

Supplementary Table S1: Standardized Tier Evaluation Rubric

Dimension	Tier 1 (Excellent / Low Risk)	Tier 2 (Good / Moderate Benefit)	Tier 3 (Weak / Moderate Risk)	Tier 4 (Poor / High Risk)
1. Preclinical Lifespan (Mouse ITP Data)	Statistically significant median and/or maximum lifespan extension demonstrated across multiple independent ITP testing sites in both sexes or strong sex-specific effect (>10%).	Reproducible median lifespan extension in non-ITP mammalian models OR positive healthspan metrics awaiting definitive ITP testing.	Mixed or non-statistically significant median lifespan extension in gold-standard ITP protocols (e.g., neutral outcome).	Demonstrated failure to extend lifespan or evidence of detriment/toxicity in standardized mammalian lifespan studies.
2. Human RCT Data (Mortality / Disease)	Multiple Phase 3 double-blind RCTs demonstrating reductions in all-cause mortality and hard cardiovascular/metabolic endpoints across broad populations.	Mixed or targeted RCT data showing organ protection or disease-specific benefit without universal all-cause mortality reduction.	Strong observational and epidemiological association data but lacking positive RCTs in humans.	Absence of completed human RCTs evaluating mortality, longevity, or major chronic disease primary prevention endpoints.

3. Safety Profile (Healthy Adults)	Exceptional long-term safety profile with decades of pharmacovigilance; minimal risk of severe adverse events (SAEs) in normoglycemic adults.	Favorable overall safety profile; predictable, self-limiting side effects (e.g., mild GI distress, transient euglycemic DKA/UTI risk) requiring basic monitoring.	Dose-dependent metabolic or immunological perturbations (e.g., dyslipidemia, dysglycemia, stomatitis) requiring ongoing lab monitoring.	High incidence of severe adverse events, narrow therapeutic window, or significant risk of severe off-target organ toxicity in off-label use.
4. Risk of Muscle Loss / Sarcopenia	Neutral or positive impact on lean body mass, muscle protein synthesis, and physical function during administration.	Minimal or clinically insignificant risk of lean mass loss; primarily drives reduction in adiposity/visceral fat or transient blunting of exercise hypertrophy.	Moderate risk of blunting exercise-induced muscle hypertrophy or modest decline in total mass requiring dietary/exercise mitigation.	Significant risk of rapid lean muscle tissue loss (e.g., >20–30%) without mandatory resistance training and high-protein intervention.
5. Cost & Accessibility	Off-patent, low-cost generic formulation widely available globally (<\$0.50/day) with minimal prescribing barriers.	Generic formulations available, but off-label indication status, supply bottlenecks, or moderate out-of-pocket costs create minor friction.	High financial friction; branded status or requiring prior authorizations and specialized clinical monitoring; high monthly cost (\$100–\$300/month).	Prohibitive out-of-pocket cost (>\$800–\$1,000+/month), active patent enforcement, strict insurance coverage criteria, and frequent global supply shortages.

Supplementary Table S2: Evidence-Based Justification and References for Figure 2 Assignments

Agent	Dimension	Assigned Tier	Underlying Evidence & Trial Justification	Main Text References
SGLTi	1. Preclinical Lifespan	Tier 1	Canagliflozin demonstrated a robust, statistically significant 14% increase in median lifespan in male mice in the NIA ITP.	Miller et al. [61]
	2. Human RCT Data	Tier 1	EMPA-REG, CANVAS, DECLARE-TIMI 58, DAPA-HF, and EMPEROR-Reduced trials demonstrate consistent reductions in CV death, HF hospitalization, renal failure, and all-cause mortality across diabetic and non-diabetic cohorts.	Zinman et al. [5], Neal et al. [6], Wiviott et al. [7], Perkovic et al. [9], McMurray et al. [10], Packer et al. [11], Anker et al. [12], Solomon et al. [13], Vaduganathan et al. [23], Movila et al. [22]
	3. Safety Profile	Tier 2	Generally well-tolerated in normoglycemic adults; primary risks include mycotic genital infections and rare, preventable euglycemic DKA or Fournier's gangrene.	FDA Communications [55, 57], McGill & Subramanian [54], Silverii et al. [56]

