

SGLT2 inhibitors beyond glucose lowering: strength of the cardiovascular and kidney mechanisms

Research summary

Sodium–glucose cotransporter-2 (SGLT2) inhibitors improve outcomes in type 2 diabetes, heart failure (HF), and chronic kidney disease (CKD), including in people without diabetes. The central mechanistic question is not whether these drugs alter sodium handling, glomerular filtration, blood counts, or cardiac metabolism—they do—but which changes plausibly account for fewer cardiovascular and kidney events. The clinical anchor is strongest for kidney protection independent of glucose lowering: in EMPA-KIDNEY, empagliflozin reduced kidney disease progression or cardiovascular death versus placebo, with consistent effects among participants with and without diabetes; a randomized-trial meta-analysis also found less CKD progression across baseline eGFR and albuminuria categories. HF benefit likewise extends to patients without diabetes, so improvement in glycemia cannot be a necessary explanation. These trials establish treatment effects, not the proportion attributable to any individual pathway.

The most clinically grounded explanations begin in the proximal tubule. Reduced sodium–glucose reabsorption changes downstream sodium delivery and can produce early natriuresis, modest volume and blood-pressure effects, and lower cardiac filling pressures. A meta-analysis of small randomized invasive-hemodynamic studies found lower pulmonary capillary wedge pressure at rest and peak exercise. This supports a preload contribution to HF benefit, while lower blood pressure offers a plausible afterload contribution. It does **not** establish sustained diuresis as the principal mediator: renal sodium and water responses adapt, and controlled-sodium studies found blood-pressure lowering without increased 24-hour sodium or volume excretion, including in CKD without diabetes. For kidney outcomes, increased macula-densa sodium delivery can restore tubuloglomerular feedback and lower intraglomerular pressure, providing a coherent explanation for an early filtration change followed by slower CKD progression. Confidence is higher in the overall renal-hemodynamic contribution than in a universal account based specifically on *afferent* arteriolar constriction; studies and physiological analyses in type 2 diabetes and advanced CKD raise plausible alternative vascular responses.

Other pathways have a clearer distinction between **measured response** and **proven mediator**. Hemoglobin and hematocrit rise during SGLT2 inhibition, and erythropoietin-driven erythropoiesis contributes alongside any hemoconcentration. In a post hoc EMPA-REG OUTCOME analysis, hematocrit change statistically mediated 51.8% of empagliflozin's effect on cardiovascular death versus placebo; that estimate cannot distinguish improved oxygen delivery from volume change or other correlated treatment effects, and it does not prove a causal pathway for kidney benefit. Ketone availability, altered myocardial

substrate use, and sodium–hydrogen exchange have experimental or small mechanistic-study support, but no clinical-grade demonstration that they mediate HF events. Anti-inflammatory, antifibrotic, and endothelial responses are similarly credible biological candidates: biomarker studies and diabetic-kidney models identify treatment-associated changes, without establishing that modifying those pathways prevents clinical events in either diabetic or nondiabetic CKD. Thus, certainty is **high for cardiovascular and kidney clinical benefit beyond glucose lowering**, **moderate for contributions from cardiorenal hemodynamics**, and **low for assigning a causal share of benefit to erythropoiesis, energetics, or tissue-remodeling pathways**.

Bottom line

- **Kidney benefit does not require diabetes:** placebo-controlled outcome trials and their meta-analysis support less CKD progression across studied populations; **high certainty for clinical effect**, not for one exclusive mechanism.
- **Altered proximal-tubular sodium handling and renal hemodynamics are leading kidney mechanisms:** tubuloglomerular feedback is physiologically persuasive, but afferent constriction is not established as universal in advanced CKD; **moderate mechanistic confidence**.
- **Reduced filling pressure supports a hemodynamic contribution to HF benefit:** small randomized invasive studies support the effect; sustained natriuresis as its main explanation has **low confidence**.
- **Hematocrit rise reflects more than simple hemoconcentration:** erythropoiesis is supported clinically, but improved oxygen delivery as a mediator of cardiovascular or kidney events has **low causal certainty**.
- **Ketone-based energetics and cardiac sodium–hydrogen exchange remain hypotheses:** predominantly experimental and surrogate-endpoint evidence gives them **low clinical mechanistic certainty**.
- **Anti-inflammatory, antifibrotic, and endothelial pathways are less directly tied to outcomes than cardiorenal hemodynamics:** biomarker and preclinical findings provide **low certainty of clinical mediation**.

Evidence at a glance

Source	Design	Population (n)	Comparison	Key result	Ref
CKD-progression meta-analysis	Meta-analysis of randomized trials	70 361 participants in 10 trials	SGLT2 inhibitor vs placebo	CKD progression: 25.4 vs 40.3 events per 1000 patient-years; hazard ratio [HR], 0.62 [95% CI, 0.57-0.68]	

Source	Design	Population (n)	Comparison	Key result	Ref
EMPA-KIDNEY	Randomized outcome trial	6609 with CKD; 3569 without diabetes	Empagliflozin vs placebo	Kidney disease progression or cardiovascular death: 432 of 3304 (13.1%) vs 558 of 3305 (16.9%); hazard ratio, 0.72; 95% CI 0.64 to 0.82	
EMPEROR-Reduced analysis discussed in <i>Kidney International</i>	Randomized-trial evidence reviewed	3730 with HFrEF	Empagliflozin vs placebo	Annual eGFR decline: -0.55 vs -2.28 ml/min per 1.73 m ² per year; P < 0.001	
Invasive HF hemodynamics	Meta-analysis of randomized trials	145 participants in 3 studies	SGLT2 inhibitor vs control	Pulmonary capillary wedge pressure was lower at rest and peak exercise	
DAPASALT and DIAMOND, CKD without diabetes	Mechanistic studies	DAPASALT stratum: 6 participants with CKD	Dapagliflozin treatment; DIAMOND compared dapagliflozin with placebo	Blood pressure decreased during standardized sodium intake without increased 24-hour sodium or volume excretion	
DAPASALT across diabetes and CKD strata	Mechanistic study and participant-level pooled analysis	People with type 2 diabetes and/or CKD	Dapagliflozin treatment across strata	Blood pressure decreased during standardized sodium intake without increased natriuresis	
EMPA-REG OUTCOME mediation analysis	Exploratory post hoc analysis of a randomized trial	7,020 with type 2 diabetes and established cardiovascular disease	Empagliflozin vs placebo	Cardiovascular death: HR 0.62 [95% CI 0.49, 0.77]; hematocrit change statistically mediated 51.8% of the effect	
Hemoglobin and hematocrit in CKD	Systematic review and meta-analysis of randomized trials	Participants with CKD	SGLT2 inhibitors vs control treatments	Hemoglobin and hematocrit increased; clinical-event mediation was not tested	
Natriuresis and HF outcomes	Critical review of physiological studies	Includes a randomized crossover study of 20 patients with diabetes and chronic HF	Empagliflozin vs placebo in the crossover study	Early fractional sodium excretion increased, but the broader evidence did not show large sustained diuresis or natriuresis	
Tubuloglomerular feedback in advanced CKD	Physiological critique	Type 2 diabetes with advanced CKD	Proposed afferent-feedback mechanism vs alternative renal vascular responses	Afferent tubuloglomerular feedback may not explain the renal response in advanced CKD	
Cardiac energy metabolism	Review of clinical and animal studies	34 studies, including 10 clinical and 24 animal studies	SGLT2 inhibitor exposure across studies	Substrate-use changes were reported, but their contribution to clinical HF outcomes was not established	
Sodium-hydrogen exchange and HF energetics	Mechanistic commentary	HF studies and experimental models	SGLT2 inhibition vs control across discussed studies	Cardiac sodium-hydrogen exchanger inhibition was not confirmed; plasma metabolite concentrations do not measure myocardial substrate flux	

