

The Comparative Impact of Immunomodulatory Therapies on The Progression of Chronic Kidney Disease and Cardiovascular Outcomes in Patients with Type 2 Diabetes: A Systematic Review

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ABSTRACT

Background: Chronic low-grade inflammation contributes to diabetic kidney disease and atherosclerotic events in type 2 diabetes (T2D), but evidence for immunomodulatory therapy is fragmented across agents and outcomes.

Objective: To compare the effects of immunomodulatory therapies on chronic kidney disease (CKD) progression and cardiovascular outcomes in adults with T2D.

Methods: Following PRISMA 2020, we included randomized trials and observational studies published from 2009 to 2026 that evaluated pentoxifylline, colchicine, interleukin-1 or interleukin-6 inhibitors, methotrexate, or Janus kinase inhibitors in adults with T2D. Risk of bias was assessed with RoB 2 and ROBINS-I, certainty with GRADE, and results were synthesized narratively because pooling was inappropriate.

Results: Eleven studies were included (eight randomized trials, two randomized-trial subgroup analyses, one cohort). In advanced diabetic CKD, pentoxifylline slowed estimated glomerular filtration rate decline (–2.1 vs –6.5 mL/min/1.73 m² over 24 months in one trial) and reduced albuminuria, whereas one short trial in early disease was null. Colchicine reduced cardiovascular events after myocardial infarction (HR 0.65, 95% CI 0.44–0.96). Canakinumab showed a similar but imprecise effect in diabetes (HR 0.85, 0.70–1.03); methotrexate was neutral (HR 1.01, 0.82–1.25). Baricitinib lowered albuminuria by 41%.

Conclusions: Effects are agent-specific. Pentoxifylline slowed CKD progression and reduced albuminuria, and colchicine reduced cardiovascular events in T2D; canakinumab showed a directionally consistent but imprecise benefit, methotrexate was neutral, and baricitinib lowered albuminuria. Certainty is low to moderate, and adequately powered T2D-specific trials with hard outcomes are needed.

Keywords: pentoxifylline; colchicine; chronic kidney disease; cardiovascular outcomes; type 2 diabetes; anti-inflammatory therapy.

INTRODUCTION

Type 2 diabetes (T2D) is one of the most common chronic diseases worldwide, and its prevalence is projected to keep rising, with more than half a billion adults currently affected.⁽¹⁾ Chronic kidney disease (CKD) is among its most frequent and consequential complications, and diabetes is now a leading cause of CKD and kidney failure across regions.^(2,3) Because T2D is largely managed in primary care and general internal medicine, prevention of kidney and cardiovascular complications is a daily clinical priority rather than a subspecialty concern.

Kidney disease and cardiovascular disease in T2D are tightly linked. Albuminuria and a reduced estimated glomerular filtration rate (eGFR) independently predict myocardial infarction, stroke, heart failure, and death, and risk rises as kidney function declines.⁽⁴⁾ Contemporary guideline-directed care, which combines renin-angiotensin system (RAS) blockade, sodium-glucose cotransporter-2 inhibitors, and other organ-protective agents with glycemic and blood pressure control, lowers but does not abolish this risk.⁽⁵⁾ A substantial residual burden of kidney failure and cardiovascular events therefore remains, which motivates the search for therapies that act on additional disease mechanisms.

Chronic low-grade inflammation is one such mechanism. T2D is characterized by activation of innate immunity and by elevated circulating interleukin (IL)-1 β , IL-6, and tumor necrosis factor- α , which contribute to insulin resistance and vascular injury.⁽⁶⁾ In the kidney, inflammatory cytokines, chemokines, and adhesion molecules promote macrophage infiltration, endothelial dysfunction, mesangial expansion, and tubulointerstitial fibrosis, and these processes accompany the progression of albuminuria and the loss of eGFR.^(7,8)

The same inflammatory axis, running from IL-1 β through IL-6 to C-reactive protein, has been proposed as a causal and druggable pathway in atherothrombosis.⁽⁹⁾ Clinical proof of principle has come from trials of colchicine, an inexpensive anti-inflammatory agent that reduced recurrent cardiovascular events after myocardial infarction and in chronic coronary disease.^(10,11) These observations raised the question of whether anti-inflammatory strategies can deliver cardiorenal benefit in the high-risk, inflammation-prone population with T2D.

Several immunomodulatory and anti-inflammatory agents have been tested in this setting, each acting on a different part of the inflammatory network. Pentoxifylline, a nonselective phosphodiesterase inhibitor with anti-inflammatory and antifibrotic properties, has been studied mainly for its antiproteinuric and renoprotective effects in diabetic kidney disease.^(12,13) Colchicine, IL-1 β and IL-6 inhibitors, low-dose methotrexate, and Janus kinase inhibitors have been evaluated for cardiovascular or kidney end points, usually within larger programs in which T2D represented all or only part of the study population.

Despite this activity, the evidence remains fragmented. Kidney-focused trials are typically small, single-center, and short, and they rely on surrogate markers such as albuminuria and eGFR slope, whereas cardiovascular trials are larger but often enroll mixed populations in which T2D is a subgroup. Agents differ in mechanism, outcome definitions, and follow-up, and we identified no recent review that examined them side by side across both kidney and cardiovascular outcomes in people with T2D. This gap limits the ability of internal medicine and family medicine clinicians to judge which, if any, anti-inflammatory add-on therapy is supported by evidence.

Accordingly, the aim of this systematic review was to synthesize and compare the available evidence on the effects of immunomodulatory therapies on CKD progression and cardiovascular outcomes in adults with T2D, to appraise the risk of bias and certainty of that evidence, and to identify which agents show consistent signals that justify further large-scale trials or cautious clinical consideration.

METHODS

Protocol and reporting

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement⁽¹⁴⁾.

Eligibility criteria

The review question was structured using the PICO framework:

- **Population:** adults (≥ 18 years) with T2D, with or without CKD or established cardiovascular disease, as managed in internal medicine and family medicine settings. Mixed populations

were eligible only when T2D-specific results or a clearly defined T2D proportion were reported.

