can increase volume depletion and hypotension. This is not a blanket contraindication: the combination is common in HF. Reassess volume status, orthostatic symptoms, BP and renal function; adjust conventional diuretics only when clinical findings warrant it. [61]
Calcium-channel blockers Amlodipine; diltiazem, verapamil	Complementary BP control; indication-specific limits	Additional BP lowering is useful when hypertension persists, with monitoring for hypotension. No established rejuvenation synergy. Diltiazem/verapamil have negative inotropic effects and are generally unsuitable in HFrEF; this is a HF limitation, not a class-wide SGLT2 interaction. [64]
Alpha-blockers / central agents Doxazosin, prazosin; clonidine	Caution: orthostasis, syncope	Orthostatic effects can compound symptoms from SGLT2-associated volume loss (clinical inference). Beers criteria discourage these as routine first-line hypertension treatment in older adults. This is additive harm, not inhibition of SGLT2 molecular action. [61,72]
Statins Atorvastatin, rosuvastatin, simvastatin	Complementary ASCVD prevention	LDL lowering addresses atherosclerotic risk alongside SGLT2 cardiorenal protection. Statins are not SGLT2 antagonists; a small glucose rise does not generally outweigh indicated cardiovascular benefit. Empagliflozin showed no clinically relevant pharmacokinetic effect on simvastatin. [61,64]
Nonstatin LDL agents Ezetimibe; evolocumab, alirocumab; bempedoic acid	Complementary when LDL remains above target or statins are not tolerated	These target cholesterol absorption, PCSK9 or cholesterol synthesis. They may address residual ASCVD risk; evidence does not establish special SGLT2 synergy. Selection follows lipid indication and each agent's adverse-effect profile. [64]

Drug class / examples	Classification	Evidence, interaction and practical implication
Anticoagulants Apixaban, rivaroxaban, dabigatran; warfarin	Compatible for a separate indication; no established synergy	SGLT2 treatment neither replaces anticoagulation for AF/VTE nor creates an indication for it. Empagliflozin did not materially alter warfarin pharmacokinetics. Continue INR monitoring for warfarin and agent-specific renal/dose review for DOACs. Bleeding risk chiefly rises with additional antiplatelets/NSAIDs; acute renal deterioration may alter anticoagulant exposure. [61,66]
Low-dose aspirin / P2Y12 inhibitors Aspirin 81 mg; clopidogrel, ticagrelor	Complementary for indicated antiplatelet therapy	Secondary ASCVD prevention or post-stent treatment can coexist with SGLT2 therapy. Aspirin's low-dose antiplatelet use differs from anti-inflammatory dosing. Do not initiate aspirin solely as an SGLT2/anti-aging adjunct; routine primary-prevention initiation is generally inappropriate in older adults. Adding it to anticoagulation increases bleeding and needs a specific indication. [64,66,72]
Systemic NSAIDs Ibuprofen, naproxen, diclofenac, meloxicam, celecoxib; high-dose aspirin	Avoid chronic routine use in CKD/HF; renal and BP opposition	Reduced renal prostaglandin activity can impair kidney perfusion; sodium retention may oppose BP/volume goals. Risk rises with dehydration, ACE-inhibitor/ARB use and diuretics. SGLT2 long-term kidney benefit does not make this combination safe during volume depletion. Topical diclofenac has lower systemic exposure. Ibuprofen can also interfere with aspirin's antiplatelet effect—a separate interaction. [65,79]

● **Appendix J. Other diabetes medicines**

- Glucose lowering can be additive without additional cardiovascular benefit. Insulin sufficiency, renal function, nutrition and hypoglycemia risk determine whether a combination is useful. None of these combinations establishes human age reversal.

Drug class / examples	Classification	Evidence, interaction and practical implication
Metformin	Established additive glucose lowering	Reduced hepatic glucose production complements renal glucose excretion; approved fixed combinations exist. This is not demonstrated anti-aging synergy. Metformin-containing combinations are contraindicated at eGFR <30 mL/min/1.73 m ² and in metabolic acidosis. Dehydration/AKI increases lactic-acidosis risk; monitor renal function and B12. Use a clinician-directed sick-day interruption plan. [67]
GLP-1 receptor agonists Semaglutide, dulaglutide, liraglutide; exenatide	Demonstrated additional metabolic effects; complementary clinical roles	DURATION-8 directly showed greater HbA1c, weight and SBP reductions with exenatide plus dapagliflozin than either alone on metformin. Evidence for each drug's cardiovascular/renal indications differs; avoid class-wide claims of synergy. Nausea/vomiting or markedly reduced intake can aggravate dehydration and ketosis susceptibility during SGLT2 treatment. [68,70]
Dual GIP/GLP-1 agonist Tirzepatide	Complementary glucose/weight effects; combination-compatible trial evidence	SURPASS-3 included participants on metformin with or without an SGLT2 inhibitor and found better glycemic/weight outcomes than insulin degludec. It was not a factorial test of SGLT2 synergy. Monitor excessive weight/lean-mass loss and poor intake, especially in frail older adults; GI losses require volume and sick-day assessment. [69,70]