Source	Design	Population (n)	Comparison	Key result	Ref
VERTIS RENAL biomarkers	Exploratory post hoc randomized-trial analysis	Type 2 diabetes and stage 3 CKD	Ertugliflozin vs placebo	Kidney injury, inflammation, and fibrosis biomarkers were assessed; contribution to clinical kidney outcomes could not be determined	
Diabetic-kidney urinary proteomics	Randomized mechanistic trial	Diabetic kidney disease	SGLT2 inhibitor vs control	Urinary proteins associated with inflammation, wound healing, and fibrosis changed; clinical-event mediation was not established	
Renal PKM2 and fibrosis	Experimental and translational study	Diabetic-kidney models and human DKD investigation	Empagliflozin exposure vs model controls	Antifibrotic effects were demonstrated in models; direct improvement of renal fibrosis in patients remains unestablished	

Findings

1. Which hemodynamic and volume effects (natriuresis, plasma-volume reduction, afterload and preload) are supported, and how strongly do they explain heart-failure outcomes independent of glycemia?

SGLT2 inhibition has a **credible but incomplete hemodynamic explanation** for heart-failure benefit. Proximal tubular sodium–glucose transport blockade can produce an early increase in sodium and water excretion; modest changes in circulating volume and ventricular filling pressure provide a plausible route to fewer worsening-heart-failure events. Blood-pressure lowering may also reduce afterload. The strongest evidence establishes the clinical benefit and the existence of several intermediate hemodynamic effects; it does **not** establish how much of the benefit is mediated by any one of them.

Natriuresis and volume: an early effect, not sustained loop-like diuresis

Blocking proximal sodium–glucose reabsorption changes tubular sodium handling and causes glucosuria-associated osmotic water loss. In a randomized crossover study of 20 clinically euvolemic patients with diabetes and chronic heart failure receiving substantial loop-diuretic doses, empagliflozin increased fractional sodium excretion immediately; the difference remained discernible after 14 days, was enhanced by bumetanide, and was unrelated to the magnitude of glycosuria. The last observation is particularly relevant to a beyond-glycemia mechanism: sodium handling in that experiment did not simply track urinary glucose loss. It does not, however, show that sustained net sodium loss mediated fewer heart-failure events.

Across settings, the distinction between **increased proximal sodium delivery** and **sustained net natriuresis** matters. A critical synthesis of renal physiology studies found substantial variation in response and no consistent large acute or chronic natriuresis or diuresis, whether SGLT2 inhibitors were used alone or with other diuretics. Under standardized sodium intake, the DAPASALT studies found blood-pressure reduction without an increase in 24-hour sodium excretion across populations with type 2 diabetes, CKD, or both. In the nondiabetic CKD stratum, the open-label DAPASALT study enrolled six patients; during standardized sodium intake, dapagliflozin lowered blood pressure without increasing 24-hour sodium or volume excretion. These findings do not negate an initial sodium loss: at a new steady state, urinary sodium excretion must again approximate intake. They do argue against describing the long-term heart-failure benefit as the consequence of continuously augmented urinary sodium output.

Compensatory renal and hormonal responses offer one explanation for the difference between an early tubular effect and later excretion measurements. In an exploratory DAPASALT analysis involving 14 people with type 2 diabetes and preserved kidney function, plasma renin and angiotensin II and urinary aldosterone and angiotensinogen rose during dapagliflozin treatment. In the nondiabetic CKD DIAMOND study, dapagliflozin increased plasma renin versus placebo by 38.5 [95% CI 7.4, 78.8]%. Such responses are consistent with volume-homeostatic adaptation, not proof of a particular amount of volume depletion or of mediation of clinical outcomes. **Evidence judgment:** direct human evidence supports an early sodium-handling effect, including in heart failure; evidence that sustained natriuresis itself explains the heart-failure outcome benefit is weak.

Preload and afterload: plausible links with measurable intermediate effects

A modest reduction in plasma volume could lower cardiac preload and ventricular filling pressure, while lower systemic pressure could reduce afterload. The preload link has more direct human support than a simple account based on urine output alone. A systematic review and meta-analysis of three randomized invasive-hemodynamic studies, comprising 145 patients, found lower pulmonary capillary wedge pressure at rest and peak exercise with SGLT2 inhibition. Wedge pressure is a clinically pertinent intermediate measure in heart failure, but these small studies cannot determine whether its change accounts for the reduction in hospitalization, cardiovascular death, or both.

Blood-pressure lowering is also observed outside diabetes, where a glucose-lowering explanation is insufficient. In EMPA-KIDNEY secondary analyses, the overall between-group systolic blood-pressure difference with empagliflozin was -2.6 mm Hg (95% CI -3.3 to -1.9) versus placebo; the investigators noted that the effect might be larger in diabetic kidney disease than in other primary kidney diagnoses. The CKD setting makes this evidence pertinent to glycemia-independent systemic action, but blood-pressure change in a CKD trial is not a direct measurement of ventricular afterload in heart failure.

Moreover, DAPASALT found lower pressure without increased measured 24-hour sodium excretion, so afterload reduction should not be attributed solely to ongoing natriuresis. **Evidence judgment:** modest pressure lowering and reductions in measured filling pressure have moderate support as intermediate effects; their separate contributions to hard heart-failure outcomes remain unquantified.

How far the mechanism explains outcomes independently of glycemia

Clinical outcome findings are more secure than mechanistic attribution. EMPEROR-Reduced and DAPA-HF demonstrated heart-failure benefit in populations that included people without diabetes, supporting an action not dependent on treating hyperglycemia. In EMPA-REG OUTCOME, which instead enrolled 7,020 people with type 2 diabetes and established cardiovascular disease, empagliflozin reduced cardiovascular death versus placebo (hazard ratio 0.62 [95% CI 0.49, 0.77]). An exploratory analysis of that trial identified changes in markers interpreted as reflecting plasma volume among the most important statistical mediators of the cardiovascular-death result. That analysis concerns **cardiovascular death in a diabetes and atherosclerotic-disease trial**, not a measured plasma-volume contribution to heart-failure hospitalization in people without diabetes. A circulating marker may also change for reasons other than plasma-volume contraction; statistical adjustment cannot isolate a causal volume pathway.

Thus, outcome-trial efficacy in heart failure without diabetes, early sodium-handling changes, lower blood pressure, and lower invasively measured filling pressure form a coherent case for hemodynamic participation. The case is weaker for hemodynamics as a *complete* explanation. Large, persistent natriuresis is not consistently observed, and more potent conventional diuretics provide an imperfect mechanistic analogy rather than evidence that SGLT2 inhibitors work by conventional decongestion alone. **Overall judgment:** high certainty that heart-failure benefit does not require glucose lowering; moderate confidence that preload- and afterload-related effects contribute; low confidence in any claim that chronic net natriuresis, plasma-volume reduction, or blood-pressure lowering individually accounts for a specified share of that benefit.

2. How does restored tubuloglomerular feedback and lower intraglomerular pressure account for kidney protection, including in CKD without diabetes?