- **Intervention/exposure:** immunomodulatory or anti-inflammatory agents: pentoxifylline, colchicine, IL-1 inhibitors (canakinumab, anakinra), IL-6 inhibitors (tocilizumab, ziltivekimab), low-dose methotrexate, and Janus kinase inhibitors (baricitinib).
- **Comparator:** placebo, usual care or no add-on therapy, an active comparator, or non-users.
- **Outcomes:** kidney outcomes (change in eGFR, albuminuria or proteinuria, doubling of serum creatinine, kidney failure) and cardiovascular outcomes (major adverse cardiovascular events, cardiovascular death, myocardial infarction, stroke, heart failure, and vascular or cardiac surrogates such as carotid intima-media thickness and left ventricular mass index). Safety outcomes were extracted when reported.

Inclusion criteria: randomized controlled trials, cohort, case-control, cross-sectional, and case-series studies; peer-reviewed full-text articles in English; human studies published between January 2009 and April 2026.

Exclusion criteria: type 1 diabetes or non-diabetic CKD populations only; corticosteroids or other systemic immunosuppressants used for glomerular disease; reviews, editorials, conference abstracts, study protocols, and preclinical studies; reports without extractable kidney or cardiovascular outcomes; and overlapping reports of the same participants (the report with T2D-specific data was retained).

Information sources and search strategy

The search was executed from February 2026 to April 2026, covering publications from January 2009 to April 2026. No date restriction was applied to trial register entries. Sources used for this review were PubMed/MEDLINE-indexed articles and PubMed Central full texts, Embase, Scopus, Cochrane CENTRAL, publisher platforms, and trial registers (ClinicalTrials.gov and the European Union Clinical Trials Information System).

Reference lists of included studies and relevant reviews were screened manually. The core search string, adapted to each source, combined three concept blocks: (“type 2

diabetes” OR “diabetic kidney disease” OR “diabetic nephropathy”) AND (pentoxifylline OR colchicine OR canakinumab OR anakinra OR tocilizumab OR ziltivekimab OR methotrexate OR baricitinib OR “anti-inflammatory” OR immunomodulat*) AND (“chronic kidney disease” OR albuminuria OR proteinuria OR “glomerular filtration rate” OR “cardiovascular events” OR “major adverse cardiovascular events” OR “carotid intima-media thickness”).

Study selection and data extraction

Titles and abstracts were screened against the eligibility criteria, and full texts of potentially eligible reports were then assessed. Screening and data extraction were performed by two reviewers, and every extracted value was verified against the source publication. Extracted items were first author, year, country, design, population and T2D proportion, sample size, intervention and comparator, follow-up, kidney and cardiovascular outcomes, safety findings, and the authors’ conclusions.

Risk of bias assessment

Randomized trials and randomized-trial subgroup analyses were appraised with the Cochrane RoB 2 tool across five domains (randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting)⁽¹⁵⁾. The cohort study was appraised with ROBINS-I.⁽¹⁶⁾ Judgments were made from the published reports and are provisional pending independent duplicate assessment.

Data synthesis

Meta-analysis was planned if at least two studies evaluated the same agent and outcome with sufficiently similar populations, outcome definitions, and follow-up, and reported usable effect sizes with measures of variance (random-effects model, with heterogeneity assessed by I^2). Otherwise, results were synthesized narratively, grouped by agent and outcome domain, following the Synthesis Without Meta-analysis (SWiM) guideline⁽¹⁷⁾. Publication bias was to be explored only if ten or more studies contributed to an outcome.

Certainty of evidence

The certainty of evidence for each agent-outcome pair was rated as high, moderate, low, or very low using the GRADE approach,

considering risk of bias, inconsistency, indirectness, imprecision, and publication bias⁽¹⁸⁾.

RESULTS

Study selection

The search identified 28 records (25 from bibliographic sources and 3 from trial registers). No duplicate records were removed. After title and abstract screening, 11 records were

excluded, and 17 reports were sought for retrieval. One report could not be retrieved, 16 were assessed in full text, and 5 were excluded (3 overall-population reports without T2D-specific data, 1 report with a biomarker-only outcome and an unverifiable T2D share, and 1 report with participants overlapping an included trial). Eleven studies were therefore included (Figure 1)⁽¹⁴⁾.