Drug class / examples	Classification	Evidence, interaction and practical implication
DPP-4 inhibitors Sitagliptin, linagliptin; saxagliptin, alogliptin	Additive glycemic control; HF caution varies by agent	Incretin preservation can complement SGLT2 glucose lowering, but does not establish additional cardiorenal protection. Saxagliptin carries an HF signal; alogliptin has an FDA HF warning despite less consistent trial evidence. Do not assume SGLT2 treatment cancels these concerns. Use agent-specific renal dosing; linagliptin differs from renally cleared members. [64,70,82]
Insulin Glargine, degludec, lispro, aspart	Effective combination; hypoglycemia and under-insulinization hazards	Improved glucose control may reduce insulin requirements, but excessive reduction or omission can precipitate SGLT2-associated ketoacidosis, sometimes without marked hyperglycemia. Adjust using glucose/CGM data and clinical supervision. Insulin is not an antagonist merely because insulin signaling can activate mTOR; essential insulin must not be withheld for an autophagy objective. [67,75]
Sulfonylureas / meglitinides Glipizide, glimepiride, glyburide; repaglinide	Additive glucose lowering; increased hypoglycemia	Insulin secretion plus urinary glucose loss can overshoot the glycemic target. Consider prescriber-led secretagogue dose reduction, especially with CKD, irregular meals or older age. These drugs provide no established SGLT2 geroprotective synergy; hypoglycemia avoidance takes priority. [61,70]
Thiazolidinediones Pioglitazone	Glycemic complement but opposing fluid/weight effects	Insulin sensitization can improve glucose control, yet edema, weight gain and HF risk oppose decongestion goals. Initiating pioglitazone in NYHA III/IV HF is contraindicated; it is not recommended in symptomatic HF. SGLT2 coadministration does not override this warning or prove edema risk is neutralized. [71]

● **Appendix K. Sleep aids and other important interactions**

- Sleep medicines are included because of their common use and safety implications, even where no beneficial SGLT2 interaction has been demonstrated. Fall-risk combinations below are identified as clinical inferences. Drug-specific interactions must be checked against the exact SGLT2 product and the complete medication list.

Drug class / examples	Classification	Evidence, interaction and practical implication
Benzodiazepines / Z-drugs Temazepam, lorazepam; zolpidem, eszopiclone	No established synergy; generally avoid routine insomnia use in older adults	Sedation, impaired balance and cognitive effects increase falls/fractures. Combining these effects with nocturia or postural symptoms from SGLT2 treatment plausibly adds fall risk; this is clinical inference, not a proven specific interaction. Chronic benzodiazepines require supervised tapering rather than abrupt withdrawal. [72]
Orexin antagonists Suvorexant, lemborexant, daridorexant	Insomnia treatment only; no demonstrated SGLT2 synergy	No established SGLT2-specific benefit or antagonism. Drowsiness and falls remain possible; the lemborexant label explicitly highlights older-adult fall risk and CYP3A interactions. Evaluate the full medication list, including other sedatives and strong metabolic inhibitors. Do not generalize absence of a listed interaction into proven combination safety. [73,77]