SGLT2 inhibition has a direct renal action that makes reduced intraglomerular pressure a credible explanation for kidney protection. By blocking proximal tubular sodium–glucose reabsorption, it increases solute delivery toward the macula densa. In a hyperfiltering nephron, the resulting tubuloglomerular-feedback signal can restrain afferent arteriolar dilation, lower glomerular capillary pressure and reduce single-nephron filtration. A fall in measured eGFR soon after treatment begins is therefore compatible with a functional hemodynamic adjustment rather than progressive nephron loss. Lower filtration

pressure may reduce albumin leakage and cumulative pressure-related glomerular injury, providing a coherent explanation for an early eGFR change followed by slower long-term decline. **The evidence is strong that SGLT2 inhibitors protect kidneys, but moderate—not definitive—that restored tubuloglomerular feedback is the principal mediator.** The sequence is physiologically plausible and supported by mechanistic observations; an outcome trial has not isolated this pathway from the drug's other renal effects.

Concordance with kidney outcome trials

The decisive test of an explanation *beyond glucose lowering* is whether kidney protection persists where glucose lowering cannot reasonably account for the outcome. In EMPA-KIDNEY, participants with CKD received empagliflozin or placebo; kidney disease progression or cardiovascular death occurred in 432 of 3304 participants (13.1%) versus 558 of 3305 (16.9%), respectively (hazard ratio 0.72; 95% CI 0.64 to 0.82). Effects were consistent with and without diabetes and across the eGFR range studied. The trial included 3569 participants (54%) without diabetes and 2282 (35%) with eGFR below 30 ml per minute per 1.73 m². DAPA-CKD also established kidney protection in CKD without diabetes, whereas CREDENCE established it in albuminuric diabetic kidney disease; these populations make a mechanism dependent solely on correction of hyperglycemia untenable. A meta-analysis of randomized trials found CKD progression rates of 25.4 versus 40.3 events per 1000 patient-years with SGLT2 inhibitors versus control (hazard ratio 0.62; 95% CI 0.57–0.68), with benefit across baseline eGFR and albuminuria categories.

These trials establish **high-certainty clinical benefit across diabetic and nondiabetic CKD**, not high-certainty attribution of that benefit to afferent vasoconstriction. EMPA-KIDNEY's composite included both kidney disease progression and cardiovascular death, although its interpretation was driven mainly by slowed kidney progression. Its inclusion of lower-albuminuria CKD broadens the clinical phenotype in which protection is observed, but fewer primary-outcome events occurred among participants with lower albuminuria; subgroup claims about the precise hemodynamic pathway should not be stronger than the event data permit. Across different primary kidney diagnoses, EMPA-KIDNEY secondary analyses found broadly similar relative effects on kidney disease progression, supporting a mechanism applicable beyond classic diabetic hyperfiltration without identifying which renal mechanism operated in each diagnosis.

Where the feedback account is strongest—and where it is incomplete

The conventional feedback model fits particularly well when enhanced proximal reabsorption and glomerular hyperfiltration coexist. In diabetes, greater proximal sodium–glucose uptake can limit macula-densa salt delivery; inhibition reverses that signal and provides a direct route to lower filtration pressure.

Clinical renal-hemodynamic findings have nevertheless challenged a *uniform afferent-constriction* account: the proposed vascular response differs across experimental settings and diabetes phenotypes, and a randomized renal-hemodynamic study in metformin-treated type 2 diabetes has been interpreted as favoring postglomerular vasodilation rather than preglomerular vasoconstriction. Thus, “lower intraglomerular pressure” and “restored afferent tubuloglomerular feedback” are related but not interchangeable claims.

The distinction matters most in advanced CKD. With reduced filtered glucose and fewer functioning nephrons, the magnitude and consequences of altered macula-densa delivery need not resemble those in a hyperfiltering diabetic kidney. A published critique argues that afferent feedback reactivation may be less likely in advanced type 2 diabetic CKD and proposes interactions with renin–angiotensin-system blockade and efferent arteriolar responses instead. That is a mechanistic interpretation, not evidence that protection disappears: EMPA-KIDNEY observed consistent clinical benefit across the eGFR range it studied, including substantial representation of advanced CKD. **Confidence is therefore lower in one universal arteriolar explanation than in an intrarenal hemodynamic contribution more broadly defined.**

Nondiabetic CKD poses the sharpest mechanistic test. SGLT2 remains a proximal tubular transport target without hyperglycemia, so altered tubular signaling and single-nephron hemodynamics can still be proposed. Physiological modeling of hypertensive CKD predicts that SGLT2 inhibition can increase afferent resistance and lower glomerular pressure, but a simulated pressure change is not a measurement of pressure in trial participants. Mechanistic analyses of nondiabetic CKD also describe possible contributions from efferent responses and adaptive tubular handling; they do not establish that the same feedback response predominates across CKD etiologies. Kidney protection in people without diabetes validates a nonglycemic explanation, while leaving its precise partition among afferent feedback, efferent tone and other renal responses unresolved.

Accordingly, the clinically useful interpretation of an early eGFR fall is conditional: it is *consistent with* reduced intraglomerular filtration pressure, and longer-term preservation of kidney function makes that interpretation compelling at the population level. Neither an individual eGFR dip nor a reduction in albuminuria directly measures glomerular capillary pressure or proves restored feedback in that person. The most defensible judgment is **moderate mechanistic evidence for intraglomerular pressure reduction as a contributor to kidney protection; weaker evidence that adenosine-mediated afferent constriction specifically explains the benefit throughout advanced and nondiabetic CKD.**

3. What is the evidence that erythropoiesis, hematocrit rise, and improved oxygen delivery mediate cardiovascular and kidney benefit?

An increase in hemoglobin and hematocrit is a reproducible biological response to SGLT2 inhibition, including in chronic kidney disease (CKD); evidence for increased erythropoiesis makes simple hemoconcentration an incomplete explanation. The more consequential claim—that the additional red-cell mass or improved oxygen delivery *causes* fewer heart-failure events or slower kidney disease progression—has substantially weaker support. The strongest outcome-related signal is an exploratory mediation analysis in type 2 diabetes and established cardiovascular disease, not a trial that independently manipulated erythropoiesis.

Erythropoiesis versus hemoconcentration

A systematic review and meta-analysis of randomized trials in CKD found higher hemoglobin and hematocrit with SGLT2 inhibitors than with control treatment. It also identified a small canagliflozin trial in CKD that measured increases in reticulocytes and erythropoietin alongside the hematologic response. These observations support increased red-cell production as a contributor: contraction of plasma volume alone raises a concentration but does not explain reticulocytosis. Conversely, an erythropoietic response does not exclude a concurrent volume contribution to measured hematocrit, particularly early in treatment. **Evidence strength is moderate for a drug-induced rise in hemoglobin and hematocrit, and suggestive for erythropoiesis as an important contributor; the relative contribution of red-cell mass and plasma-volume change cannot be inferred from hematocrit alone.**

The erythropoietic explanation remains pertinent in advanced CKD, where an uncomplicated account based on substantial urinary sodium loss is less persuasive. Hematocrit increases have been described in stage 3b/4 CKD and renal anemia, despite diminished distal sodium delivery in these settings. That observation supports a mechanism extending beyond hemoconcentration, but it does not establish that every CKD phenotype has the same erythropoietin response or that correction of anemia accounts for kidney protection. Similarly, erythropoietic responses in patients with heart failure receiving loop diuretics argue against a single explanation based on increased distal tubular transport work, without identifying the operative signal.