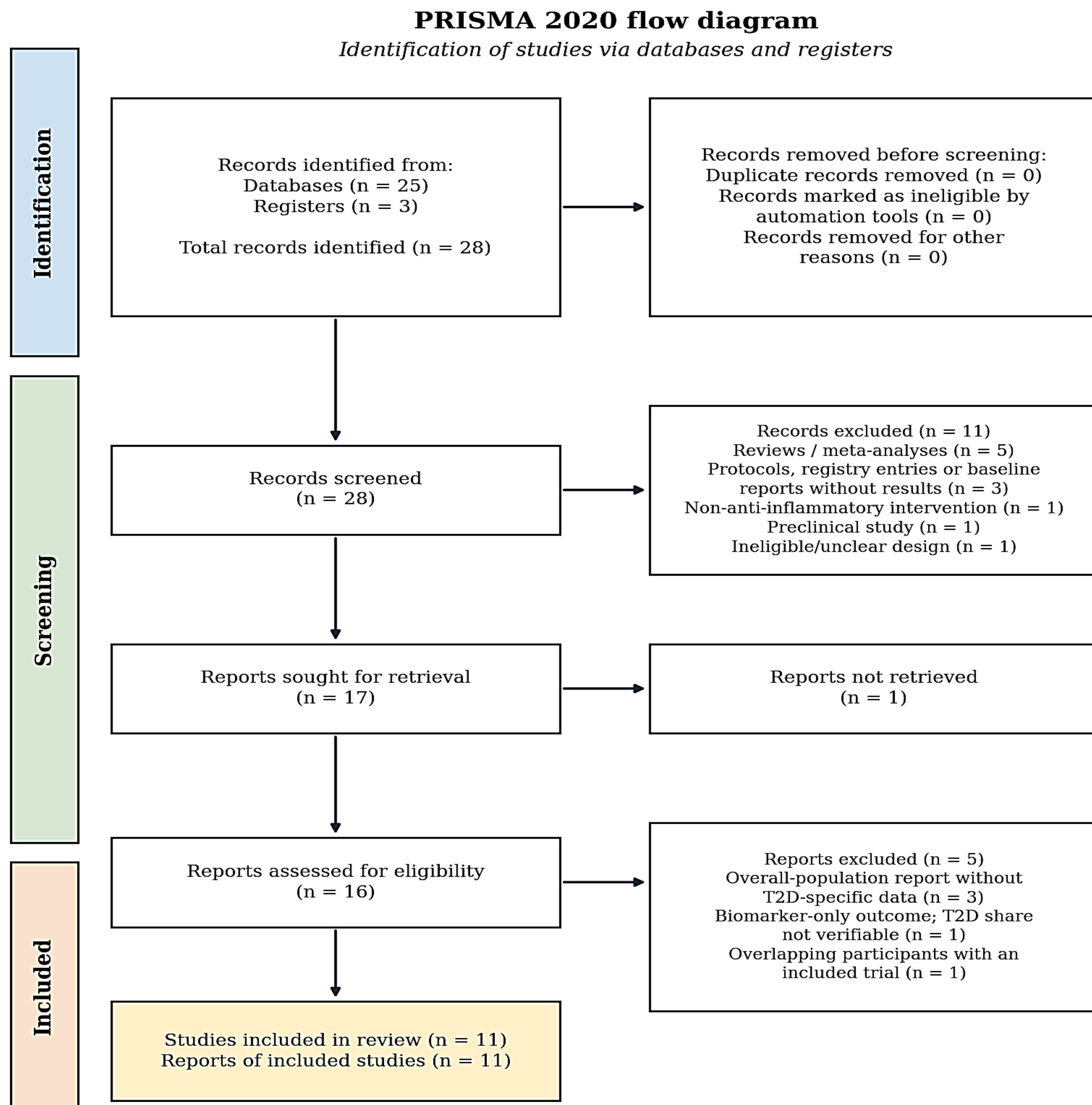


Figure 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Characteristics of included studies

The 11 included studies comprised eight randomized trials (seven in T2D-specific populations and one in a mixed population), two prespecified subgroup analyses of randomized trials, and one retrospective cohort; no case-control, cross-sectional, or case-series study met the criteria. They were published between 2015 and 2026 (Table 1). Seven studies evaluated pentoxifylline⁽¹⁹⁻²⁵⁾, and one study

each evaluated colchicine⁽²⁶⁾, canakinumab⁽²⁷⁾, methotrexate⁽²⁸⁾, and baricitinib⁽²⁹⁾. In randomized trials, sample sizes ranged from 40 to 4,786 participants and follow-up from 3 months to a median of 3.7 years. T2D made up 100% of the population in eight studies, about 68% in the methotrexate trial, and 40.3% (diabetes at baseline) in the canakinumab trial; the cohort did not stratify by diabetes type.

Table 1. Characteristics of the included studies

Study	Design; setting	Population (n; T2D share)	Intervention vs comparator	Follow-up
Navarro-González et al. (2015) ⁽¹⁹⁾	Open-label RCT (PREDIAN); Spain, single center	T2D with CKD stages 3–4 on RAS blockade; n = 169 (PTF 82, control 87); mean eGFR $\approx$ 37 mL/min/1.73 m ² ; T2D 100%	Pentoxifylline (PTF) 1200 mg/day + RAS blockade vs RAS blockade alone	24 months
Han et al. (2015) ⁽²⁰⁾	Double-blind placebo-controlled RCT; Korea, multicenter	T2D with albuminuria (UACR>30 mg/g) on ACEI/ARB; n = 174 (87/87); T2D 100%	PTF 400 mg three times daily vs placebo	6 months
Shahidi et al. (2015) ⁽²¹⁾	Double-blind placebo-controlled RCT; Iran	T2D with microalbuminuria and eGFR>60; n = 40 (20/20); T2D 100%	PTF (1200 mg/day) vs placebo, add-on to usual care	6 months
Shayanpour et al. (2024) ⁽²²⁾	Double-blind RCT (country not verified)	T2D nephropathy, albuminuria 30–300 mg/24 h on RAS blockers; n = 58 (29/29); T2D 100%	PTF 400 mg/day vs placebo	3 months
Donate-Correa et al. (2024) ⁽²³⁾	Open-label three-arm pilot RCT; Spain, single center	T2D with CKD stage 3 (eGFR 30–59) on RAS blockers and statins, no clinical ASCVD; n = 102; T2D 100%	PTF vs aspirin vs usual care	18 months
Mejía-Rodríguez et al. (2026) ⁽²⁴⁾	Double-blind placebo-controlled RCT, per-protocol analysis; Mexico	Diabetic nephropathy, CKD stages III–IV (T2D keyworded); n = 93 analyzed (PTF 52, placebo 41)	PTF 400 mg every 8 h vs placebo	12 months
Wang et al. (2024) ⁽²⁵⁾	Retrospective cohort with mechanistic experiments; Taiwan	DKD (diabetes + CKD) without established CVD, 2008–2019; n = 129,764; diabetes type not stratified	Long-term PTF (>763 days) vs short-term PTF vs non-use	Not extracted
Roubille et al. (2024) ⁽²⁶⁾	Prespecified subgroup of double-blind RCT (COLCOT); multinational	T2D with MI within 30 days; n = 959 (colchicine 462, placebo 497), 20.2% of COLCOT (n = 4,745); T2D 100%	Colchicine 0.5 mg/day vs placebo	Median 22.6 months

Study	Design; setting	Population (n; T2D share)	Intervention vs comparator	Follow-up
Everett et al. (2018) ⁽²⁷⁾	Subgroup analysis of double-blind RCT (CANTOS); multinational	Prior MI and hsCRP ≥ 2 mg/L; N = 10,061; diabetes at baseline 4,057 (40.3%)	Canakinumab 50, 150, or 300 mg every 3 months vs placebo	Median 3.7 years
Ridker et al. (2019) ⁽²⁸⁾	Double-blind placebo-controlled RCT (CIRT); USA/Canada	Prior MI or multivessel CAD plus T2D or metabolic syndrome; N = 4,786; T2D $\approx$ 68% (34% diabetes alone, 34% diabetes with metabolic syndrome)	Methotrexate 15–20 mg weekly (+ folate) vs placebo	Median 2.3 years
Tuttle et al. (2018) ⁽²⁹⁾	Phase 2 double-blind dose-ranging RCT; multinational	T2D with DKD, eGFR 25–70, UACR >300 and <5000 mg/g; n = 129; T2D 100%	Baricitinib 0.75–4 mg daily vs placebo	24 weeks (+4–8 weeks washout)

ABI, ankle-brachial index; ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CIMT, carotid intima-media thickness; DKD, diabetic kidney disease; PTF, pentoxifylline; RAS, renin-angiotensin system; RCT, randomized controlled trial; T2D, type 2 diabetes.