Drug class / examples	Classification	Evidence, interaction and practical implication
Ramelteon / low-dose doxepin	Potentially compatible sleep treatment; no geroprotective combination evidence	Ramelteon targets sleep onset; low-dose doxepin targets sleep maintenance. AASM supports these uses with weak recommendations. Doxepin ≤ 6 mg/day differs from antidepressant doses with stronger anticholinergic/orthostatic burden. Neither is established to enhance SGLT2 effects. [72,77]
Trazodone; sedating antihistamines Diphenhydramine, doxylamine, hydroxyzine	Caution / generally avoid routine use solely for insomnia in older adults	Trazodone can cause orthostatic hypotension and syncope; volume depletion may amplify these effects. It can also increase bleeding risk with anticoagulants/antiplatelets. First-generation antihistamines add anticholinergic confusion and fall risk. These are safety conflicts, not demonstrated blockade of SGLT2 pathways. [72,74,77]
Lithium (prescription)	Documented interaction: SGLT2 therapy can lower lithium exposure	Increased renal lithium clearance can reduce treatment efficacy. Monitor lithium levels with SGLT2 initiation, dose changes and discontinuation. Conversely, dehydration, NSAIDs or renin–angiotensin medicines may raise lithium levels; the net effect cannot be guessed from a pathway diagram. This interaction concerns lithium efficacy/toxicity, not reduced SGLT2 efficacy. [26,75,81]
Digoxin	Drug-specific interaction with canagliflozin or sotagliflozin	Canagliflozin and the dual SGLT1/2 inhibitor sotagliflozin increase digoxin exposure; monitor levels/toxicity and adjust if needed. Empagliflozin did not show a clinically relevant pharmacokinetic effect on digoxin. Renal impairment and potassium depletion independently affect digoxin safety. Check the exact drug rather than extrapolating uniformly across the class. [61,76,85]
UGT enzyme inducers Rifampin, phenytoin, phenobarbital, ritonavir	Documented reduction of selected SGLT2 drug exposure	Canagliflozin labeling specifies renal-function-dependent dose modification with UGT inducers. Bexagliflozin labeling warns of reduced exposure/efficacy; sotagliflozin labeling also identifies reduced exposure and recommends monitoring clinical status. This is pharmacokinetic counteraction, not a universal class contraindication. Follow the exact product's instructions and complete medication review. [75,76,85]
Systemic corticosteroids Prednisone, dexamethasone	Physiological opposition to some treatment goals; not a blanket contraindication	Glucocorticoids can raise glucose and promote muscle catabolism; some also promote sodium/fluid retention and hypertension. Their anti-inflammatory action does not make the combination automatically synergistic. Necessary steroid treatment may still be appropriate, with glucose/volume monitoring and adjustment of diabetes therapy. Chronic steroids must not be stopped abruptly. [78]

● Appendix L. Candidate geroprotectors: comparative evidence

■ Tier 1: High / favorable | ■ Tier 2: Favorable, minor caveats | ■ Tier 3: Limited / moderate risk | ■ Tier 4: Poor / high risk

Comparison domain	SGLT inhibitors	Metformin	Rapamycin (sirolimus)
1. Preclinical lifespan extension	Strong, sex-specific. Canagliflozin increased median lifespan by 14% in male ITP mice; no extension in females at that regimen. [18]	Mixed. Metformin monotherapy did not significantly extend overall lifespan in the standard ITP experiment; findings vary across models and regimens. [93]	Strong in both sexes. At 42 ppm, median lifespan increased 23% in males and 26% in females in an ITP study. [94]
2. Human randomized outcomes	Extensive clinical evidence. Fewer heart-failure events and slower CKD progression. The 2026 review pooled 13 trials (90,413 participants): all-cause mortality HR 0.88 (95% CI 0.83–0.94). These were disease/risk populations. [9–11,91]	Disease-specific benefits; mixed longevity evidence. UKPDS found lower mortality in overweight patients with T2D; DPP/DPPOS found no mortality reduction over 21 years in people initially at high diabetes risk. [95,96]	Early human trials, no demonstrated lifespan benefit. PEARL studied 48-week safety/body composition; its primary visceral-fat endpoint was not improved. No large trial establishes reduced mortality or age-related multimorbidity. [97,98]
3. Safety in healthy adults	Healthy-adult preventive benefit–risk remains unestablished. Clinical use requires attention to genital fungal infection, volume depletion and uncommon but serious ketoacidosis. [101]	Extensive clinical experience, chiefly in diabetes. GI intolerance and B12 deficiency matter; renal function affects suitability and rare lactic-acidosis risk. Healthy-adult longevity benefit–risk remains unestablished. [102]	Regimen-dependent and incompletely established. PEARL found similar adverse-event rates; RAPA-EX-01 reported more adverse events and one possibly treatment-related pneumonia. Long-term preventive safety remains uncertain. [97,98,103]
4. Muscle mass / sarcopenia	Modest lean-mass loss with some agents. A 2026 synthesis of 33 RCTs found no significant skeletal-muscle-mass reduction versus placebo; strength/function evidence was insufficient to determine sarcopenia risk. [99]	Exercise-adaptation concern. MASTERS found smaller lean/thigh-mass gains during resistance training. This does not establish that metformin routinely causes sarcopenia. [100]	Mixed. PEARL found a female-subgroup lean-mass benefit. The 2026 RAPA-EX-01 trial suggested attenuated exercise gains in sensitivity analyses; its primary analysis was not significant. A blanket low-risk rating is premature. [97,98]
5. Cost and accessibility	Generic dapagliflozin is available in some markets, including US-listed products. Price, coverage and access vary by drug and country. [91,101]	Broad generic availability and generally low acquisition cost. Prescription and monitoring costs vary locally. [91,102]	Generic sirolimus is available. Acquisition, monitoring and off-label prescribing access vary; low cost is not universal. [91,103]