	4. Sarcopenia Risk	Tier 2	Weight reduction is predominantly driven by visceral fat loss, glucosuria-induced caloric deficit, and fluid loss rather than total skeletal muscle mass depletion.	Pan et al. [S1]
	5. Cost & Access	Tier 1	Multiple generic SGLT inhibitors (e.g., Dapagliflozin) are available globally, significantly lowering financial and prescription barriers.	US Food and Drug Administration [S2]
Metformin	1. Preclinical Lifespan	Tier 3	Failed to significantly extend median or maximum lifespan in standard-dose ITP testing in male or female mice.	Strong et al. [S3]; Barzilai et al. [3], Kulkarni et al. [4]
	2. Human RCT Data	Tier 2	UKPDS demonstrated long-term cardiovascular benefits in diabetic populations; however, broad human outcomes data across non-diabetic longevity cohorts remain mixed (awaiting primary outcome data from TAME).	Barzilai et al. [3], Kulkarni et al. [4]
	3. Safety Profile	Tier 1	Decades of global clinical safety data; benign side-effect profile dominated by transient, self-limiting gastrointestinal distress.	Kulkarni et al. [4]

	4. Sarcopenia Risk	Tier 3	Shown to modestly blunt resistance exercise-induced skeletal muscle hypertrophy and mitochondrial adaptations in older adults.	Walton et al. [S4]
	5. Cost & Access	Tier 1	Off-patent, ubiquitous global generic available at negligible out-of-pocket expense (<\$0.10/dose).	Barzilai et al. [3], Kulkarni et al. [4]
Rapamycin	1. Preclinical Lifespan	Tier 1	The most reproducible and robust geroprotective agent in NIA ITP history; extends male and female mouse median/maximum lifespan up to 26% even when initiated in mid-life.	Harrison et al. [1]; Miller et al. [S5]
	2. Human RCT Data	Tier 4	Lacks completed Phase 3 clinical trials evaluating hard disease endpoints, all-cause mortality, or primary disease prevention in healthy human cohorts.	Mannick et al. [2]; Moel et al. [S6]
	3. Safety Profile	Tier 3	Low/intermittent dosing improves safety, but continuous exposure carries risks of hyperlipidemia, impaired glucose tolerance, aphthous stomatitis, and immune alterations requiring routine clinical laboratory tracking.	Mannick et al. [2]; Moel et al. [S6]

	4. Sarcopenia Risk	Tier 2	Continuous high-dose mTORC1 suppression inhibits muscle protein synthesis, but low-dose or intermittent pulsatile schedules preserve muscle architecture without accelerating sarcopenia.	Moel et al. [S6]
	5. Cost & Access	Tier 2	Generic Sirolimus is off-patent and moderately priced, but clinical reluctance regarding off-label prescribing creates access bottlenecks.	—

Supplementary Table S3: Trial-Level Data for Figure 3 (All-Cause Mortality)

All 13 placebo-controlled SGLT inhibitor outcome trials contributing to the Figure 3 forest plot. Every hazard ratio was verified against the primary publication cited. Pooled estimate (random effects, DerSimonian–Laird, generic inverse variance on log HR): HR 0.88 (95% CI 0.83–0.94), $p < 0.001$; $I^2 = 39\%$ (95% CI 0–68%); 95% prediction interval 0.75–1.04; 90,413 patients randomized.