Kidney outcomes

Among pentoxifylline trials in advanced diabetic CKD, **Navarro-González et al. (2015)** ⁽¹⁹⁾ reported a smaller decline in eGFR over 24 months with pentoxifylline than with control (-2.1 ± 0.4 vs -6.5 ± 0.4 mL/min/1.73 m²; difference 4.3; $P < 0.001$), with albuminuria falling from 1100 to 973 mg/day while it rose from 1000 to 1117 mg/day in controls (Table 2).

Donate-Correa et al. (2024) ⁽²³⁾ observed an eGFR decline of 1.93 ± 0.33 mL/min/1.73 m² with pentoxifylline, 1.52 and 1.65 mL/min/1.73 m² less than in the control and aspirin groups, respectively, and urinary albumin/creatinine ratio (UACR) changes of -9.6% versus $+3.6\%$ and $+12.6\%$. **Mejía-Rodríguez et al. (2026)** ⁽²⁴⁾ found at 6 months a non-significant difference in cystatin C-creatinine eGFR ($+1.40 \pm 7.28$ vs -1.55 ± 7.10 mL/min/1.73 m²; $P = 0.083$) but a significant difference in microalbuminuria (-30.27 ± 41.48 vs $+27.96 \pm 43.06$ mg/24 h; $P < 0.001$), which persisted at 12 months (-43.18 ± 52.13 vs $+24.10 \pm 43.28$ mg/24 h; $P < 0.001$), when placebo-group eGFR had declined by 6.55 ± 10.18 mL/min/1.73 m².

In patients with albuminuria receiving ACEI or ARB therapy, **Han et al. (2015)** ⁽²⁰⁾ reported a 23% reduction in proteinuria with pentoxifylline versus 4% with placebo ($P = 0.012$), together with lower fasting glucose, HbA1c, and HOMA-IR. **Shayanpour et al. (2024)** ⁽²²⁾ reported a more than 50% albuminuria reduction in 89.7% of

pentoxifylline-treated patients versus 0% of controls after 3 months ($P < 0.0001$). By contrast, **Shahidi et al. (2015)** ⁽²¹⁾ found no significant difference in albumin/creatinine ratio or eGFR at 3 or 6 months in patients with preserved eGFR and microalbuminuria. Overall, albuminuria or proteinuria fell significantly in four of six pentoxifylline trials, showed a non-significant trend in one, and did not change in one.

Among non-pentoxifylline agents with kidney outcomes, **Tuttle et al. (2018)** ⁽²⁹⁾ reported that baricitinib 4 mg daily reduced UACR by 41% compared with placebo at 24 weeks (ratio to baseline 0.59; 95% CI 0.38–0.93; $P = 0.022$), with a dose-related pattern, persistence of the effect after washout, and reductions in inflammatory biomarkers.

Cardiovascular outcomes

In patients with T2D and a recent myocardial infarction, **Roubille et al. (2024)** ⁽²⁶⁾ found that the primary composite end point occurred in 8.7% of the colchicine group and 13.1% of the placebo group (HR 0.65; 95% CI 0.44–0.96; $P = 0.03$).

In the canakinumab trial, **Everett et al. (2018)** ⁽²⁷⁾ reported that 150 mg of canakinumab produced a hazard ratio for major adverse cardiovascular events of 0.85 (95% CI 0.70–1.03) in participants with diabetes, which was similar to that in participants with prediabetes (0.86; 0.70–1.06) and normoglycemia (0.81; 0.49–1.35); canakinumab did not reduce incident diabetes (all doses, HR 1.02; 0.87–1.19).

In contrast, **Ridker *et al.* (2019)** ⁽²⁸⁾ found no effect of low-dose methotrexate on major adverse cardiovascular events (HR 1.01; 95% CI 0.82–1.25) or on an expanded end point (HR 0.96; 0.79–1.16), and no reduction in IL-1 β , IL-6, or C-reactive protein.

Vascular and cardiac surrogates and observational data were available for pentoxifylline.

Donate-Correa *et al.* (2024) ⁽²³⁾ reported less CIMT progression with pentoxifylline than with aspirin or usual care, accompanied by higher Klotho expression and lower inflammatory markers, and **Mejía-Rodríguez *et al.* (2026)** ⁽²⁴⁾ reported that left ventricular mass index changed by -2.71 ± 19.52 g/m² with pentoxifylline versus $+10.86 \pm 16.40$ g/m² with placebo at 6 months (P = 0.001).

In the cohort of **Wang *et al.* (2024)** ⁽²⁵⁾, long-term pentoxifylline use (>763 days) was associated with a 47% lower cumulative incidence of ASCVD than non-use, whereas short-term use was associated with a higher risk.

Safety

Safety data were reported unevenly (Table 2). In **Roubille *et al.* (2024)** ⁽²⁶⁾, nausea (2.7% vs 0.8%; P = 0.03) and pneumonia (2.4% vs 0.4%; P = 0.008) were more frequent with colchicine. In **Ridker *et al.* (2019)** ⁽²⁸⁾, non-basal-cell skin cancers were more frequent with methotrexate (31 vs 10 events; rate ratio 3.08; P = 0.002).

Shayanpour *et al.* (2024) ⁽²²⁾ reported no adverse effects with pentoxifylline. Safety was not extracted for the remaining studies.