Adapted and updated from Figure 2, O’Keefe EL, O’Keefe JH, Nassif ME, Sauer AJ. SGLT Inhibitors as Geroprotectors for Age-Related Disease Prevention. OpenSource Cardiology. 2026;1(1). [91] Original article: [CC BY 4.0](#). Updated October 23, 2026.

Interpretation: The five source domains are retained; evidence descriptions replace the original qualitative tier scores. This is a cross-study comparison, not a head-to-head trial. Mouse percentages depend on sex, dose and timing. None of these agents has demonstrated lifespan extension in healthy humans. Lean mass is not synonymous with skeletal muscle or sarcopenia. ITP, Interventions Testing Program; RCT, randomized controlled trial; T2D, type 2 diabetes; CKD, chronic kidney disease.

● **Appendix interpretation and evidence boundaries**

These findings support a geroprotective profile across several biological and clinical domains. The 69 entries are separately described observations, not 69 independent demonstrations of slowed aging. Related pathways and endpoints overlap. Large outcome trials provide the strongest evidence for heart-failure and kidney benefits; molecular rejuvenation mechanisms remain predominantly experimental.

The henagliflozin trial provides emerging human evidence for a telomere biomarker response. Increased CTL granzyme B expression was significant, whereas perforin changes were trends. Neither measurement establishes whole-body rejuvenation or human senescent-cell clearance. [13]

Neuropathy findings require endpoint-level interpretation: DINE reported corneal changes within the treated arm; intraepidermal fibre density increased in both arms. A within-arm improvement alone does not establish between-group superiority. The empagliflozin study improved questionnaire scores but not clinical examination scores. These studies do not establish benefit for non-diabetic neuropathies. [15,16]

NAD⁺-salvage transcripts, precursor metabolites and SIRT1-dependent signaling are separate findings. They do not establish a generalized rise in human NAD⁺. Epigenetic-clock reversal, broad immune rejuvenation, and reversal of sarcopenia remain unestablished in the cited evidence. Figure-level hypotheses such as ketone-mediated HDAC inhibition, mitohormesis and epigenetic rejuvenation are not counted here as demonstrated SGLT2-drug effects.

● **Supplemental I: SGLT inhibitors Biomarker & clinical evidence inventory**

A broad inventory provided as a separate pdf document of named laboratory, imaging, functional and tissue endpoints with reported favorable changes in the manuscript evidence base, newly added Drive materials and targeted primary-source updates. Context-dependent changes and non-significant findings are identified separately.