Trial	Agent	Population	Randomized (n)	Deaths, SGLTi / placebo	HR (95% CI)	Median follow-up (y)	Source of the estimate
EMPA-REG OUTCOME	Empagliflozin	T2D + ASCVD	7,020	269/4,687 vs 194/2,333	0.68 (0.57–0.82)	3.1	Zinman 2015 [5]: Table 1, Results text, Figure 1C
CANVAS Program	Canagliflozin	T2D + high CV risk	10,142	17.3 vs 19.5 per 1,000 py	0.87 (0.74–1.01)	2.4	Neal 2017 [6]: Results text and Figure 3; outside the hierarchical testing sequence
DECLARE-TIMI 58	Dapagliflozin	T2D + ASCVD or risk factors	17,160	529/8,582 vs 570/8,578	0.93 (0.82–1.04)	4.2	Wiviott 2019 [7]: secondary endpoint, paper body
VERTIS-CV	Ertugliflozin	T2D + ASCVD	8,246	473/5,499 vs 254/2,747	0.93 (0.80–1.08)	3.0	Cannon 2020 [8]: Table 2, outside tested hierarchy

Trial	Agent	Population	Randomized (n)	Deaths, SGLTi / placebo	HR (95% CI)	Median follow-up (y)	Source of the estimate
SCORED	Sotagliflozin	T2D + CKD	10,584	3.5 vs 3.5 per 100 py	0.99 (0.83–1.18)	1.3	Bhatt 2021 [17]: Table 2
DAPA-HF	Dapagliflozin	HFrEF	4,744	276/2,373 vs 329/2,371	0.83 (0.71–0.97)	1.5	McMurray 2019 [10]: abstract, Table 2, Figure 2D
EMPEROR-Reduced	Empagliflozin	HFrEF	3,730	249/1,863 vs 266/1,867	0.92 (0.77–1.10)	1.3	Packer 2020 [11]: Table 2, prespecified analyses
EMPEROR-Preserved	Empagliflozin	HFpEF	5,988	422/2,997 vs 427/2,991	1.00 (0.87–1.15)	2.2	Anker 2021 [12]: Table 2, main text; outside tested hierarchy
DELIVER	Dapagliflozin	HFmrEF / HFpEF	6,263	497/3,131 vs 526/3,132	0.94 (0.83–1.07)	2.3	Solomon 2022 [13]: Table 2
SOLOIST-WHF	Sotagliflozin	T2D + worsening HF	1,222	13.5 vs 16.3 per 100 py	0.82 (0.59–1.14)	0.8	Bhatt 2021 [16]: abstract and Table 2; testing hierarchy already stopped
CREDENCE	Canagliflozin	T2D + albuminuric CKD	4,401	168/2,202 vs 201/2,199	0.83 (0.68–1.02)	2.6	Perkovic 2019 [9]: Results text and Table 2; not formally tested (P = NA)
DAPA-CKD	Dapagliflozin	CKD ± T2D	4,304	101/2,152 vs 146/2,152	0.69 (0.53–0.88)	2.4	Heerspink 2020 [14]: abstract, Results text, Table 2
EMPA-KIDNEY	Empagliflozin	CKD ± T2D	6,609	148/3,304 vs 167/3,305	0.87 (0.70–1.08)	2.0	EMPA-KIDNEY Collaborative Group 2023 [15]: Results text and Table 2

In several trials all-cause mortality lay outside, or after the stop of, the hierarchical testing sequence (noted per row), so those individual confidence intervals are nominal. Pooling uses each trial's estimate and its variance and is unaffected by within-trial multiplicity control. HR, hazard ratio; py, patient-years; T2D, type 2 diabetes; ASCVD, atherosclerotic cardiovascular disease; HF, heart failure; HFrEF/HFmrEF/HFpEF, heart failure with reduced/mildly reduced/preserved ejection fraction; CKD, chronic kidney disease. Bracketed numbers refer to the main manuscript reference list.

Supplementary Table S4: Trial-Level Data for Figure 4 (All-Cause Hospitalization)

The five placebo-controlled SGLT inhibitor outcome trials reporting a first all-cause admission estimate. Pooled estimate (random effects): HR 0.90 (95% CI 0.87–0.93), $p < 0.001$; $I^2 = 0\%$ (95% CI 0–79%); 95% prediction interval 0.85–0.94; 43,027 patients randomized.

