

Supplemental I: SGLT Inhibitors Biomarker & Clinical Evidence Inventory

Addendum to: SGLT1 and SGLT2 Inhibitors: Geroprotection, Disease Amelioration and Safe Use.
by Michael Slattery, Email:Michael@Age-Regression.com
Human, animal and cellular findings | Updated 24 October 2026

Purpose

A broad inventory 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.

How to read the evidence

H-R - Randomized human intervention evidence; study size and endpoint strength vary.

H-R* - Exploratory, post-hoc, small or primarily within-group randomized-study finding; read the qualification.

H-I - Human intervention/physiology study without an adequate placebo comparison for the listed effect.

H-O - Human observational cohort or case series; association, not established causation.

A - Animal experiment; no automatic extrapolation to humans.

C - Cell culture or ex vivo experiment; human-derived cells are not a human treatment trial.

Scope and limits

Reviewed 34 distinct PDF resources from the maintained collection, including the new TGF- β /Smad and lipodystrophy materials, against the manuscript and citation registry. Targeted online searches checked the primary sources. This is a comprehensive working inventory of verified named endpoints, not a claim that every omics feature or every published SGLT study has been exhaustively extracted.

Three macOS alias files in the senescence folder were not readable source documents; accessible originals of the two underlying papers were used. Reference numbers below are the plugin's canonical registry numbers, not the manuscript's local Vancouver numbering. No manuscript text was changed.

Key interpretation

The strongest human evidence concerns glucose regulation, heart-failure and kidney outcomes. Senescence, TGF- β signaling and lifespan findings have important preclinical support. IL-2 suppression is a laboratory immunosuppressive finding; it should not be described as improved immune surveillance. Lipodystrophy evidence includes metabolic improvements and a small long-term fat-distribution signal, not reversal of missing adipose tissue.

1. Glucose regulation, adiposity and routine metabolic markers

Weight and fat reduction can be beneficial in excess adiposity; they are not automatically desirable in frailty or lipoatrophy.

Marker / endpoint	Change / evidence	Study context and qualification
HbA1c	↓ H-R	Improved glycemic control; multiple agents, including henagliflozin and bexagliflozin. [7, 73]
Fasting plasma glucose	↓ H-R	Human diabetes trials; also improved in several animal models. [7, 73]
Postprandial glucose / meal glucose exposure	↓ H-I	Empagliflozin metabolic physiology study. [95]
Insulin sensitivity	↑ H-I / A	Physiological studies and obese-mouse experiments; not universal across models. [95, 5]
Excess fasting/circulating insulin	↓ H-R	Reported with empagliflozin in the NLRP3 mechanistic trial. [4]
Body weight	↓ H-R	Placebo-controlled reductions in participants with diabetes and excess weight. [7, 116]
Body mass index	↓ H-R	Henagliflozin trial; also genetic-lipodystrophy cohort. [7, 108]
Waist circumference	↓ H-R	Dapagliflozin: placebo-adjusted -1.52 cm at 24 weeks. [116]
Total body fat mass	↓ H-R	Dapagliflozin: placebo-adjusted -1.48 kg by DXA. [116]
Visceral adipose tissue volume	↓ H-R	MRI subset; nominal statistical significance. [116]
Subcutaneous adipose tissue volume	↓ H-R	MRI subset; context-specific finding, not restoration of deficient fat. [116]
Serum uric acid / urate	↓ H-R	Significant placebo-controlled reduction in henagliflozin study. [7]
Serum magnesium in refractory hypomagnesemia	↑ H-O	Three-patient case series; correction of deficiency, not evidence for higher-is-better. [14]

2. Cardiac structure, function and physical capacity

Imaging and functional gains depend on the population. Benefits in heart failure do not establish improved performance in healthy adults.