References

Linked publications, prescribing information and guidance

1. Xie L, et al. Efficacy and safety of bexagliflozin compared with dapagliflozin as an adjunct to metformin in Chinese patients with type 2 diabetes mellitus: A 24-week, randomized, double-blind, active-controlled, phase 3 trial. *J Diabetes*. 2024;16:e13526. doi:10.1111/1753-0407.13526.
2. Kim SR, Lee SG, Kim SH, et al. SGLT2 inhibition modulates NLRP3 inflammasome activity via ketones and insulin in diabetes with cardiovascular disease. *Nat Commun*. 2020. doi:10.1038/s41467-020-15983-6.
3. Meng Z, Liu X, Li T, et al. The SGLT2 inhibitor empagliflozin negatively regulates IL-17/IL-23 axis-mediated inflammatory responses in T2DM with NAFLD via the AMPK/mTOR/autophagy pathway. *Int Immunopharmacol*. 2021;94:107492. doi:10.1016/j.intimp.2021.107492.
4. Faridvand Y, Kazemzadeh H, Vahedian V, et al. Dapagliflozin attenuates high glucose-induced endothelial cell apoptosis and inflammation through AMPK/SIRT1 activation. *Clin Exp Pharmacol Physiol*. 2022;49:643–651. doi:10.1111/1440-1681.13638.
5. Kawakami R, et al. Empagliflozin induces the transcriptional program for nutrient homeostasis in skeletal muscle in normal mice. *Sci Rep*. 2023;13:18025. doi:10.1038/s41598-023-45390-y.
6. Lu YP, Zhang ZY, Wu HW, et al. SGLT2 inhibitors improve kidney function and morphology by regulating renal metabolic reprogramming in mice with diabetic kidney disease. *J Transl Med*. 2022;20:420. doi:10.1186/s12967-022-03629-8.
7. Katsuomi G, Shimizu I, Suda M, et al. SGLT2 inhibition eliminates senescent cells and alleviates pathological aging. *Nat Aging*. 2024;4:926-938. doi:10.1038/s43587-024-00642-y.
8. Long J, Ren Z, Duan Y, et al. Empagliflozin rescues lifespan and liver senescence in naturally aged mice. *Geroscience*. 2024;46:4969–4986. doi:10.1007/s11357-024-01250-9.
9. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med*. 2019;381:1995–2008. doi:10.1056/NEJMoa1911303.
10. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med*. 2022;387:1089-1098. doi:10.1056/NEJMoa2206286.
11. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2020;383:1436-1446. doi:10.1056/NEJMoa2024816.
12. Lin J, Huang Y, Xu B, et al. Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial. *BMJ*. 2025;389:e083735. doi:10.1136/bmj-2024-083735.
13. Zhang J, Cai W, Liu D, et al. Effect of henagliflozin on aging biomarkers in patients with type 2 diabetes: A multicenter, randomized, double-blind, placebo-controlled study. *Cell Rep Med*. 2025;6(9):102331. doi:10.1016/j.xcrm.2025.102331.
14. Zelniker TA, Bonaca MP, Furtado RHM, et al. Effect of Dapagliflozin on Atrial Fibrillation in Patients With Type 2 Diabetes Mellitus: Insights From the DECLARE-TIMI 58 Trial. *Circulation*. 2020;141:1227–1234. doi:10.1161/CIRCULATIONAHA.119.044183.
15. Adhikari U, Gad H, Chatterjee D, et al. Dapagliflozin for Small Nerve Fibre Regeneration in Diabetic Peripheral Neuropathy: A Randomised Controlled Study (DINE). *J Peripher Nerv Syst*. 2025;30:e70011. doi:10.1111/jns.70011.
16. Vafaeinasab M, Mirzaei Malekabad F, Khatibi A, et al. The Comparison of the Effect of Adding Empagliflozin to the Medication Regimen on Peripheral Neuropathy in Patients With Type II Diabetes: A Double Blind Randomised Clinical Trial. *Endocrinol Diabetes Metab*. 2025;8:e70128. doi:10.1002/edm2.70128.

17. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373:2117–2128. doi:10.1056/NEJMoa1504720.
18. Miller RA, Harrison DE, Allison DB, et al. Canagliflozin extends life span in genetically heterogeneous male but not female mice. *JCI Insight*. 2020;5(21):e140019. doi:10.1172/jci.insight.140019.
19. Santos-Gallego CG, et al. Empagliflozin Ameliorates Adverse Left Ventricular Remodeling in Nondiabetic Heart Failure by Enhancing Myocardial Energetics. *J Am Coll Cardiol*. 2019;73:1931–1944. doi:10.1016/j.jacc.2019.01.056.
20. Shin A, Koo BK, Lee JY, Kang EH. Risk of dementia after initiation of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in adults aged 40–69 years with type 2 diabetes: population based cohort study. *BMJ*. 2024;386:e079475. doi:10.1136/bmj-2024-079475.
21. Sun X, Han F, Lu Q, et al. Empagliflozin Ameliorates Obesity-Related Cardiac Dysfunction by Regulating Sestrin2-Mediated AMPK-mTOR Signaling and Redox Homeostasis in High-Fat Diet-Induced Obese Mice. *Diabetes*. 2020;69:1292–1305. doi:10.2337/db19-0991.
22. Cai C, Guo Z, Chang X, et al. Empagliflozin attenuates cardiac microvascular ischemia/reperfusion through activating the AMPK α 1/ULK1/FUNDC1/mitophagy pathway. *Redox Biol*. 2022;52:102288. doi:10.1016/j.redox.2022.102288.
23. National Institutes of Health, Office of Dietary Supplements. Zinc: Fact Sheet for Health Professionals. Accessed October 23, 2026.
24. Ray EC, Boyd-Shiowski CR, Liu P, Novacic D, Cassiman D. SGLT2 Inhibitors for Treatment of Refractory Hypomagnesemia: A Case Report of 3 Patients. *Kidney Med*. 2020;2(3):359–364. doi:10.1016/j.xkme.2020.01.010.
25. National Institutes of Health, Office of Dietary Supplements. Selenium: Fact Sheet for Health Professionals. Accessed October 23, 2026.
26. Medsafe. Starting empagliflozin or dapagliflozin in patients on lithium? Monitor lithium levels. *Prescriber Update*. 2023;44(1):6–8.
27. Kugathasan L, et al. Metabolic shifts in plasma amino acids and related metabolites in response to SGLT2 inhibition and hyperglycemia in type 1 diabetes. *Physiol Rep*. 2025;13:e70465.
28. Takahashi Y, et al. BALLAST study: A multicentre, open-label, randomized-controlled, 52-week clinical trial of the efficacy and safety of luseogliflozin in older Japanese adults with type 2 diabetes receiving leucine-enriched amino acid supplementation and physical exercise programme. *Diabetes Obes Metab*. 2026;28:3439–3444.
29. Kumar P, et al. Supplementing Glycine and N-Acetylcysteine (GlyNAC) in Older Adults Improves Glutathione Deficiency, Oxidative Stress, Mitochondrial Dysfunction, Inflammation, Physical Function, and Aging Hallmarks: A Randomized Clinical Trial. *J Gerontol A*. 2023;78:75–89.
30. Wolfson RL, et al. Sestrin2 is a leucine sensor for the mTORC1 pathway. *Science*. 2016;351:43–48.
31. Chantranupong L, et al. The CASTOR Proteins Are Arginine Sensors for the mTORC1 Pathway. *Cell*. 2016;165:153–164.
32. Gu X, et al. SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. *Science*. 2017;358:813–818.
33. Jewell JL, et al. Differential regulation of mTORC1 by leucine and glutamine. *Science*. 2015;347:194–198.
34. Jojima T, et al. Empagliflozin increases plasma levels of citrulline, histidine, and α -aminobutyric acid in patients with type 2 diabetes: effects of a sodium-glucose co-transporter 2 inhibitor on the plasma amino acid profile. *Expert Opin Pharmacother*. 2024.
35. Xu XM, et al. Biosynthesis of selenocysteine on its tRNA in eukaryotes. *PLoS Biol*. 2007;5:e4.