What the cardiovascular mediation analysis establishes

In EMPA-REG OUTCOME, empagliflozin reduced cardiovascular death versus placebo in participants with type 2 diabetes and established cardiovascular disease: hazard ratio 0.62 (95% CI 0.49, 0.77). In a subsequent exploratory analysis, changes from baseline in hematocrit and hemoglobin statistically mediated 51.8% and 48.9%, respectively, of that treatment association. The investigators interpreted changes in markers of plasma volume as the most important candidate mediators. This is a substantial association between a treatment-responsive biomarker and a hard cardiovascular endpoint, but the

percentages are **statistical mediation estimates**, not demonstrated fractions of deaths prevented by enhanced erythropoiesis. Both hemoglobin and hematocrit respond to changes in red-cell mass *and* plasma volume; they can also track other treatment responses. Adjustment for a post-randomization variable does not reproduce a randomized comparison of patients with and without an erythropoietic response.

The distinction matters when extending the result beyond its trial population. EMPA-REG OUTCOME enrolled participants with type 2 diabetes and established cardiovascular disease; its cardiovascular-death mediation estimate should not be assigned to heart failure without diabetes or to CKD without diabetes. Heart-failure trials demonstrating benefit in patients with and without diabetes establish that glucose lowering is not required for clinical benefit, but do not determine how much of that benefit is attributable to red-cell production or oxygen delivery. Thus, evidence that erythropoiesis *mediates heart-failure outcomes* remains low-certainty, despite stronger evidence that the hematologic response occurs.

Oxygen delivery and kidney outcomes

Greater red-cell mass could increase oxygen-carrying capacity and potentially relieve myocardial or renal tissue hypoxia. Whether tissue oxygenation actually improves where it matters, and whether that improvement slows clinical disease, is a separate proposition. Mechanistic accounts disagree even about the renal oxygen signal: one attributes erythropoietin production to relief of cortical hypoxia and recovery of erythropoietin-producing cells; another proposes increased oxygen consumption and hypoxia near the corticomedullary junction after solute transport shifts downstream. A further analysis argues that neither a straightforward cortical-oxygenation explanation nor increased distal tubular workload adequately accounts for erythropoiesis across nondiabetic kidneys, advanced CKD and heart failure treated with loop diuretics, and proposes additional cellular signaling and possible hepatic erythropoietin synthesis. These are competing physiological explanations, not proof that better renal oxygen delivery mediates a kidney outcome.

The outcome anchor is nevertheless strong. In EMPA-KIDNEY, the composite of kidney disease progression or cardiovascular death occurred in 432 of 3304 participants (13.1%) receiving empagliflozin and 558 of 3305 (16.9%) receiving placebo: hazard ratio 0.72 (95% CI 0.64 to 0.82). Results were consistent with or without diabetes, and 3569 participants (54.0%) did not have diabetes. This demonstrates kidney protection without a requirement for glucose lowering; it does **not** identify erythropoiesis as the causal pathway. The CKD hematology trials establish a treatment effect on hemoglobin and hematocrit, whereas EMPA-KIDNEY establishes a treatment effect on clinical outcomes. Connecting those effects through improved renal oxygen delivery remains an inference rather than a tested clinical mediation result.

Overall, the evidence is strong that SGLT2 inhibition raises hemoglobin and hematocrit, moderate that increased erythropoiesis contributes to that rise, low that erythropoiesis or improved oxygen delivery mediates cardiovascular benefit, and very low that either mediates prevention of kidney failure. The hematologic response is therefore a credible component of the cardiorenal mechanism, but neither an established explanation for the treatment effect nor a validated surrogate for its magnitude in an individual patient.

4. Do shifts in substrate use and myocardial energetics (ketones, sodium-hydrogen exchange) have clinical-grade support, or only preclinical support?

Shifts in substrate availability have human biochemical support, but enhanced myocardial ketone oxidation is not an established mediator of clinical benefit. Direct cardiac sodium–hydrogen exchanger inhibition has weaker support: it remains predominantly a cellular and animal hypothesis, without confirmation as a clinically important mechanism in humans. These distinctions matter because SGLT2 inhibitors improve outcomes in heart failure and CKD, including in people without diabetes, but efficacy in those populations does not identify which nonglycemic pathway produced the benefit.

Ketones and myocardial energetics

SGLT2 inhibition can alter systemic fuel availability. Increased ketogenesis and circulating ketone concentrations offer a biologically plausible alternative fuel for a failing myocardium with impaired metabolic flexibility. Experimental work has reported greater cardiac use of ketones alongside other substrates and improved indices of myocardial energy supply in treated animals. This is evidence for *plausibility*, not for the proposition that ketones are the necessary—or dominant—link between SGLT2 inhibition and fewer heart-failure events.

The human evidence is narrower than the phrase “improved myocardial energetics” sometimes implies. A synthesis of **34 included studies, including 10 clinical and 24 animal studies**, reported metabolic changes broadly consistent with altered substrate use, but also noted **2 studies** in which cardiac ketone metabolism did not change significantly. Circulating metabolite measurements in heart failure can show that the drug changes the substrates available to the heart; concentrations alone cannot establish myocardial uptake, oxidation, ATP production or contractile efficiency. In particular, targeted plasma metabolomics does not measure metabolic flux, and experimental transcatheter findings cannot be assumed to describe the human failing heart. Thus, apparent disagreement between accounts describing a favorable fuel switch and more cautious interpretations largely reflects a difference in *what was measured*: biochemical availability or animal myocardial metabolism versus a demonstrated human myocardial mechanism.

Nor would greater ketone use, if established in a human subgroup, by itself prove mediation of clinical outcomes. The failing heart already uses ketones, and a change in ketone availability may accompany other treatment-induced changes rather than cause improved function. The small phase I investigation of exogenous ketone esters described in patients with heart failure with reduced ejection fraction examined responses according to background SGLT2-inhibitor use; giving an additional ketone substrate does not test whether SGLT2-inhibitor-derived ketones account for the drug's outcome-trial effects. **Evidence judgment:** moderate support that substrate availability and circulating metabolic profiles change; preclinical and limited translational support for a favorable myocardial fuel switch; insufficient clinical evidence that increased ketone oxidation mediates reductions in heart-failure hospitalization or cardiovascular death.

Cardiac sodium–hydrogen exchange

The cardiac sodium–hydrogen exchanger hypothesis proposes that an SGLT2 inhibitor inhibits cardiomyocyte NHE1, lowers intracellular sodium and thereby improves calcium handling and energetics. Reports of reduced cytosolic sodium and altered calcium handling arise principally from rat and mouse myocyte experiments, including work discussed as potentially relevant beyond diabetes. A review of direct cardiac mechanisms identifies NHE inhibition as an emerging possibility, not a demonstrated explanation for benefit in patients. A separate assessment explicitly notes that the initially proposed sodium–hydrogen exchanger inhibition has **not been confirmed**. These accounts need not be read as contradictory: an effect observed under experimental conditions can justify investigation without establishing that therapeutically exposed human myocardium exhibits a comparable effect, or that such an effect changes clinical events.

“Exchange inhibition” also requires anatomical precision. Proposed effects on renal tubular NHE3 and sodium transport are not evidence that cardiac NHE1 is inhibited in vivo. Even a reproducible change in cardiomyocyte sodium or calcium would remain an intermediate endpoint; assigning it a share of the benefit would require human target-engagement and mediation evidence linked to clinical outcomes. **Evidence judgment:** predominantly preclinical for direct cardiac NHE1 inhibition, with no clinical-grade demonstration that it mediates cardiovascular benefit.