Table 2. Key quantitative findings of the included studies

Study	Outcome(s)	Key findings	Safety / other
Navarro-González <i>et al.</i> (2015) ⁽¹⁹⁾	eGFR change; albuminuria	eGFR change -2.1 ± 0.4 (PTF) vs -6.5 ± 0.4 (control) mL/min/1.73 m ² , difference 4.3, $P < 0.001$. Albuminuria 1100 → 973 mg/day (PTF) vs 1000 → 1117 mg/day (control)	Not extracted
Han <i>et al.</i> (2015) ⁽²⁰⁾	Proteinuria; glycemic indices	Proteinuria change -23% (PTF) vs -4% (placebo), $P = 0.012$. Fasting glucose, HbA1c, and HOMA-IR significantly lower with PTF; serum TNF- α unchanged	—
Shahidi <i>et al.</i> (2015) ⁽²¹⁾	Albumin/creatinine ratio; eGFR	No significant between-group difference in ACR or eGFR at 3 or 6 months ($P > 0.05$)	—
Shayanpour <i>et al.</i> (2024) ⁽²²⁾	Albuminuria response	$>50\%$ reduction in albuminuria: 89.7% (PTF) vs 0% (placebo), $P < 0.0001$	Authors reported no adverse effects
Donate-Correa <i>et al.</i> (2024) ⁽²³⁾	CIMT; ABI; eGFR; UACR	Less CIMT progression with PTF. eGFR decline 1.93 ± 0.33 with PTF (mean difference 1.52 vs control, 1.65 vs aspirin). UACR -9.6% (PTF) vs $+3.6\%$ (control) and $+12.6\%$ (aspirin); Klotho mRNA increased, inflammatory markers decreased	—
Mejía-Rodríguez <i>et al.</i> (2026) ⁽²⁴⁾	Microalbuminuria; eGFR (cystatin C-creatinine); LVMI	6 months: microalbuminuria -30.27 ± 41.48 (PTF) vs $+27.96 \pm 43.06$ mg/24 h (placebo), $P < 0.001$; eGFR $+1.40 \pm 7.28$ vs -1.55 ± 7.10 , $P = 0.083$; LVMI -2.71 ± 19.52 vs $+10.86 \pm 16.40$ g/m ² , $P = 0.001$. 12 months: microalbuminuria -43.18 ± 52.13 vs $+24.10 \pm 43.28$ mg/24 h, $P < 0.001$; placebo eGFR -6.55 ± 10.18	—
Wang <i>et al.</i> (2024) ⁽²⁵⁾	Incident ASCVD	Long-term PTF (>763 days) associated with 47% lower cumulative ASCVD incidence than non-use; short-term PTF (<763 days) associated with higher risk than non-use	In experiments, PTF raised Klotho and reduced endothelial apoptosis
Roubille <i>et al.</i> (2024) ⁽²⁶⁾	Primary composite (CV death, resuscitated arrest, MI, stroke, urgent revascularization for angina)	8.7% (colchicine) vs 13.1% (placebo); HR 0.65 (95% CI 0.44–0.96), $P = 0.03$	Nausea 2.7% vs 0.8% ($P = 0.03$); pneumonia 2.4% vs 0.4% ($P = 0.008$)
Everett <i>et al.</i> (2018) ⁽²⁷⁾	MACE (CV death, MI, stroke); incident diabetes	Canakinumab 150 mg vs placebo, MACE HR 0.85 (0.70–1.03) in diabetes; 0.86 (0.70–1.06) in prediabetes; 0.81 (0.49–1.35) in normoglycemia. Incident diabetes not reduced (all doses, HR 1.02, 0.87–1.19)	Not extracted
Ridker <i>et al.</i> (2019) ⁽²⁸⁾	MACE (nonfatal MI, nonfatal stroke, CV death)	HR 1.01 (0.82–1.25); expanded 4-component endpoint HR 0.96 (0.79–1.16). No reduction in IL-1 β , IL-6, or CRP	Non-basal-cell skin cancer 31 vs 10 (rate ratio 3.08, $P = 0.002$)

Study	Outcome(s)	Key findings	Safety / other
Tuttle <i>et al.</i> (2018) (29)	UACR at week 24	Baricitinib 4 mg: UACR –41 % vs placebo (ratio to baseline 0.59, 95% CI 0.38–0.93, P = 0.022); dose-related; effect persisted after washout; inflammatory biomarkers decreased	Not extracted

CRP, C-reactive protein; HR, hazard ratio; LVMI, left ventricular mass index; MACE, major adverse cardiovascular events; UACR, urinary albumin/creatinine ratio. Values are reported as in the source publications.

Authors' conclusions and certainty of evidence

The conclusions of the included studies and their direction of effect are summarized in Table 3A. Certainty of evidence ranged from very low to moderate (Table 3B). Moderate certainty was assigned to the colchicine and methotrexate findings, low certainty to pentoxifylline kidney outcomes, canakinumab in diabetes, and baricitinib, and very low certainty to the observational pentoxifylline cardiovascular data.

Table 3A. Authors' principal conclusions and direction of effect

Study	Principal conclusion (paraphrased)	Direction of effect
Navarro-González <i>et al.</i> (2015) (19)	Adding PTF to RAS blockade slowed eGFR decline and reduced residual albuminuria in T2D with CKD stages 3–4.	Favors PTF
Han <i>et al.</i> (2015) (20)	PTF reduced proteinuria and improved glycemic control and insulin resistance; a potential therapeutic alternative.	Favors PTF
Shahidi <i>et al.</i> (2015) (21)	No additive antialbuminuric effect over placebo in early-stage disease; further studies needed.	No difference
Shayanpour <i>et al.</i> (2024) (22)	Add-on PTF to RAS blockers may reduce microalbuminuria without side effects.	Favors PTF
Donate-Correa <i>et al.</i> (2024) (23)	PTF reduced progression of subclinical atherosclerosis (CIMT), related to Klotho expression.	Favors PTF
Mejía-Rodríguez <i>et al.</i> (2026) (24)	PTF was safe and effective, with combined nephroprotective and cardioprotective effects in advanced diabetic nephropathy.	Favors PTF
Wang <i>et al.</i> (2024) (25)	Long-term PTF was associated with lower ASCVD risk; benefit may extend to primary prevention in DKD.	Favors long-term PTF
Roubille <i>et al.</i> (2024) (26)	Colchicine 0.5 mg daily after MI in T2D produced a large reduction in CV events; supports a primary-prevention trial.	Favors colchicine
Everett <i>et al.</i> (2018) (27)	Canakinumab had similar CV efficacy with and without diabetes and did not reduce incident diabetes.	Favors canakinumab (imprecise)
Ridker <i>et al.</i> (2019) (28)	Low-dose methotrexate did not lower IL-1 β , IL-6, or CRP and did not reduce CV events in stable atherosclerosis.	No difference
Tuttle <i>et al.</i> (2018) (29)	Baricitinib decreased albuminuria in T2D with DKD.	Favors baricitinib