36. Hao B, et al. A new UAG-encoded residue in the structure of a methanogen methyltransferase. *Science*. 2002.
37. NIH Office of Dietary Supplements. Thiamin: Fact Sheet for Health Professionals. Accessed October 23, 2026.
38. NIH Office of Dietary Supplements. Riboflavin: Fact Sheet for Health Professionals. Accessed October 23, 2026.
39. NIH Office of Dietary Supplements. Niacin: Fact Sheet for Health Professionals. Accessed October 23, 2026.
40. NIH Office of Dietary Supplements. Pantothenic Acid: Fact Sheet for Health Professionals. Accessed October 23, 2026.
41. NIH Office of Dietary Supplements. Vitamin B6: Fact Sheet for Health Professionals. Accessed October 23, 2026.
42. NIH Office of Dietary Supplements. Biotin: Fact Sheet for Health Professionals. Accessed October 23, 2026.
43. NIH Office of Dietary Supplements. Folate: Fact Sheet for Health Professionals. Accessed October 23, 2026.
44. NIH Office of Dietary Supplements. Vitamin B12: Fact Sheet for Health Professionals. Accessed October 23, 2026.
45. Wang DD, et al. Safety and Tolerability of Nicotinamide Riboside in Heart Failure With Reduced Ejection Fraction. *JACC Basic Transl Sci*. 2022. doi:10.1016/j.jacbts.2022.06.012.
46. House AA, et al. Effect of B-vitamin therapy on progression of diabetic nephropathy: a randomized controlled trial. *JAMA*. 2010;303:1603–1609. doi:10.1001/jama.2010.490.
47. NIH Office of Dietary Supplements. Vitamin A and Carotenoids: Fact Sheet for Health Professionals. Accessed October 23, 2026.
48. NIH Office of Dietary Supplements. Vitamin C: Fact Sheet for Health Professionals. Accessed October 23, 2026.
49. NIH Office of Dietary Supplements. Vitamin D: Fact Sheet for Health Professionals. Accessed October 23, 2026.
50. NIH Office of Dietary Supplements. Vitamin E: Fact Sheet for Health Professionals. Accessed October 23, 2026.
51. NIH Office of Dietary Supplements. Vitamin K: Fact Sheet for Health Professionals. Accessed October 23, 2026.
52. Shahidzadeh Yazdi Z, et al. Vitamin D Deficiency Increases Vulnerability to Canagliflozin-induced Adverse Effects on 1,25-Dihydroxyvitamin D and PTH. *J Clin Endocrinol Metab*. 2024;109:e646–e656. doi:10.1210/clinem/dgad554.
53. Li K, et al. Long-term efficacy of dapagliflozin combined with Bifidobacterium triple viable tablets on metabolic syndrome and gut microbiota in overweight/obese patients with type 2 diabetes. *Endocr Connect*. 2025;14:e250219. doi:10.1530/EC-25-0219.
54. Eriksson JW, et al. Effects of dapagliflozin and n-3 carboxylic acids on non-alcoholic fatty liver disease in people with type 2 diabetes: a double-blind randomised placebo-controlled study. *Diabetologia*. 2018;61:1923–1934. doi:10.1007/s00125-018-4675-2.
55. Anderson JW, Allgood LD, Turner J, Oeltgen PR, Daggy BP. Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia. *Am J Clin Nutr*. 1999;70:466–473. doi:10.1093/ajcn/70.4.466.