Marker / endpoint	Change / evidence	Study context and qualification
Systolic blood pressure	↓ H-R / H-O	Clinical trials and lipodystrophy cohorts. [65, 108, 118]
Diastolic blood pressure	↓ H-O	Significant in the small 2022 partial-lipodystrophy cohort; not in the 2026 cohort. [118, 108]
LV end-diastolic volume	↓ H-R	Reverse remodeling in nondiabetic HFrEF, EMPA-TROPISM. [113]
LV end-systolic volume	↓ H-R	Reverse remodeling in EMPA-TROPISM. [113]
LV mass	↓ H-R / A	Human cardiac MRI; corroborating rabbit pressure-overload model. [113, 109]
LV sphericity index	↓ H-R	More favorable ventricular geometry in EMPA-TROPISM. [113]
LV ejection fraction	↑ H-R / A	Improved systolic function in selected HFrEF studies. [113, 109]
Fractional shortening	↑ A	Dapagliflozin-treated normoglycemic rabbits with heart failure. [109]
LV end-systolic diameter	Improved A	Rabbit model; post-treatment diameter approached sham values. [109]
E/A ratio / diastolic filling pattern	Restored A	HIV-Tg26 mice treated with dapagliflozin. [110]
NT-proBNP	↓ H-R / A	DAPA-HF: placebo-adjusted reduction of about 303 pg/mL at 8 months; rabbit data also supportive. [123, 109]
Brachial flow-mediated dilation (FMD)	↑ H-I	Small 2-day dapagliflozin physiology study. [121]
Aortic pulse-wave velocity / arterial stiffness	↓ H-I	Acute reduction persisted after adjustment for mean blood pressure. [121]
Elevated heart rate	↓ A	Rabbit CHF model; not a universal clinical drug effect. [109]
Myocardial collagen / fibrosis area	↓ A	Rabbit CHF and HIV-transgenic mouse experiments. [109, 110]
Myocardial ectopic fat / steatosis	↓ A	Oil-red staining in HIV-transgenic mice. [110]
Peak oxygen consumption (peak VO ₂)	↑ H-R	Exercise capacity in nondiabetic HFrEF. [113]
Six-minute walking distance	↑ H-R	Functional capacity in EMPA-TROPISM. [113]
Heart-failure health status / quality-of-life score	↑ H-R	Patient-reported benefit in EMPA-TROPISM. [113]

3. Kidney injury, filtration and renal pathology

The principal clinical filtration benefit is slower loss over time. An early eGFR dip is common and should not be misclassified as failed treatment or as a beneficial rise in filtration.

Marker / endpoint	Change / evidence	Study context and qualification
Urine albumin-to-creatinine ratio (UACR)	↓ H-R / H-O / A	Albuminuria reduction; also reported in lipodystrophy with elevated baseline UACR. [115, 108, 76]
Urinary albumin excretion	↓ H-R / A	Urine albumin burden; overlaps biologically with UACR. [115, 76]
Chronic eGFR decline / slope	Slower H-R	Long-term kidney-function preservation in CKD outcome trials. [1, 91, 92]
Urinary KIM-1	↓ H-R*	Post-hoc crossover analysis: -22.6%, P=.05. [115]
Urinary IL-6 excretion	↓ H-R*	Post-hoc crossover analysis: -23.5%, P=.04. [115]
Renal resistive index	↓ H-I	Small acute dapagliflozin physiology study. [121]
Urinary nephrin loss	↓ H-I	Albuminuric T2D; active-agent randomized study, mainly pre/post comparisons. [112]
Serum cystatin C	↓ A	Empagliflozin in db/db diabetic-kidney-disease mice. [76]
Blood urea nitrogen	↓ A	Improved biochemical renal-injury profile in db/db mice. [76]
Serum creatinine	↓ A	Reduced in the db/db experiment; not a universal human short-term response. [76]
Glomerular hypertrophy / area	↓ A	Significant area reduction; perimeter result was not significant. [76]
Glomerulosclerosis / glomerular fibrosis	↓ A	Histological improvement in db/db mice. [76]
Renal interstitial fibrosis	↓ A	Histological improvement in db/db mice. [76]
Mesangial expansion and tubular-basement-membrane abnormalities	Improved A	Histological descriptions; not all features separately quantified. [76]

4. Liver injury, steatosis, fibrosis and lipodystrophy

ALT, AST and GGT are injury-associated enzymes, not direct measurements of hepatic synthetic function. Elastography and fibrosis scores are distinct from biopsy-proven fibrosis regression.