Table 3B. Certainty of evidence (GRADE) by agent and outcome

Agent → outcome	Evidence base	Direction of effect	Certainty	Main reasons for rating
PTF → eGFR decline (T2D, CKD 3–4)	3 RCTs (19, 23, 24)	Significantly slower decline in 2; non-significant at 6 months in 1	Low	Open-label/per-protocol designs; imprecision; inconsistency
PTF → albuminuria/proteinuria	6 RCTs (19–24)	Significant reduction in 4; non-significant trend in 1; no effect in 1 (early disease)	Low	Risk of bias; inconsistency (disease stage, dose); small trials
PTF → ASCVD events / vascular surrogates	1 cohort (25); 2 RCTs with surrogates (23, 24)	Favorable	Very low	Confounding, immortal-time bias; surrogate outcomes; indirectness
Colchicine → MACE after MI in T2D	1 subgroup analysis (26)	Reduction (HR 0.65)	Moderate	Subgroup analysis; upper CI near 1
Canakinumab → MACE in diabetes	1 subgroup analysis (27)	Reduction not significant (HR 0.85; CI includes 1)	Low	Imprecision; subgroup; diabetes type not specified
Methotrexate → MACE (~68% T2D)	1 RCT (28)	No effect (HR 1.01)	Moderate	Indirectness (mixed population)
Baricitinib → albuminuria	1 phase 2 RCT (29)	UACR –41% at 4 mg	Low	Surrogate outcome; single small trial; short follow-up

GRADE ratings are reviewer judgments based on the published reports and should be confirmed by independent assessment.

Risk of bias

Among the ten randomized reports, one trial was judged at low risk of bias overall and nine raised some concerns, mainly from open-label designs, per-protocol analysis, unverified attrition, small samples, and the subgroup nature of two analyses (Table 4A). The cohort study was judged at serious risk of bias, chiefly from confounding by indication and possible immortal-time bias in duration-based exposure categories (Table 4B).

Synthesis and meta-analysis

A quantitative meta-analysis was considered but not performed. Studies differed in agent, dose,

comparator, and follow-up (3 months to 3.7 years); measured kidney function with different equations and markers (MDRD, cystatin C-creatinine, percentage change, absolute change) and albuminuria with different metrics (mg/day, mg/24 h, UACR percentage change, and binary response); several reports did not provide variance for between-group differences; and the cardiovascular reports came from different drug classes and mixed populations. Pooling would have produced an uninterpretable estimate, so the synthesis is narrative, grouped by agent and outcome. Fewer than ten studies contributed to any outcome, so publication bias was not assessed.

Table 4. Risk-of-bias assessment of the included studies

Panel A. RoB 2 for randomized trials and randomized-trial subgroup analyses (D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, outcome measurement; D5, selective reporting).

Study	D1	D2	D3	D4	D5	Overall	Principal concern
Navarro-González <i>et al.</i> (2015) ⁽¹⁹⁾	Some concerns	Some concerns	Some concerns	Low	Some concerns	Some concerns	Open-label; concealment not verified
Han <i>et al.</i> (2015) ⁽²⁰⁾	Low	Low	Some concerns	Low	Low	Some concerns	Attrition not verified
Shahidi <i>et al.</i> (2015) ⁽²¹⁾	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	Small sample (n = 40)
Shayanpour <i>et al.</i> (2024) ⁽²²⁾	Some concerns	Low	Some concerns	Low	Some concerns	Some concerns	Abstract-level reporting
Donate-Correa <i>et al.</i> (2024) ⁽²³⁾	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	Open-label pilot
Mejía-Rodríguez <i>et al.</i> (2026) ⁽²⁴⁾	Low	Some concerns	Some concerns	Low	Low	Some concerns	Per-protocol analysis
Roubille <i>et al.</i> (2024) ⁽²⁶⁾	Low	Low	Low	Low	Some concerns	Some concerns	Subgroup analysis
Everett <i>et al.</i> (2018) ⁽²⁷⁾	Low	Low	Low	Low	Some concerns	Some concerns	Subgroup analysis
Ridker <i>et al.</i> (2019) ⁽²⁸⁾	Low	Low	Low	Low	Low	Low	Stopped for futility
Tuttle <i>et al.</i> (2018) ⁽²⁹⁾	Low	Low	Some concerns	Low	Low	Some concerns	Small dose groups

Panel B. ROBINS-I for the non-randomized cohort study (columns: confounding; participant selection; classification of interventions; deviations from intended interventions; missing data; outcome measurement; selection of reported result; overall)

Study	Confound .	Selection	Classific.	Deviation s	Missing	Measure.	Reportin g	Overall
Wang <i>et al.</i> (2024) ⁽²⁵⁾	Serious	Moderat e	Moderat e	Low	Low	Moderat e	Moderate	Serious

Green, low risk; yellow, some concerns or moderate risk; red, serious risk. Ratings are provisional and based on published reports.

DISCUSSION

Chronic low-grade inflammation links type 2 diabetes (T2D), the progression of diabetic kidney disease, and atherosclerotic events. It has therefore emerged as a therapeutic target that sits alongside, rather than within, glycemic, blood pressure, and lipid control ⁽⁶⁻⁸⁾. The premise that inflammation is a modifiable driver of vascular risk, and not merely a marker, rests on the interleukin (IL)-1 β -IL-6-C-reactive protein axis.⁽⁹⁾ This review compared immunomodulatory agents evaluated in adults with T2D for kidney and cardiovascular outcomes. Its central message is that benefit is agent-specific and outcome-specific rather than a class effect. Pentoxifylline produced the most consistent kidney signals. Colchicine and IL-1 β blockade produced cardiovascular signals in the same direction as in broader populations. Methotrexate was neutral, and Janus kinase inhibition showed an early antialbuminuric signal. Because these agents differ in mechanism, study population, and end points, the comparison is most informative for what it reveals about which inflammatory pathways appear to matter in which organ.