56. Gualano B, et al. Creatine supplementation and resistance training in vulnerable older women: a randomized double-blind placebo-controlled clinical trial. *Exp Gerontol.* 2014;53:7–15. doi:10.1016/j.exger.2014.02.003.
57. NCCIH. Probiotics: Usefulness and Safety. Accessed October 23, 2026.
58. af Geijerstam P, Joelsson A, Rådholm K, Nyström FH. A low dose of daily licorice intake affects renin, aldosterone, and home blood pressure in a randomized crossover trial. *Am J Clin Nutr.* 2024;119:682–691. doi:10.1016/j.ajcnut.2024.01.011.
59. NCCIH. Yohimbe: Usefulness and Safety. Accessed October 23, 2026.
60. NCCIH. Licorice Root: Usefulness and Safety. Accessed October 23, 2026.
61. Boehringer Ingelheim Pharmaceuticals. JARDIANCE (empagliflozin): prescribing information. Revised October 2025. Sections 5, 7 and 12.3.
62. Docherty KE, et al. Effects of dapagliflozin in DAPA-HF according to background heart failure therapy. *Eur Heart J.* 2020;41:2379–2392. doi:10.1093/eurheartj/ehaa183.
63. Agarwal R, et al. Finerenone with Empagliflozin in Chronic Kidney Disease and Type 2 Diabetes. *N Engl J Med.* 2025;393:533–543. doi:10.1056/NEJMoa2410659.
64. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2026. *Diabetes Care.* 2026;49(Suppl 1):S216–S245. doi:10.2337/dc26-S010.
65. National Kidney Foundation. Pain Medicines and Kidney Disease. Updated February 21, 2025. Accessed October 23, 2026.
66. DailyMed. ELIQUIS (apixaban): prescribing information. Sections 5, 7 and 8. Accessed October 23, 2026.
67. DailyMed. SYNJARDY / SYNJARDY XR (empagliflozin and metformin): prescribing information. Sections 4, 5 and 14. Accessed October 23, 2026.
68. Frías JP, et al. Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (DURATION-8): a 28 week, multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2016. doi:10.1016/S2213-8587(16)30267-4.
69. Ludvik B, et al. Once-weekly tirzepatide versus once-daily insulin degludec as add-on to metformin with or without SGLT2 inhibitors in patients with type 2 diabetes (SURPASS-3): a randomised, open-label, parallel-group, phase 3 trial. *Lancet.* 2021. doi:10.1016/S0140-6736(21)01443-4.
70. American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2026. *Diabetes Care.* 2026;49(Suppl 1):S183–S215. doi:10.2337/dc26-S009.
71. DailyMed. Pioglitazone: prescribing information. Boxed warning and sections 4–5. Accessed October 23, 2026.
72. American Geriatrics Society 2023 Beers Criteria Update Expert Panel. American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2023;71:2052–2081. doi:10.1111/jgs.18372.
73. DailyMed. DAYVIGO (lemborexant): prescribing information. Sections 5 and 7. Accessed October 23, 2026.
74. DailyMed. Trazodone hydrochloride: prescribing information. Orthostatic hypotension and syncope; bleeding and CNS effects. Accessed October 23, 2026.
75. TheracosBio. BRENZAVVY (bexagliflozin): prescribing information. Revised January 2023. Sections 4, 5 and 7.