Marker / endpoint	Change / evidence	Study context and qualification
ALT	↓ H-O	Significant short-term decrease in genetic lipodystrophy. [108]
AST	↓ H-O	Decrease in the small treated-HIV cohort. [111]
GGT	↓ H-O	Significant short-term decrease in genetic lipodystrophy. [108]
Liver stiffness by elastography	↓ H-R / H-O	Dapagliflozin MASH trial and lipodystrophy cohort. [79, 108]
Steatosis assessed by FibroScan	↓ H-R	Reduced steatosis in the MASH trial. [79]
Fatty liver index (FLI)	↓ H-O	Comparative observational NAFLD study. [120]
AST-to-platelet ratio index (APRI)	↓ H-O	Non-invasive fibrosis-associated index; not histological proof. [120]
NAFLD activity score / MASH activity	Improved H-R	Biopsy-based improvement without worsened fibrosis. [79]
MASH resolution	More frequent H-R	Resolution without fibrosis worsening in the dapagliflozin trial. [79]
Biopsy fibrosis stage	Improved H-R	At least one-stage improvement without worsened MASH. [79]
Hepatic triglyceride content / histological fat	↓ A	Seipin-knockout lipoatrophic mice; preventive and established-steatosis settings. [117]
Excess liver mass	↓ A	Reduced hepatomegaly in lipoatrophic mice. [117]
Trunk-to-lower-limb fat ratio	↓ H-O	Genetic lipodystrophy: long-term P=.03; only 7 long-term observations. Short-term P=.08. [108]
Lipodystrophy metabolic complications	Improved H-O	HbA1c, BMI, systolic BP, ALT, GGT, stiffness and elevated UACR improved; not a cure. [108, 118]

5. Inflammation, chemokines and immune-cell measures

A cytokine can have protective and harmful roles. Entries describe a measured change in a specified context, not a universal desirable target. H-O findings remain vulnerable to confounding.

Marker / endpoint	Change / evidence	Study context and qualification
IL-6, circulating	↓ H-R* / H-O / A	Canagliflozin biomarker substudy and observational/animal studies; null in henagliflozin RCT. [122, 10, 77, 7]
TNF receptor 1 (TNFR1)	↓ H-R*	Canagliflozin versus glimepiride stored-sample analysis: -9.2%. [122]
IL-1β release / circulating IL-1β	↓ H-R+ex vivo / H-O	Reduced stimulated macrophage release; lower circulating levels in HIV and NAFLD cohorts. [4, 111, 120]
TNF-α / Tnf	↓ H-O / A	NAFLD cohort; aged mice; adipose Tnf reduction in canagliflozin-treated obese mice. [120, 77, 5]
IL-8 / CXCL8	↓ H-O	Small HIV cohort; exploratory circulating cytokine profile. [111]
MCP-1 / CCL2	↓ H-O / A	Circulating reduction in cohorts; liver transcript reduction in preventive lipotrophy model. [111, 120, 117]
MIP-1α / CCL3	↓ H-O	Reported decrease in HIV cohort; exploratory. [111]
MIP-1β / CCL4	↓ H-O	Reported decrease in HIV cohort; exploratory. [111]
Eotaxin / CCL11	↓ H-O	Reported decrease in HIV cohort; exploratory. [111]
RANTES / CCL5	↓ H-O	Reported decrease in HIV cohort; exploratory. [111]
IL-13	↓ H-O	Reported decrease in HIV cohort; context-dependent immune modulation. [111]
IL-4	Context-dependent H-O	Increased in NAFLD cohort, decreased in HIV cohort; no universal favorable direction. [120, 111]
IL-10	↑ H-O	Increase in NAFLD cohort; not significant in henagliflozin RCT. [120, 7]
VEGF, circulating	↓ H-O	Reduction in NAFLD cohort; not necessarily favorable in every vascular setting. [120]
CXCL9	↓ A	Reduced in naturally aged mice; not a confirmed human class effect. [77]
IL-17 / IL-23 axis activity	↓ A	Empagliflozin in diabetic fatty-liver mice. [3]
NLRP3 inflammasome activation	↓ H-R+ex vivo	Human treatment study with isolated macrophage functional assays. [4]
Adipose crown-like structures	↓ A	Less adipose inflammation in high-fat-fed canagliflozin-treated mice. [5]
Cytotoxic T-cell granzyme B expression	↑ H-R*	Exploratory henagliflozin immune subset; P=.033. Infection/cancer prevention not tested. [7]
Tissue NK-cell and CD8+ T-cell numbers	↑ A	Restoration in obese-mouse tissues; not established across human immune compartments. [5]