For kidney outcomes, the pentoxifylline trials form the largest and most coherent body of evidence. **Navarro-González et al.**⁽¹⁹⁾ and **Mejía-Rodríguez et al.**⁽²⁴⁾ both showed that adding pentoxifylline to standard therapy in advanced diabetic kidney disease attenuated the loss of kidney function and lowered albuminuria. **Han et al.**⁽²⁰⁾ observed a clear antiproteinuric effect in a larger double-blind trial of patients already receiving renin-angiotensin system blockade. **Donate-Correa et al.**⁽²³⁾ also reported slower functional decline, with favorable changes in inflammatory and vascular markers. These findings agree with the pooled evidence summarized by **McCormick et al.**⁽¹³⁾ and **Chen et al.**⁽¹²⁾, who concluded that pentoxifylline reduces proteinuria while cautioning that the underlying trials were small and short. The trials differed in an informative way across disease stages. The benefits were clearest in patients with reduced kidney function and substantial albuminuria, who presumably carry the greatest inflammatory burden. The null result of **Shahidi et al.**⁽²¹⁾ came from patients with preserved kidney function and early microalbuminuria followed for a short time. It may therefore reflect less inflammatory injury to modify, too little time for a difference to emerge, or insufficient power, rather than true ineffectiveness. **Shayanpour et al.**⁽²²⁾ reported a

high response rate with a low dose over a short period, but the trial was small and is best regarded as hypothesis-generating.

Several mechanisms plausibly explain these renal effects. Pentoxifylline is a nonselective phosphodiesterase inhibitor that raises intracellular cyclic adenosine monophosphate. It suppresses nuclear factor- κ B signaling and the production of tumor necrosis factor- α and other cytokines, and it reduces mesangial proliferation and extracellular matrix deposition.⁽¹²⁾ Improved erythrocyte deformability and microvascular flow may contribute through better renal perfusion. The upregulation of the antiaging protein Klotho reported by **Donate-Correa et al.**⁽²³⁾ links reduced inflammation to slower vascular and tubular injury, because Klotho deficiency is itself associated with oxidative stress and endothelial dysfunction. The improvement in glycemic indices described by **Han et al.**⁽²⁰⁾ suggests a further, indirect route, since better insulin sensitivity and glucose control would be expected to lessen glomerular stress. Serum tumor necrosis factor- α did not change in that trial, so the dominant mechanism in humans remains uncertain and may involve local renal rather than circulating cytokines.

For cardiovascular outcomes, the evidence comes from a different set of agents. **Roubille et al.**⁽²⁶⁾ showed that low-dose colchicine after myocardial infarction was beneficial in patients with T2D, in line with the overall findings of **Tardif et al.**⁽¹⁰⁾ and with the results in chronic coronary disease reported by **Nidorf et al.**⁽¹¹⁾. This consistency suggests that diabetes does not blunt the effect of colchicine. Patients with T2D may even represent a high-risk group that gains more in absolute terms. Similarly, **Everett et al.**⁽²⁷⁾ reported that canakinumab produced a relative effect on major cardiovascular events in people with diabetes that was of similar magnitude to that in people without diabetes. The diabetes-specific estimate was less precise because it rested on fewer events, so the absence of statistical significance in that subgroup should not be read as absence of benefit. The two agents act at different points of the same pathway. Colchicine disrupts microtubule polymerization, limits neutrophil activation and chemotaxis, and inhibits assembly of the NLRP3 inflammasome, thereby reducing IL-1 β maturation.⁽³⁰⁾ Canakinumab neutralizes IL-1 β directly and thus suppresses downstream IL-6 and C-reactive protein.⁽³¹⁾

The neutral result of low-dose methotrexate in the trial of **Ridker et al.**⁽²⁸⁾, which enrolled patients with T2D or metabolic syndrome, provides an instructive contrast. Methotrexate did not lower IL-1 β , IL-6, or C-reactive protein in that trial. This supports the view that cardiovascular benefit depends on interrupting the IL-1 β -IL-6-C-reactive protein axis rather than on generalized immunosuppression⁽³¹⁾. Comparing the groups of agents, those that engage this axis, namely colchicine and canakinumab, showed benefit, whereas the one that did not engage it showed none. This comparison is indirect and based on trials in different populations, so it generates a hypothesis and does not prove it. Safety also differed across agents. Colchicine was associated with gastrointestinal and respiratory infection signals, and methotrexate with an excess of skin cancers. This matters in a population that is already prone to infection and in which kidney impairment alters drug handling.

Kidney and cardiovascular responses did not always travel together, and this dissociation deserves emphasis. Ziltivekimab, an IL-6 inhibitor evaluated by **Ridker et al.**⁽³²⁾ in patients with chronic kidney disease, produced profound reductions in C-reactive protein without an apparent change in estimated glomerular filtration rate or albuminuria. This indicates that lowering systemic inflammatory markers does not automatically equate to kidney protection. It also suggests that cardiovascular and renal benefit may require different degrees or sites of inflammatory suppression. The ongoing cardiovascular outcome trial of this agent will clarify its clinical value in the population most relevant to this review.

Janus kinase inhibition offers a mechanistically distinct approach. In the phase 2 trial of **Tuttle et al.**⁽²⁹⁾, baricitinib reduced albuminuria in a dose-related manner alongside lower inflammatory biomarkers, and the effect persisted after treatment was withdrawn. This fits the role of Janus kinase-signal transducer and activator of transcription signaling in transmitting cytokine signals into glomerular and tubular cells.⁽³³⁾ Whether this surrogate effect translates into preserved kidney function is unknown. The safety profile of Janus kinase inhibitors, particularly regarding infection and thrombosis, will need careful evaluation before any role in a population with substantial cardiovascular risk can be defined.