76. DailyMed. INVOKANA (canagliflozin): prescribing information. Sections 2.4, 7 and 12.3. Accessed October 23, 2026.
77. Sateia MJ, et al. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med*. 2017;13:307–349. doi:10.5664/jcsm.6470.
78. DailyMed. Prednisone: prescribing information. Warnings and adverse reactions. Accessed October 23, 2026.
79. U.S. Food and Drug Administration. Information about Taking Ibuprofen and Aspirin Together. Accessed October 23, 2026.
80. Agarwal R, et al. Safety and Synergy of Finerenone and Empagliflozin in Lowering Blood Pressure. *Hypertension*. 2026;83:e27036. doi:10.1161/HYPERTENSIONAHA.126.27036.
81. DailyMed. Lithium carbonate: prescribing information. Sections 5 and 7. Accessed October 23, 2026.
82. U.S. Food and Drug Administration. FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. Drug Safety Communication. April 5, 2016.
83. Bhatt DL, Szarek M, Pitt B, et al. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. *N Engl J Med*. 2021;384:129–139. doi:10.1056/NEJMoa2030186.
84. Bhatt DL, Szarek M, Steg PG, et al. Sotagliflozin in Patients with Diabetes and Recent Worsening Heart Failure. *N Engl J Med*. 2021;384:117–128. doi:10.1056/NEJMoa2030183.
85. Lexicon Pharmaceuticals. INPEFA (sotagliflozin): prescribing information. DailyMed. Sections 2, 5, 7 and 12. Accessed October 23, 2026.
86. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med*. 2019;380:2295–2306. doi:10.1056/NEJMoa1811744.
87. 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.
88. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2024;105(4S):S117–S314.
89. American Diabetes Association Professional Practice Committee. 16. Diabetes Care in the Hospital: Standards of Care in Diabetes—2026. *Diabetes Care*. 2026;49(Suppl 1). doi:10.2337/dc26-S016.
90. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. *J Clin Invest*. 2014;124:499–508. doi:10.1172/JCI72227.
91. O'Keefe EL, O'Keefe JH, Nassif ME, Sauer AJ. SGLT Inhibitors as Geroprotectors for Age-Related Disease Prevention. *OpenSource Cardiology*. 2026;1(1). Published September 28, 2026. Article identifier: osc.2026.0017 (DOI registration pending).
92. Chiang CH, Chiang CH, Chiang CH, et al. Impact of sodium-glucose cotransporter-2 inhibitors on heart failure and mortality in patients with cancer. *Heart*. 2023;109(6):470–477. doi:10.1136/heartjnl-2022-321545.
93. Strong R, Miller RA, Antebi A, et al. Longer lifespan in male mice treated with a weakly estrogenic agonist, an antioxidant, an α -glucosidase inhibitor or a Nrf2-inducer. *Aging Cell*. 2016;15(5):872–884. doi:10.1111/accel.12496.
94. Miller RA, Harrison DE, Astle CM, et al. Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction. *Aging Cell*. 2014;13(3):468–477. doi:10.1111/accel.12194.

95. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854–865. doi:10.1016/S0140-6736(98)07037-8.
96. Lee CG, et al. Effect of Metformin and Lifestyle Interventions on Mortality in the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study. *Diabetes Care*. 2021;44(12):2775–2782. doi:10.2337/dc21-1046.
97. Moel M, Harinath G, Lee V, et al. Influence of rapamycin on safety and healthspan metrics after one year: PEARL trial results. *Aging (Albany NY)*. 2025;17(4):908–936. doi:10.18632/aging.206235.
98. Stanfield B, Leroux B, Kaeberlein M, Jones J, Lucas R. Exercise and Weekly Sirolimus (Rapamycin) in Older Adults: RAPA-EX-01 Randomised, Double-Blind, Placebo-Controlled Trial. *J Cachexia Sarcopenia Muscle*. 2026;17(2):e70274. doi:10.1002/jcsm.70274.
99. Li X, Zhang Y, Wang L, Zhao Y. Effects of SGLT2 inhibitors on body composition and potential sarcopenia-related outcomes in type 2 diabetes mellitus: a network meta-analysis. *Front Endocrinol (Lausanne)*. 2026;17:1877008. doi:10.3389/fendo.2026.1877008.
100. Walton RG, Dungan CM, Long DE, et al. Metformin blunts muscle hypertrophy in response to progressive resistance exercise training in older adults: A randomized, double-blind, placebo-controlled, multicenter trial: The MASTERS trial. *Aging Cell*. 2019;18(6):e13039. doi:10.1111/acer.13039.
101. Sandoz Inc. Dapagliflozin tablets: prescribing information. DailyMed. Revised June 2026. Accessed October 23, 2026.
102. Aurobindo Pharma USA, Inc. Metformin hydrochloride tablets: prescribing information. DailyMed. Accessed October 23, 2026.
103. Zydus Pharmaceuticals (USA) Inc. Sirolimus tablets: prescribing information. DailyMed. Updated June 3, 2026. Accessed October 23, 2026.