6. Oxidative injury and senescence

Senescence markers and telomeres are research endpoints. Their improvement alone does not establish human lifespan extension.

Marker / endpoint	Change / evidence	Study context and qualification
Leukocyte relative telomere length	↑ H-R	Henagliflozin 26-week trial: between-group difference 0.06 relative units; P=.011. [7]
SA-β-gal activity / positive senescent cells	↓ A	Reduced tissue senescence-associated staining/activity. [5]
p16 / Cdkn2a	↓ A	Reduced senescence-associated expression in adipose tissue and/or liver. [5, 77]
p21 / Cdkn1a	↓ A	Reduced expression in mouse tissue experiments. [5, 77]
Senescence-associated p53 expression	↓ A	Obese-mouse adipose tissue; not a rationale for indiscriminate p53 suppression. [5]
p19Arf-reporter-positive cell burden	↓ A	Reduced senescent-cell reporter signal after canagliflozin. [5]
PD-L1-positive senescent-cell burden	↓ A	Immune-evasion-associated senescent population reduced. [5]
Immune-mediated senescent-cell clearance	↑ A	Functional experiments support a T-cell-dependent component. [5]
Urinary isoprostanes	↓ H-I	Reduced oxidative-stress measure in acute dapagliflozin pilot. [121]
Tissue superoxide / DHE oxidative-stress signal	↓ A	Reduced oxidative injury signal in obese adipose tissue. [5]
Glutathione peroxidase activity	↑ H-R*	DINE: increased within dapagliflozin arm, P=.02; small open-label trial. [81]
Malondialdehyde (MDA)	↓ H-R*	DINE: fell in both groups; cannot attribute incremental benefit to dapagliflozin. [81]
MDA-protein adducts	↓ H-O	Reduced circulating lipid-peroxidation products in NAFLD cohort. [120]
4-hydroxynonenal (HNE)-protein adducts	↓ H-O	Reduced circulating oxidative injury products. [120]

7a. Fibrotic signaling and matrix remodeling

These are measured tissue, gene-expression or cellular changes associated with protection. They are not routine clinical biomarkers or established targets for dose escalation.

Marker / endpoint	Change / evidence	Study context and qualification
Myocardial TGF-β1 expression	↓ A	Rabbit CHF; tissue result, not a universal circulating-TGF-β1 claim. [109]
Smad2 and Smad3 expression	↓ A	Reduced profibrotic signaling in rabbit myocardium. [109]
Smad7 expression	↑ A	Inhibitory Smad restored in rabbit myocardium. [109]
TGF-β1-induced Smad2 phosphorylation	↓ C	Cellular experiments accompanying HIV mouse study. [110]
TGF-β1-induced PAI-1 promoter activity	↓ C	Reporter assay; not evidence of lower circulating PAI-1 in patients. [110]
Collagen I / COL1A1 and collagen III	↓ A	Reduced myocardial matrix expression; hepatic COL1A1 also reduced in models. [109, 77, 117]
α-smooth-muscle actin (α-SMA)	↓ A	Reduced myofibroblast-associated marker in heart and liver. [109, 77]
Connective-tissue growth factor (CTGF)	↓ A	Reduced myocardial expression in rabbit CHF. [109]
Plasma matrix metalloproteinase-7 (MMP-7)	↓ H-R*	Canagliflozin versus glimepiride biomarker substudy: -24.9%. [122]
MMP-2, MMP-9 and TIMP-1	↓ A	Pathologically increased matrix-remodeling proteins reduced in rabbit heart. [109]

7b. Energy sensing and cellular adaptation

Measured pathways associated with protection in experimental models; gene expression is not interchangeable with enzyme activity or clinical benefit.