The relationship between inflammation and metabolic control adds a further dimension. The improvement in glycemia seen with interleukin-1 receptor antagonism in earlier work by **Larsen et al.**⁽³⁴⁾ is compatible with the glycemic changes reported with pentoxifylline, and it supports the idea that targeting inflammation may benefit metabolic and organ outcomes together. However, canakinumab did not prevent incident diabetes in the large trial by **Ridker et al.**⁽³⁵⁾, so the glycemic benefit of anti-inflammatory therapy should not be assumed to be uniform across agents. In that trial, the degree of IL-6 reduction achieved on treatment was associated with the magnitude of benefit, as reported by **Ridker et al.**⁽³⁶⁾. This is consistent with the possibility that patients with T2D, whose inflammatory activity is often high, might derive greater benefit from agents that reduce IL-6 effectively.

Surrogate and observational data extend these findings to the vasculature and heart, with caveats. The cohort of **Wang et al.**⁽²⁵⁾ associated prolonged pentoxifylline use with fewer atherosclerotic events. This agrees with the vascular and cardiac structural benefits suggested by **Donate-Correa et al.**⁽²³⁾ and **Mejía-Rodríguez et al.**⁽²⁴⁾. However, the opposite association with short-term use, and the susceptibility of such cohorts to confounding by indication and immortal-time bias, argue for cautious interpretation. Reduced progression of carotid wall thickness or left ventricular mass is encouraging but is not equivalent to a lower rate of myocardial infarction, stroke, or heart failure. No pentoxifylline trial in T2D has yet been powered for such events, and this is the most important evidence gap identified by the review.

Several considerations limit how directly these findings can inform practice. Most kidney trials predate the widespread use of sodium-glucose cotransporter-2 inhibitors and nonsteroidal mineralocorticoid receptor antagonists, which now form part of standard care for diabetic kidney disease.^(5, 37-39) The incremental benefit of anti-inflammatory therapy on top of these agents is therefore unknown, although the mechanisms are distinct enough that additive effects are plausible. Colchicine is cleared in part by the kidney, and trials such as that of **Nidorf et al.**⁽¹¹⁾ excluded advanced renal disease. This limits extrapolation to patients with T2D and advanced chronic kidney disease, despite their high cardiovascular risk. The consistency of colchicine's effect across coronary

populations, as summarized by **Fiolet et al.**⁽⁴⁰⁾, strengthens confidence in the cardiovascular signal but does not resolve questions about dosing and safety in kidney impairment.

The strengths of this review include its attention to both kidney and cardiovascular outcomes, its explicit reporting of the proportion of participants with T2D in mixed populations, and its transparent appraisal of risk of bias and certainty. Its limitations are those of the underlying evidence and of the review process. The evidence base is small and heterogeneous, relies heavily on surrogate end points, and includes mixed populations in which T2D is a subgroup. Studies used different measures of kidney function and albuminuria, which precluded pooling. Screening and data extraction were performed by a single reviewer, the search was restricted to English-language publications, and publication bias could not be assessed.

For internal medicine and family medicine practice, current evidence most strongly supports considering low-dose colchicine for secondary cardiovascular prevention in patients with T2D, with attention to kidney function and drug interactions. Pentoxifylline remains a promising but investigational adjunct for diabetic kidney disease, pending adequately powered trials with hard kidney outcomes. Future studies should enroll participants with T2D specifically, report results stratified by diabetes status, standardize kidney and cardiovascular end points, and test these agents on top of contemporary organ-protective therapy. They should also evaluate whether biomarkers of inflammation can identify patients most likely to respond, so that anti-inflammatory therapy can be targeted rather than applied broadly.

CONCLUSION

In adults with T2D, immunomodulatory therapy does not confer a uniform class benefit; rather, effects are specific to each agent and outcome domain. Pentoxifylline consistently slows kidney function decline and reduces albuminuria in advanced diabetic kidney disease, though evidence in early-stage disease is null and cardiovascular data remain observational. Colchicine reduces major cardiovascular events after myocardial infarction in patients with T2D, with a magnitude of benefit comparable to that observed in the broader coronary population. Canakinumab shows a directionally consistent but statistically imprecise cardiovascular effect in diabetes, methotrexate is neutral, and baricitinib

produces an early antialbuminuric signal that has not yet been shown to translate into preserved kidney function. Certainty of evidence is low to moderate across all agent-outcome pairs, constrained by small trials, surrogate endpoints, subgroup analyses, open-label designs, and the absence of T2D-specific cardiovascular outcome trials for most agents.

These findings carry several implications for practice and research:

For clinical practice: Low-dose colchicine may be considered for secondary cardiovascular prevention in patients with T2D, provided kidney function and drug interactions are carefully assessed. Pentoxifylline should be regarded as a promising but investigational adjunct for diabetic kidney disease rather than a standard therapy. Neither agent should replace contemporary guideline-directed care, including RAS blockade, SGLT2 inhibitors, and nonsteroidal mineralocorticoid receptor antagonists, on which the included trials largely did not background.

For future research: Large, adequately powered randomized controlled trials enrolling T2D-specific populations are needed. These trials should (1) evaluate hard kidney outcomes (doubling of serum creatinine, kidney failure) and hard cardiovascular outcomes (MACE, cardiovascular death, heart failure) rather than surrogate markers alone; (2) test agents on top of contemporary organ-protective therapy; (3) standardize endpoint definitions and measurement methods to permit pooling; (4) report T2D-specific results in mixed populations; and (5) incorporate biomarkers of inflammation to identify patients most likely to respond, enabling targeted rather than broad application of anti-inflammatory therapy. Until such evidence is available, immunomodulatory agents should not be adopted routinely for cardiorenal protection in T2D outside of clinical trial settings or specific secondary prevention contexts supported by existing evidence.

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Authors contribution:

Conceptualization and study design were led by AAF and NMA, with critical input from MSH, HBAA, and ASNS. Methodology development and experimental protocols were established by MHA and MMA. Formal statistical analysis and software implementation were performed by MSH and MHA. Project administration and supervision were provided by AAF and NMA, who also secured institutional resources. The original draft of the manuscript was written by AAF. All authors—AAF, NMA, MSH, HBAA, ASNS, MHA, and MMA—participated in data interpretation, critically reviewed and edited successive drafts, and read and approved the final version for submission.

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