Relevance across diabetes status and to kidney outcomes

The nonglycemic clinical effect is established more securely than either energetic mechanism. In EMPA-KIDNEY, the composite of kidney disease progression or cardiovascular death occurred in **432 of 3304 patients (13.1%)** receiving empagliflozin and **558 of 3305 patients (16.9%)** receiving placebo (hazard

ratio, 0.72; 95% CI 0.64 to 0.82); the trial reported consistent results in participants with and without diabetes. Heart-failure trials likewise demonstrated benefit in participants with and without diabetes. Those observations rule out glucose lowering as a complete explanation, but they do not distinguish ketone-mediated cardiac protection from other nonglycemic actions.

For the kidney, proposals that altered substrate utilization improves tubular energetics have still less direct clinical linkage than the cardiac fuel hypothesis. A kidney-mechanism review identifies optimization of energy substrate use and delivery as an emerging possibility while emphasizing that multiple mechanisms may contribute to protection. Physiological modeling in hypertensive, nondiabetic CKD also notes that metabolic hypotheses have largely been examined in diabetic animal models and that direct renal mechanisms in nondiabetic CKD remain unclear. **Evidence judgment:** outcome-trial support is strong for kidney protection without diabetes, but support for altered renal fuel use as its mediator remains experimental and hypothesis-generating. Across heart and kidney disease, altered energetics should therefore be described as a candidate pathway, not as a clinically proven explanation for the observed outcome reductions.

5. How strong is the evidence for anti-inflammatory, antifibrotic, and endothelial pathways relative to the hemodynamic and kidney hemodynamic effects already tied to trials?

Anti-inflammatory, antifibrotic and endothelial effects are biologically plausible, but none is established as a mediator of the cardiovascular or kidney outcome benefits. Their evidence is weaker than the evidence for renal and systemic hemodynamic responses: randomized mechanistic studies have measured changes in filling pressure, while clinical studies have documented blood-pressure and kidney-function responses; by contrast, inflammation, fibrosis and endothelial studies chiefly measure circulating or urinary biomarkers, and much of the tissue-specific work remains preclinical. Neither tier of mechanistic evidence, however, proves what proportion of the benefit in an outcome trial is mediated by its measured pathway.

Inflammation and tubular injury

The most clinically relevant inflammatory hypothesis is that reduced proximal-tubular transport stress attenuates kidney injury and its downstream inflammatory response. In a post hoc biomarker analysis of the randomized VERTIS RENAL study, participants had type 2 diabetes and stage 3 CKD; ertugliflozin was compared with placebo. A reduction in kidney injury molecule-1 (KIM-1) was interpreted as a possible early kidney-protective signal, but the analysis could not determine whether that change contributed to clinical kidney outcomes. A randomized study of urinary proteins in diabetic kidney disease likewise identified treatment-associated changes in proteins linked to inflammation and wound healing. Proteomic

enrichment identifies candidate processes, not a reduction in renal inflammatory-cell activity or mediation of kidney failure prevention.

In heart failure, SiN-HF reported suppression of soluble ST2 during SGLT2 inhibition and a correlation with improvement in left ventricular ejection fraction. Soluble ST2 is relevant to myocardial stress and remodeling, but its change does not establish that altering the underlying inflammatory or fibrotic process caused a clinical benefit; the investigators cautioned against strong mechanistic conclusions from their heterogeneous heart-failure population. A systematic review and meta-analysis reporting reductions in inflammatory markers after SGLT2 inhibition studied *rodents*. It strengthens preclinical plausibility, not clinical-grade evidence for prevention of heart-failure admission or CKD progression through cytokine suppression. **Evidence-strength judgment:** human evidence supports changes in selected injury and inflammatory-associated biomarkers; evidence that anti-inflammatory action independently mediates hard cardiovascular or kidney outcomes is **low**.

Fibrosis: plausible downstream consequence, unproved independent pathway

Less glomerular and tubular injury could eventually limit interstitial fibrosis, making antifibrotic effects compatible with sustained kidney protection. Compatibility is not a direct measurement of treatment-induced fibrosis regression. In a randomized diabetic kidney disease proteomics study, urinary collagen-derived peptides changed during SGLT2 inhibition, but some increased; greater peptide excretion could reflect altered collagen turnover rather than less tissue fibrosis. Experimental work in diabetic kidney disease models and cultured tubular cells identified an empagliflozin-associated pathway involving ESRRB and PKM2 and reported reduced renal fibrosis. That is **preclinical evidence in diabetic models**, not evidence that the same pathway accounts for protection in human CKD without diabetes. Other mouse and cell experiments implicate proximal-tubular Hmgcs2 and Btg2 and epithelial–macrophage signaling, again without establishing an effect on human kidney-failure outcomes.

This distinction matters when interpreting EMPA-KIDNEY. Empagliflozin reduced kidney disease progression or cardiovascular death compared with placebo—432 of 3304 participants (13.1%) versus 558 of 3305 (16.9%); hazard ratio, 0.72; 95% CI 0.64 to 0.82—with consistent findings in participants with and without diabetes. Secondary analyses found broadly similar proportional effects on kidney disease progression across primary kidney diagnoses, including nondiabetic causes. Those results make a mechanism dependent *exclusively* on diabetic hyperglycemia implausible. They do not identify fibrosis reversal as the mechanism shared across diagnoses: outcome events and kidney-function trajectories cannot distinguish direct antifibrotic action from less injury following altered glomerular or tubular physiology. **Evidence-strength judgment:** antifibrotic activity is supported by **preclinical experiments and exploratory human biomarkers**, but has **very low certainty as an independent mediator** of cardiovascular or kidney outcomes.

Endothelial and microvascular pathways in context

Improved endothelial function or microvascular health could, in principle, link kidney protection with reduced cardiac loading and remodeling. The clinical signal is less coherent than that proposition suggests. A review of vascular ion-channel studies notes that empagliflozin did not increase plasma nitrite or cGMP compared with placebo and slightly reduced nitrite—findings that do not substantiate a uniform nitric-oxide-mediated endothelial response. Experimental vascular or renal capillary findings and proposals concerning oxidative stress and microvascular function remain indirect for patients with heart failure or CKD without diabetes. Moreover, a vascular biomarker can change because blood pressure, flow or tissue injury has changed; that does not make the endothelium the initiating therapeutic target.

The comparator for these hypotheses is not a fully solved hemodynamic mechanism. A meta-analysis of three randomized invasive-hemodynamic studies, comprising 145 patients, found lower pulmonary capillary wedge pressure at rest and peak exercise with SGLT2 inhibitors, but could not establish that those pressure changes mediate clinical outcomes. Similarly, dapagliflozin lowered blood pressure during standardized sodium intake across diabetes and CKD strata without a sustained increase in sodium excretion, complicating a simple natriuresis-only explanation. Hemodynamic responses nevertheless have **more direct human physiological support** than tissue antifibrotic or endothelial explanations. For kidney disease, the large randomized outcome benefit, including in nondiabetic CKD, is secure; assigning it to any one downstream pathway is not. Anti-inflammatory, antifibrotic and endothelial effects should therefore be described as **candidate contributors or consequences of reduced cardiorenal injury**, rather than demonstrated explanations for the trial effects.