Marker / endpoint	Change / evidence	Study context and qualification
AMPK activation / phosphorylation	↑ A	Canagliflozin obese-mouse experiments and other tissue studies. [5, 86]
mTOR pathway activity	↓ A	Linked to improved autophagy in fatty-liver/cardiac models. [3, 86]
Autophagy	↑ A	Hepatic macrophage autophagy improved in diabetic fatty-liver model. [3]
SIRT1-associated signaling	↑ A / C	Aged liver and endothelial-cell studies; not universal across tissues. [77, 74]
NF-κB inflammatory signaling	Attenuated A	Regulation in aged-liver experiments. [77]
Sestrin2-related signaling	Enhanced A	Empagliflozin obesity-related cardiac dysfunction model. [86]
Nrf2 / HO-1 antioxidant response	↑ A	Cardiac obesity model; not increased in every muscle study. [86]
AMPKα1, NAMPT and PGC-1α transcripts	↑ A	Normal-mouse skeletal muscle; transcription is not proof of higher NAD+. [75]
UCP2 transcript	↑ A	Normal-mouse muscle; adaptive oxidative-stress response. [75]
Hepatic ACLY, ACC and FAS lipogenic transcripts	↓ A	Seipin-knockout prevention experiment; ACLY/ACC also reduced with established steatosis. [117]
Hepatic ADRP / lipid-droplet-associated transcript	↓ A	Less liver lipid accumulation in lipoatrophic mice. [117]

8. Blood formation and iron handling

The following changes support enhanced erythropoiesis. Several are mechanistic adaptations rather than independently proven benefits; ferritin reduction can reflect iron use and should not be interpreted as universally desirable.

Marker / endpoint	Change / evidence	Study context and qualification
Hemoglobin	↑ H-R	Increased in the dapagliflozin erythropoiesis study. [114]
Hematocrit	↑ H-R	Increased; cannot be interpreted solely as hemoconcentration. [114]
Hepcidin	↓ H-R	Reduced suppression of iron availability. [114]
Ferritin	↓ H-R	Iron-handling change; assess alongside iron status. [114]
Erythroferrone	↑ H-R	Increased hepcidin-inhibitory signal. [114]
Erythropoietin	Transient ↑ H-R	Early erythropoietic response. [114]
Transferrin	↑ H-R	Increased circulating iron-transport protein. [114]
Transferrin receptors 1 and 2	↑ H-R / cells	Increased expression in sampled mononuclear cells. [114]
HIF-1α expression	↓ H-R / cells	Mononuclear-cell mechanistic endpoint. [114]
Prolyl hydroxylase-2 expression	↑ H-R / cells	HIF-regulating enzyme in mononuclear cells. [114]

9. Peripheral nerves and animal physical function

The DINE findings primarily support a small-nerve structural signal; not every clinical neuropathy endpoint improved.

Marker / endpoint	Change / evidence	Study context and qualification
Corneal nerve fiber density (CNFD)	↑ H-R*	DINE: significant within dapagliflozin arm, absent in control arm. [81]
Corneal nerve branch density (CNBD)	↑ H-R*	Small open-label randomized study. [81]
Corneal nerve fiber length (CNFL)	↑ H-R*	Small open-label randomized study. [81]
Intraepidermal nerve fiber density (IENFD)	↑ H-R*	Improved in both trial groups; incremental drug benefit not established. [81]
Neuropathic symptom questionnaire	Improved H-R*	Small empagliflozin trial; clinical examination score was not significantly different. [82]
Learning / memory and motor balance	Improved A	Naturally aged mice receiving empagliflozin. [77]

10. Disease outcomes and survival (not biomarkers)

These outcomes belong in the inventory because they measure patient benefit directly. RCT effects are population- and endpoint-specific; observational associations do not establish causality.