Trial	Population	Endpoint as published	HR (95% CI)	Placebo admissions	Median follow-up (y)	Source of the estimate
EMPA-REG OUTCOME	T2D + ASCVD	Time to first hospitalization, any cause (any admission)	0.89 (0.82–0.96)	not reported per arm	3.1	McGuire 2020 [S7]
CANVAS Program	T2D + high CV risk	First hospitalization, any cause (any admission)	0.94 (0.88–1.00)	131.1 per 1,000 py	2.4	Neal 2017 [6], supplementary appendix
DECLARE-TIMI 58	T2D + ASCVD or risk factors	First non-elective hospitalization, any cause	0.89 (0.85–0.94)	3,036/8,578 (35.4%)	4.2	Schechter 2023 [S8]
CREDENCE	T2D + albuminuric CKD	First non-elective hospitalization, any cause	0.88 (0.80–0.98)	809/2,199 (36.8%)	2.6	Oshima 2025 [S9]
DAPA-CKD	CKD ± T2D	First hospitalization, any cause (any admission)	0.84 (0.75–0.94)	658/2,152 (30.6%)	2.4	Schechter 2023 [S10]

Because all-cause hospitalization is rarely a prespecified outcome, four of the five estimates come from secondary or post-hoc analyses rather than the primary trial reports; the source of each is given above. Endpoint definitions are not uniform: DECLARE-TIMI 58 and CREDENCE analyzed non-elective admissions only, so the pooled placebo-arm baseline used in Figure 4B is a conservative estimate of all-cause admission risk. For EMPA-REG OUTCOME the time-to-first-event hazard ratio is shown; the same source also reports a first-event rate ratio of 0.88 (0.81–0.96). S-numbers refer to the supplementary reference list below; bracketed numbers without S refer to the main manuscript reference list.

Supplementary References

- S1. Pan R, Zhang Y, Wang R, Xu Y, Ji H, Zhao Y. Effect of SGLT-2 inhibitors on body composition in patients with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *PLoS One*. 2022;17(12):e0279889.
- S2. US Food and Drug Administration. First generic drug approvals. Silver Spring (MD): FDA; updated 2026 Aug 6.
- S3. Strong R, Miller RA, Antebi A, Astle CM, Bogue M, Denzel MS, 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.
- S4. Walton RG, Dungan CM, Long DE, Tuggle SC, Kosmac K, Peck BD, 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.
- S5. Miller RA, Harrison DE, Astle CM, Fernandez E, Flurkey K, Han M, 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.

- S6. Moel M, Harinath G, Lee V, Nyquist A, Morgan SL, Isman A, et al. Influence of rapamycin on safety and healthspan metrics after one year: PEARL trial results. *Aging (Albany NY)*. 2025;17(4):908-936.
- S7. McGuire DK, Zinman B, Inzucchi SE, Wanner C, Fitchett D, Anker SD, et al. Effects of empagliflozin on first and recurrent clinical events in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a secondary analysis of the EMPA-REG OUTCOME trial. *Lancet Diabetes Endocrinol*. 2020;8(12):949-959.
- S8. Schechter M, Wiviott SD, Raz I, Goodrich EL, Rozenberg A, Yanuv I, et al. Effects of dapagliflozin on hospitalisations in people with type 2 diabetes: post-hoc analyses of the DECLARE-TIMI 58 trial. *Lancet Diabetes Endocrinol*. 2023;11(4):233-241.
- S9. Oshima M, Buizen L, Jongs N, Levin A, Chertow GM, Wheeler DC, et al. Sodium-glucose cotransporter 2 inhibition and hospitalizations in patients with CKD: a meta-analysis of kidney outcome trials. *Clin J Am Soc Nephrol*. 2025;20(9):1206-1214.
- S10. Schechter M, Jongs N, Chertow GM, Mosenzon O, McMurray JJV, Correa-Rotter R, et al. Effects of dapagliflozin on hospitalizations in patients with chronic kidney disease: a post hoc analysis of DAPA-CKD. *Ann Intern Med*. 2023;176(1):59-66.