Certainty and limitations

Certainty is high that SGLT2 inhibition improves kidney outcomes beyond glucose lowering, but substantially lower for any single proposed mechanism. The clearest test of glycemia as a necessary explanation is efficacy in people without diabetes. In EMPA-KIDNEY, the primary composite of kidney disease progression or cardiovascular death occurred in 432 of 3304 participants (13.1%) assigned empagliflozin and 558 of 3305 (16.9%) assigned placebo (hazard ratio 0.72; 95% CI 0.64 to 0.82); effects were consistent with and without diabetes, and 3569 participants (54.0%) did not have diabetes. A meta-analysis of 10 randomized trials comprising 70 361 participants found less CKD progression with SGLT2 inhibitors than with placebo: 25.4 versus 40.3 events per 1000 patient-years (hazard ratio 0.62; 95% CI 0.57–0.68). These trials establish a treatment effect, not the fraction attributable to tubuloglomerular feedback, volume regulation, erythropoiesis, or another pathway. Similarly, randomized heart-failure trials establish benefit in people with and without diabetes, whereas analyses of kidney events within heart-

failure trials vary with event frequency, follow-up, and composite definitions; the prespecified renal composite in DAPA-HF was not significantly reduced.

Renal hemodynamic protection has moderate mechanistic support, not direct proof as the universal mediator of kidney benefit. Inhibition of proximal sodium–glucose reabsorption can increase macula-densa sodium delivery and lower intraglomerular pressure; an early fall in eGFR and subsequent improvement in the longer-term trajectory are physiologically concordant with that account. Its directness weakens when the explanation is extended from hyperfiltering diabetic kidneys to advanced or nondiabetic CKD. A physiological modeling study explored tubuloglomerular feedback in hypertensive nondiabetic CKD but cannot establish that the modeled response causes clinical benefit. A published critique argues that afferent-arteriolar feedback may be less important in advanced diabetic CKD and proposes other renal hemodynamic responses, including interaction with renin–angiotensin system blockade; that is a challenge to a universal afferent-vasoconstriction account, not a refutation of the outcome trials. The appropriate inference is that reduced intraglomerular pressure is a credible contributor whose operative vascular mechanism and relative importance may differ by CKD phenotype.

Evidence for a hemodynamic contribution to heart-failure benefit is moderate; evidence that sustained natriuresis alone explains it is weak. A meta-analysis of three randomized studies involving 145 participants found lower pulmonary capillary wedge pressure at rest and peak exercise with SGLT2 inhibition, directly supporting an effect on filling pressure but not identifying how much of the reduction in clinical heart-failure events it mediates. The distinction matters because proximal sodium transport inhibition need not produce persistent net sodium loss: a critical synthesis found no consistent large acute or chronic natriuresis or diuresis across clinical settings. Under standardized sodium intake, mechanistic studies in CKD without diabetes found lower blood pressure without increased 24-hour sodium or volume excretion; a pooled DAPASALT analysis likewise reported blood-pressure reduction without increased natriuresis across diabetes and CKD strata. Compensation can therefore coexist with a hemodynamic treatment effect. Nor should a modest blood-pressure difference be treated as a complete account of kidney protection: the overall systolic difference in EMPA-KIDNEY was -2.6 mm Hg (95% CI -3.3 to -1.9) versus placebo. Congestion relief, vascular effects, and intrarenal responses remain plausible jointly rather than competing as a demonstrated single cause.

Hematocrit rise is a well-supported drug response but an uncertain causal mediator. A systematic review and meta-analysis of randomized CKD studies assessed hemoglobin and hematocrit changes, while physiological accounts distinguish red-cell production from hemoconcentration and caution against interpreting either from hematocrit alone. In an exploratory post hoc analysis of EMPA-REG OUTCOME, changes in hematocrit and hemoglobin statistically mediated 51.8% and 48.9%, respectively, of the effect of empagliflozin versus placebo on cardiovascular death when assessed as changes from baseline. Those percentages are model-dependent associations, **not** experimentally established shares of the survival benefit due to erythropoiesis or improved oxygen delivery. Hematocrit reflects both red-cell mass

and plasma volume; changes in each may accompany several treatment effects. The analysis also concerned cardiovascular death in type 2 diabetes with established cardiovascular disease, so it cannot be transferred quantitatively to heart failure or CKD without diabetes.

Myocardial substrate switching and sodium–hydrogen exchange have lower clinical mechanistic certainty. A review encompassing 10 clinical and 24 animal studies found metabolic signals consistent with altered fuel use, but this mixture of designs does not show that myocardial ketone oxidation mediates fewer cardiovascular events. Animal experiments reporting changes in cardiac substrate use and ATP content supply biological plausibility, not an effect size for human heart-failure outcomes. Circulating metabolite concentrations do not measure myocardial substrate flux, and a review of human metabolomic work noted that the proposed sodium–hydrogen exchanger mechanism had not been confirmed. Cell and animal observations concerning cardiomyocyte sodium handling must therefore remain preclinical mechanistic evidence rather than a clinical-grade explanation.

Anti-inflammatory, antifibrotic, and endothelial explanations are less directly tied to outcomes than the renal and systemic hemodynamic hypotheses. Exploratory analyses in randomized diabetic CKD cohorts identify changes in injury, inflammation, or fibrosis-related biomarkers, but they do not establish that altering those biomarkers prevents kidney failure. A heart-failure biomarker investigation reported suppression of sST2 correlated with improvement in left ventricular ejection fraction; correlation between two responses to treatment does not establish mediation of hospitalization or mortality. Experimental diabetic-kidney work identifies candidate fibrosis pathways, while a meta-analysis of inflammatory markers was conducted in rodents, not in patients experiencing clinical events. Even for vascular pathways, reported clinical endothelial measurements are not uniformly supportive. The principal risk of bias across these mechanistic claims is not necessarily bias in the large randomized outcome trials: it is **causal overinterpretation of smaller, short-duration, exploratory or post hoc measurements.** Trial concordance across diabetes status strongly excludes glucose lowering as a sufficient explanation, but it does not select a single nonglycemic pathway as necessary or dominant.

Clinical reasoning

1. Frame the question as an inference about mechanism, not a requirement to identify a single mediator before treatment. For a clinician, the operative decision is whether an SGLT2 inhibitor is likely to improve a patient's heart-failure or kidney prognosis in the relevant disease phenotype, even when glucose lowering is absent or attenuated. For a researcher, it is which physiological changes can reasonably be described as mediators of that benefit. The standards differ: randomized outcome trials can establish that treatment improves outcomes in a population; they do not, without additional evidence, establish which treatment-induced change caused the improvement. The strongest test of a proposed glucose-independent mechanism is therefore a combination of benefit in people without diabetes, a reproducible

physiological effect in humans, and a plausible relationship between that effect and the clinical endpoint. DAPA-CKD and EMPA-KIDNEY establish the importance of the first test for kidney protection, while heart-failure trials extend the inference beyond a glucose-lowering indication.

2. Match the outcome evidence to the population before interpreting physiology. The distinction between type 2 diabetes with established cardiovascular disease, symptomatic heart failure, and progressive CKD matters more than a generic label of “cardiorenal benefit.” In EMPA-REG OUTCOME, the cardiovascular-death finding came from 7,020 participants with type 2 diabetes and established cardiovascular disease: empagliflozin versus placebo yielded a hazard ratio of 0.62 (95% CI 0.49, 0.77) for cardiovascular death. That result should not be presented as the expected mortality effect in every person with CKD. Conversely, EMPA-KIDNEY directly tested kidney outcomes in CKD with and without diabetes. Its primary outcome of kidney disease progression or cardiovascular death occurred in 432 of 3304 participants (13.1%) assigned empagliflozin and 558 of 3305 (16.9%) assigned placebo; hazard ratio 0.72 (95% CI 0.64 to 0.82). The effect was consistent by diabetes status, and 3569 participants (54.0%) did not have diabetes. The trial’s composite result was driven mainly by slowing kidney disease progression, not by proof of a comparably sized cardiovascular effect in every nondiabetic CKD subgroup.