Marker / endpoint	Change / evidence	Study context and qualification
Heart-failure hospitalization / worsening HF	↓ H-R	Multiple trials, including patients without diabetes and across ejection-fraction ranges. [78, 2]
Kidney-disease progression / kidney failure	↓ H-R	DAPA-CKD, CREDENCE and EMPA-KIDNEY. [1, 91, 92]
Major adverse cardiovascular events	↓ H-R	Demonstrated in selected high-risk T2D populations, not uniformly every trial. [83]
Cardiovascular death	↓ H-R	Demonstrated in selected cardiovascular/HF populations. [83, 78]
All-cause mortality	↓ H-R	Reduced in selected disease cohorts; not a healthy-human lifespan trial. [83, 1]
Atrial fibrillation / flutter events	↓ H-R*	Post-hoc DECLARE-TIMI 58 analysis. [80]
Incident dementia	↓ association H-O	Comparative observational T2D cohort; residual confounding remains. [85]
HF and mortality in patients with cancer	↓ association H-O	Cancer-patient cohort; does not demonstrate prevention of all cancers. [96]
CV death / HF events with dual SGLT1/2 inhibition	↓ H-R	Sotagliflozin SCORED and SOLOIST-WHF composite endpoints. [88, 89]
Lifespan / survival in mice	↑ A	Canagliflozin benefit in genetically heterogeneous males, not females; other aging models supportive. [6, 5, 77]

11. Measured changes requiring separate interpretation

These findings are included for completeness but must not be counted as established clinical or geroprotective benefits.

Marker / endpoint	Change / evidence	Study context and qualification
IL-2 production	↓ C	Canagliflozin-treated human T cells: suppressed effector function, not demonstrated improved surveillance. [119]
T-cell CD25, CD44, CD69 and proliferation	↓ C	Immunosuppressive laboratory phenotype; potential relevance to autoimmunity. [119]
T-cell IFN-γ, IL-4, IL-10, IL-17 and IL-21 release	↓ C	Effector-cell cytokine suppression; neither human infection protection nor clinical autoimmune remission established. [119]
Urinary TGF-β1	↑ H-I	Increased urinary excretion while nephrin/albuminuria decreased; compartment matters. [112]
IGF-binding protein-3	↑ H-R	Henagliflozin; significance for human longevity is not established. [7]
β-hydroxybutyrate	↑ H-R	Metabolic shift, not a target to maximize; excessive ketosis is harmful. [7, 4]
Plasma AICAR	↑ A	Linked experimentally to AMPK activation and senescent-cell clearance. [5]
Thiamine; phosphatidylcholine, phosphatidylethanolamine and sphingosine	Altered H-R*	Henagliflozin metabolomics: thiamine up, listed lipids down; exploratory, not validated anti-aging endpoints. [7]
Renal nicotinic-acid mononucleotide / NAD-related metabolism	Altered A	Metabolomic pathway findings; do not equate with demonstrated systemic NAD+ restoration. [76]

12. Findings not to count as established benefits

Universal inflammation/SASP suppression

Not demonstrated. Cytokine responses differ by drug, compartment and disease. A SASP label does not establish the cellular source of a circulating cytokine. [5, 7, 111, 119]

Henagliflozin: IL-6, IL-10, IFN- γ ; perforin; IGF-1 reduction

No significant between-group benefit for measured inflammatory markers, perforin trends or IGF-1/IGFBP-3 ratio. Do not promote trends to positive findings. [7]

Katsuumi mouse adipose CCL2

Short-treatment main-figure comparison was nonsignificant ($P=.1097$), despite significant Tnf reduction. [5]

Fibronectin-1 (FN1)

Canagliflozin substudy reduction did not reach statistical significance ($P=.055$). [122]

Urinary NGAL, L-FABP and MCP-1

No significant change in the Dekkers crossover analysis. [115]

HIV cohort: LDL, HDL, oxLDL, Lp-PLA2, CRP and sCD14

Lipids/oxidized lipid markers were unchanged; CRP and sCD14 decreases were nonsignificant. [111]