This population match changes the mechanistic interpretation. Benefit in nondiabetic CKD makes correction of hyperglycemia an untenable *necessary* explanation for kidney protection. It does not prove that the same intrarenal pathway dominates in diabetic hyperfiltration, advanced CKD and every nondiabetic kidney disease. Similarly, heart-failure benefit in people without diabetes supports a nonglycemic cardiac or systemic action, but cannot distinguish unloading from renal preservation, erythropoiesis or a direct myocardial effect merely because each is biologically plausible. A randomized-trial meta-analysis of kidney outcomes provides an additional check on generalizability: CKD progression occurred at 25.4 versus 40.3 events per 1000 patient-years with SGLT2 inhibition versus control, hazard ratio 0.62 (95% CI 0.57–0.68), across the trials pooled. That is strong evidence for the *clinical effect*, not for one exclusive mediator.

3. Rank mechanisms by the distance between their measurement and the clinical endpoint. Renal proximal-tubule inhibition is the established initiating pharmacology. Reduced sodium–glucose reabsorption can increase macula-densa solute delivery, engage tubuloglomerular feedback and lower glomerular capillary pressure. An early fall in eGFR followed by slower subsequent loss of filtration is compatible with such a hemodynamic reset rather than, by itself, evidence of tubular injury. The confidence levels must nevertheless be separated. Confidence that SGLT2 inhibitors slow clinically important CKD progression, including without diabetes, is **high** because it rests on randomized outcomes. Confidence that lower intraglomerular pressure contributes is **moderate**: it is supported by pharmacology and human physiological observations but is not established as the sole cause of fewer kidney failures. Confidence in the narrower claim that *afferent vasoconstriction caused by restored tubuloglomerular feedback* explains protection in all CKD is **low**. Renal hemodynamic responses may differ in type 2

diabetes and advanced CKD, with postglomerular effects also proposed; physiological modeling in nondiabetic hypertensive CKD cannot substitute for direct demonstration in the full outcome-trial population.

For heart failure, separate an initial renal response from sustained net salt loss. Small randomized studies support a change in filling pressures: a meta-analysis of three invasive-hemodynamic studies encompassing 145 participants found lower pulmonary capillary wedge pressure at rest and peak exercise with SGLT2 inhibition. Proximal natriuresis, osmotic water loss, changes in plasma or interstitial volume, and lower blood pressure provide a credible route to reduced preload or afterload. Yet reviews of measured sodium and water balance do not find a consistently large, persistent diuretic effect; distal-nephron and neurohormonal compensation matter. Under standardized sodium intake, dapagliflozin lowered blood pressure without increasing measured 24-hour sodium or volume excretion in nondiabetic CKD, and the broader DAPASALT analysis reached a similar conclusion across diabetes and CKD strata. Thus confidence is **moderate** that altered volume distribution and loading conditions contribute to heart-failure benefit, but **low** that sustained natriuresis alone explains the outcome-trial effects. The clinical mistake would be to treat an SGLT2 inhibitor as either an inert drug in a patient without glycosuria or an interchangeable substitute for a loop diuretic in overt congestion.

Erythropoiesis is a distinct, credible physiological response, not simply a synonym for volume contraction. An increase in hemoglobin and hematocrit during SGLT2 inhibition has been documented in CKD trials, and evidence reviewed from studies measuring erythropoietin, reticulocytes and red-cell mass supports increased red-cell production as at least part of that response. The tempting outcome link comes from an exploratory EMPA-REG OUTCOME mediation analysis: changes from baseline in hematocrit and hemoglobin statistically mediated 51.8% and 48.9%, respectively, of the empagliflozin-versus-placebo cardiovascular-death effect. Those percentages are **not** estimates of the fraction of deaths prevented by *oxygen delivery*. Hematocrit also reflects plasma-volume changes and may track other treatment responses; post-randomization mediator analyses cannot isolate a causal pathway. Confidence that erythropoiesis occurs is **moderate to high**; confidence that it mediates a clinically important proportion of cardiovascular or kidney protection is **low**.

Apply a more demanding standard to direct myocardial and cellular explanations. Altered ketone availability, myocardial substrate selection and sodium–hydrogen exchange offer coherent hypotheses, but much of the evidence linking them to energetics and remodeling comes from animal experiments, cellular models or blood-metabolite measurements rather than demonstrated mediation of clinical events in humans. In particular, a circulating substrate concentration is not myocardial substrate flux, and proposed cardiac sodium–hydrogen-exchanger inhibition has not been confirmed as the explanation for heart-failure outcomes. Likewise, human inflammation-, fibrosis- and endothelial-related biomarker observations are hypothesis-generating; experimental renal antifibrotic effects do not establish that fibrosis reversal caused fewer kidney failures in patients. Confidence in these pathways as explanations

of trial outcomes is **low or preclinical**, below confidence in an intrarenal hemodynamic contribution or altered loading conditions. They should be prespecified as mechanisms to test, not used as proven reasons to select one eligible patient over another.

4. Weigh benefit against risk without confusing a mechanistic marker for a treatment target. The absolute EMPA-KIDNEY event proportions—13.1% with empagliflozin versus 16.9% with placebo over a median 2.0 years—are useful for discussing the trial’s kidney-dominant composite in a comparable CKD population. They must not be transferred to a patient whose underlying progression risk differs. Neither a large hematocrit rise nor a conspicuous early eGFR dip is required to declare treatment effective. Conversely, a favorable mechanistic change cannot outweigh a contraindication or an intolerable adverse effect. Before prescribing, assess the indication and kidney-function range, volume status and blood pressure, concurrent diuretics and renin–angiotensin-system treatment, and susceptibility to dehydration or ketoacidosis. Genital infection and hypovolemia are recognized treatment harms to consider alongside cardiorenal benefit. In an acutely unwell or fasting patient, evaluate the risk of ketoacidosis and temporarily withhold treatment when clinically indicated; a normal or only modestly elevated glucose level does not exclude that complication.

5. Apply the evidence using outcome eligibility, then monitor for predictable physiology. For an eligible person with heart failure or CKD, diabetes status is not a prerequisite for expecting benefit. Select an agent and indication supported by the relevant outcome-trial population and current prescribing requirements rather than choosing according to an unvalidated ketone, hematocrit or inflammatory “responder” phenotype. Record baseline kidney function, albuminuria when evaluating CKD, blood pressure and volume status; reconcile diuretics and other therapies. After initiation, reassess symptoms, blood pressure, volume status and kidney function in the context of the patient’s clinical risk. Interpret an early filtration change together with perfusion, intercurrent illness and its subsequent trajectory; do not automatically call it progressive kidney injury, but do not assume every creatinine rise is benign. In a congested patient, adjust conventional diuresis according to congestion rather than presuming SGLT2 inhibition will produce sustained sodium loss. Persistent intolerance, symptomatic volume depletion or suspected ketoacidosis warrants reassessment or interruption independently of any favorable biomarker change.

For research, the actionable counterpart is to prespecify mediator measurements at appropriate times: early renal hemodynamics and volume measures, later erythropoietic measures, and endpoints capable of distinguishing kidney progression from cardiovascular events. Analyses must account for changing concomitant diuretics, renin–angiotensin-system blockade and baseline CKD phenotype. A treatment-associated marker that predicts outcomes is not, without a suitable causal design, proof that manipulating that marker reproduces the drug’s benefit.