Lipodystrophy cure / restored missing adipose tissue

Not shown. Long-term fat-ratio signal is small and uncontrolled; total-fat-percentage change was nonsignificant. Mouse adipose mass and insulin sensitivity were unchanged. [108, 117]

Liver synthetic function

Lower enzymes or stiffness do not prove improved albumin synthesis, INR, bilirubin clearance or prevention of decompensation. [108, 79]

Normal-mouse muscle SIRT1, Nrf2, SOD2, PPAR α / δ and UCP3

The cited muscle study did not show significant treatment increases for these transcripts; correlations are not treatment effects. [75]

Global protection from infections or cancers; human lifespan extension

Not demonstrated by these biomarker studies. Clinical mortality reduction in diseased populations is distinct from extending healthy-human lifespan. [7, 83, 96]

Protocol endpoints and non-SGLT supplement studies

REPROGRAM is a protocol; aging-biomarker consensus papers are frameworks. GlyNAC, metformin or rapamycin findings cannot be credited to an SGLT inhibitor.

References

Canonical registry identities are preserved. Numbering gaps are intentional: only sources cited in this inventory appear below.

- [1] 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
- [2] 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
- [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] 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
- [5] 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
- [6] 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
- [7] 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
- [10] Esen B, Yildiz D, Atay AE. Effects of Metformin Monotherapy Versus Metformin Plus SGLT-2 Inhibitor Therapy on Molecular and Cellular Inflammatory Markers in Patients with Newly Diagnosed Type 2 Diabetes Mellitus. *J Clin Med*. 2026;15:6700. doi:10.3390/jcm15176700
- [14] Ray EC, Boyd-Shiwerski 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. doi:10.1016/j.xkme.2020.01.010
- [65] TheracosBio. BRENZAVVY (bexagliflozin): prescribing information. Revised January 2023. Sections 4, 5 and 7.
- [73] 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. doi:10.1111/1753-0407.13526
- [74] 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. doi:10.1111/1440-1681.13638
- [75] 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. doi:10.1038/s41598-023-45390-y
- [76] 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. doi:10.1186/s12967-022-03629-8
- [77] 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. doi:10.1007/s11357-024-01250-9
- [78] 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. doi:10.1056/NEJMoa1911303
- [79] 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. doi:10.1136/bmj-2024-083735

- [80] 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. doi:10.1161/CIRCULATIONAHA.119.044183
- [81] 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. doi:10.1111/jns.70011
- [82] 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. doi:10.1002/edm2.70128
- [83] 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. doi:10.1056/NEJMoa1504720
- [85] 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. doi:10.1136/bmj-2024-079475
- [86] 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. doi:10.2337/db19-0991
- [88] 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. doi:10.1056/NEJMoa2030186
- [89] 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. doi:10.1056/NEJMoa2030183
- [91] 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. doi:10.1056/NEJMoa1811744
- [92] 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. doi:10.1056/NEJMoa2204233
- [95] 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. doi:10.1172/JCI72227
- [96] 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. doi:10.1136/heartjnl-2022-321545
- [108] Robert L, Belalem I, Vigouroux C, et al. Efficacy and Safety of SGLT2 Inhibitors in Patients With Genetic Lipodystrophy: A Real-Life Experience From a National Reference Network. *Diabetes Obes Metab*. 2026;28:10318–10329. doi:10.1111/dom.71126
- [109] Chen X, Yang Q, Bai W, et al. Dapagliflozin Attenuates Myocardial Fibrosis by Inhibiting the TGF-beta1/Smad Signaling Pathway in a Normoglycemic Rabbit Model of Chronic Heart Failure. *Front Pharmacol*. 2022;13:873108. doi:10.3389/fphar.2022.873108
- [110] Laurence J, Subramani K, Babii D, Walker B, Word T, Ahamed J. SGLT2 inhibitor dapagliflozin attenuates HIV-associated cardiac fibrosis, steatosis and diastolic dysfunction in a mouse model via inhibition of TGF-beta signaling. *AIDS*. 2026;40:863–865. doi:10.1097/QAD.0000000000004464
- [111] Guiraud V, Sauce D, Bittar R, et al. Clinical, biological, metabolic, and immune changes associated with the use of sodium-glucose cotransporter 2 inhibitors in people living with HIV. *Infect Dis Now*. 2025;55:105040. doi:10.1016/j.idnow.2025.105040
- [112] Tian Y, Chen XM, Liang XM, Wu XB, Yao CM. SGLT2 inhibitors attenuate nephrin loss and enhance TGF-beta1 secretion in type 2 diabetes patients with albuminuria: a randomized clinical trial. *Sci Rep*. 2022;12:15695. doi:10.1038/s41598-022-19988-7

- [113] Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA, et al. Randomized Trial of Empagliflozin in Nondiabetic Patients With Heart Failure and Reduced Ejection Fraction. *J Am Coll Cardiol*. 2021;77:243-255. doi:10.1016/j.jacc.2020.11.008
- [114] Ghanim H, Abuaysheh S, Hejna J, et al. Dapagliflozin Suppresses Hepcidin And Increases Erythropoiesis. *J Clin Endocrinol Metab*. 2020;105:dga057. doi:10.1210/clinem/dgaa057
- [115] Dekkers CCJ, Petrykiv S, Laverman GD, Cherney DZ, Gansevoort RT, Heerspink HJL. Effects of the SGLT-2 inhibitor dapagliflozin on glomerular and tubular injury markers. *Diabetes Obes Metab*. 2018;20:1988-1993. doi:10.1111/dom.13301
- [116] Bolinder J, Ljunggren O, Kullberg J, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. *J Clin Endocrinol Metab*. 2012;97:1020-1031. doi:10.1210/jc.2011-2260
- [117] Smati S, Sotin T, Deniel P, et al. Empagliflozin mitigates metabolic dysfunction-associated steatotic liver disease by reducing de novo lipogenesis in a mouse model of lipoatrophic diabetes. *Diabetes Obes Metab*. 2024;26:3466-3470. doi:10.1111/dom.15634
- [118] Bansal R, Cochran E, Startzell M, Brown RJ. Clinical Effects of Sodium-Glucose Transporter Type 2 Inhibitors in Patients With Partial Lipodystrophy. *Endocr Pract*. 2022;28:610-614. doi:10.1016/j.eprac.2022.03.006
- [119] Jenkins BJ, Blagih J, Ponce-Garcia FM, et al. Canagliflozin impairs T cell effector function via metabolic suppression in autoimmunity. *Cell Metab*. 2023;35:1132-1146.e9. doi:10.1016/j.cmet.2023.05.001
- [120] Bellanti F, Lo Buglio A, Dobrakowski M, et al. Impact of sodium glucose cotransporter-2 inhibitors on liver steatosis/fibrosis/inflammation and redox balance in non-alcoholic fatty liver disease. *World J Gastroenterol*. 2022;28:3243-3257. doi:10.3748/wjg.v28.i26.3243
- [121] Solini A, Giannini L, Seghieri M, et al. Dapagliflozin acutely improves endothelial dysfunction, reduces aortic stiffness and renal resistive index in type 2 diabetic patients: a pilot study. *Cardiovasc Diabetol*. 2017;16:138. doi:10.1186/s12933-017-0621-8
- [122] Heerspink HJL, et al. Canagliflozin reduces inflammation and fibrosis biomarkers: a potential mechanism of action for beneficial effects of SGLT2 inhibitors in diabetic kidney disease. *Diabetologia*. 2019. doi:10.1007/s00125-019-4859-4
- [123] Butt JH, Adamson C, Docherty KF, et al. Efficacy and Safety of Dapagliflozin in Heart Failure With Reduced Ejection Fraction According to N-Terminal Pro-B-Type Natriuretic Peptide: Insights From the DAPA-HF Trial. *Circ Heart Fail*. 2021;14:e008837. doi:10.1161/CIRCHEARTFAILURE.121.008837