6. Check the facts that would change the inference. Confirm whether the clinical question concerns

established heart failure, CKD at risk of progression, or cardiovascular risk in type 2 diabetes; whether diabetes is present; the eGFR and albuminuria phenotype; and whether congestion, hypotension, acute illness or competing safety risks alter the immediate prescribing decision. These facts determine which trial comparison is closest. Avoid three common readings of the evidence: attributing nondiabetic benefit to improved glycemia; equating an early eGFR dip with proof of one specific arteriolar response; and converting statistical mediation by hematocrit into demonstrated benefit from increased oxygen delivery. Equally, absence of sustained urinary natriuresis does not refute a transient hemodynamic contribution or the randomized heart-failure benefit.

Illustrative scenario — diabetes status changes. Consider two otherwise comparable people with trial-eligible progressive CKD, differing only in whether type 2 diabetes is present. Diabetes may alter glycosuria and the balance of candidate mechanisms, but it does not change the conclusion that kidney-outcome benefit can be expected in an eligible person without diabetes: EMPA-KIDNEY observed a consistent primary-outcome effect by diabetes status. Neither person needs a demonstrated hematocrit or ketone response before treatment is considered.

Illustrative scenario — congestion changes. Consider two otherwise comparable people with heart failure, one clinically congested and the other euvolemic. Both may be candidates for outcome-directed SGLT2 inhibition, but the congested patient additionally requires assessment and treatment of current fluid overload. Evidence of modest filling-pressure improvement does not justify replacing effective decongestion with an assumption of sustained SGLT2-induced natriuresis. In the euvolemic patient, reassess volume and blood pressure after starting rather than escalating diuresis solely because the new drug acts in the nephron.

Illustrative scenario — CKD stage changes. Consider two otherwise comparable people with CKD and the same diabetes status, differing in whether kidney function is relatively preserved or substantially reduced. The rationale for lowering glomerular pressure may remain relevant to both, but a textbook afferent-arteriolar tubuloglomerular-feedback account becomes less secure in advanced CKD; it should not be used to predict that the latter person cannot benefit. Match each patient's kidney function and albuminuria to the studied and permitted treatment range, then judge treatment by clinical benefit and tolerability rather than by whether one proposed physiological pathway can be demonstrated.

What this means in practice

Use cardiovascular and kidney indications, not glucose lowering, to frame the expected benefit.

Randomized CKD evidence extends to people without diabetes: in EMPA-KIDNEY, kidney disease progression or cardiovascular death occurred in 432 of 3304 participants (13.1%) assigned empagliflozin

and 558 of 3305 (16.9%) assigned placebo (hazard ratio 0.72; 95% CI 0.64 to 0.82), with consistent results by diabetes status. This is strong evidence for a clinical effect beyond glucose lowering, but it does not identify a single responsible pathway. For a person with heart failure or CKD, a small anticipated glycemic effect should therefore not be mistaken for a small anticipated cardiorenal effect.

Expect a hemodynamic contribution to heart-failure benefit, but do not treat SGLT2 inhibitors as interchangeable with loop diuretics. Proximal tubular sodium–glucose transport inhibition provides a credible route to changes in volume distribution, filling pressures and blood pressure. A meta-analysis of randomized invasive-hemodynamic studies found lower pulmonary capillary wedge pressure at rest and peak exercise, although it included only 3 studies and 145 patients. The evidence is stronger for a treatment effect on hemodynamics than for sustained natriuresis as the dominant explanation of fewer heart-failure events. A critical synthesis found no consistent large, persistent diuresis or natriuresis; in CKD without diabetes, dapagliflozin lowered blood pressure during standardized sodium intake without increasing 24-hour sodium or volume excretion. Continue to assess congestion and adjust conventional diuretic treatment according to the clinical volume state rather than assuming an SGLT2 inhibitor provides equivalent decongestion.

Interpret the early eGFR change in the context of longer-term kidney protection. Reduced proximal sodium reabsorption can increase macula-densa delivery and lower glomerular filtration pressure; this is a biologically well-supported explanation for an initial filtration change followed by slower kidney-function decline. The kidney outcome benefit itself has high-certainty randomized support across diabetic and nondiabetic CKD populations. Attribution specifically to afferent arteriolar tubuloglomerular feedback is less certain in advanced CKD and type 2 diabetes, where postglomerular effects and background renin–angiotensin-system blockade may matter. Thus, an early eGFR decline should be evaluated alongside volume status and the subsequent trajectory, not automatically equated with progressive kidney injury; equally, an early decline cannot be used as proof that tubuloglomerular feedback mediated that individual's benefit.

Do not convert biomarker or experimental hypotheses into treatment targets. Hemoglobin and hematocrit increases are reproducible in CKD trials, and enhanced erythropoiesis may contribute alongside volume change. Yet the often-cited EMPA-REG OUTCOME analysis was exploratory: changes in hematocrit and hemoglobin statistically mediated 51.8% and 48.9%, respectively, of the empagliflozin-versus-placebo effect on cardiovascular death in its change-from-baseline models. Those percentages do not establish that raising either measure causes the survival benefit. Hematocrit is consequently not a validated target for titrating SGLT2 inhibition. Proposed ketone-fuel and myocardial sodium–hydrogen-exchange mechanisms have still weaker clinical causal support; changes in circulating metabolites do not establish improved myocardial energy flux, and direct sodium–hydrogen-exchange inhibition has not been confirmed as the explanation of heart-failure outcomes. Likewise, inflammatory and fibrosis biomarkers may illuminate biology, but neither their change nor an experimental antifibrotic effect

currently substitutes for demonstrated cardiovascular or kidney outcomes.

Open questions

- **How much heart-failure benefit is actually mediated by altered filling pressure or volume distribution?** The invasive-hemodynamic signal is based on small randomized studies, whereas natriuretic responses vary by setting and duration. A larger randomized mechanistic trial spanning heart-failure phenotypes and diabetes status, with serial directly measured plasma and interstitial volume, invasive exercise filling pressures, and prespecified clinical-event follow-up, could test whether sustained hemodynamic change lies on the causal path to benefit rather than merely accompanying it.
- **Which renal vascular response dominates in nondiabetic and advanced CKD?** Tubuloglomerular feedback is plausible, but models of nondiabetic CKD are indirect evidence, and afferent-versus-efferent explanations remain contested in advanced diabetic CKD. Randomized physiology studies stratified by CKD cause, filtration level, albuminuria and renin–angiotensin-system blockade could combine measured GFR and renal plasma flow with acute drug withdrawal and re-exposure. Linking those measurements prospectively to eGFR slope and kidney events would test whether the proposed pressure change predicts protection.
- **Does erythropoiesis cause benefit, and does myocardial substrate use change enough to matter?** Hematocrit mediation is observational within a randomized treatment comparison, while metabolite concentrations cannot establish myocardial substrate flux. Serial red-cell-mass and erythropoietin measurements paired with cardiovascular and kidney outcomes could distinguish erythropoiesis from hemoconcentration. For energetics, randomized human studies need direct myocardial flux and energetic measurements, not circulating ketones alone, linked to remodeling and clinical outcomes.
- **Are anti-inflammatory, antifibrotic or endothelial effects independent mediators rather than downstream consequences?** Biomarker studies in heart failure and diabetic CKD suggest candidate pathways, while direct evidence of reduced renal fibrosis in patients remains unestablished. Prespecified biomarker and tissue- or imaging-based substudies embedded in outcome trials—including participants without diabetes—would be more informative if they measured pathway change before organ-function change and tested whether that change explains subsequent clinical events.