Erythrocytosis during SGLT2 Inhibitor Therapy: Should We Be Concerned?

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https://doi.org/10.71749/pkj.168

Abstract
Sodium-glucose cotransporter-2 (SGLT2) inhibitors have become a cornerstone in the management of type 2 diabetes mellitus, chronic kidney disease and heart failure because of their established cardiovascular and renal benefits. Alongside these effects, consistent increases in hemoglobin and hematocrit have emerged as a characteristic hematologic response. Initially attributed primarily to hemoconcentration resulting from osmotic diuresis, accumulating evidence indicates that enhanced erythropoiesis, driven predominantly by increased erythropoietin production and improved iron availability, represents the principal mechanism. While these changes are usually modest, a subset of patients develops erythrocytosis exceeding conventional diagnostic thresholds, raising important questions regarding differential diagnosis, thrombotic risk, and clinical management. Recent observational studies, systematic evidence syntheses, and emerging hematologic data have refined our understanding of SGLT2 inhibitor-associated erythrocytosis. Reported incidence varies considerably according to the population studied, follow-up duration, and diagnostic criteria. Although most available evidence does not demonstrate a consistent association between SGLT2 inhibitor-associated erythrocytosis and arterial or venous thromboembolic events, recent studies suggest that increased risk in selected subgroups cannot be excluded. Consequently, the clinical significance of this increasingly recognized phenomenon remains incompletely defined. This narrative review critically appraises the current evidence regarding the incidence, pathophysiological mechanisms, thrombotic implications, differential diagnosis, and management of SGLT2 inhibitor-associated erythrocytosis. We also present four real-world clinical cases illustrating its heterogeneous presentation, the frequent coexistence of alternative contributors to secondary erythrocytosis, and its reversibility following drug withdrawal. Integrating current evidence with these clinical observations, we propose a pragmatic diagnostic approach aimed at excluding primary hematologic disorders and alternative secondary causes while supporting individualized decisions regarding continuation of SGLT2 inhibitor therapy. Given the substantial cardiorenal benefits of these agents, management should remain individualized, balancing the degree and clinical context of erythrocytosis against the expected benefits of continued treatment.

Keywords: Hemoglobins; Polycythemia; Renal Insufficiency, Chronic; Sodium-Glucose Transporter 2 Inhibitors

INTRODUCTION
Sodium-glucose cotransporter-2 (SGLT2) inhibitors have reshaped the therapeutic landscape of type 2 diabetes mellitus, chronic kidney disease (CKD) and heart failure (HF), extending well beyond glycemic control to provide substantial cardiovascular and renal protection.[1] Their benefits are consistent across a broad spectrum of patients, including those without diabetes, and have led to their widespread adoption in nephrology and cardiology practice.[1,2] Notably, these agents reduce the risk of end-stage kidney disease and improve outcomes in HF, regardless of ejection fraction.[1,2]

Alongside these well-established effects, clinical trials and real-world studies have consistently observed increases in hemoglobin and hematocrit.[3-5] Initially attributed largely to hemoconcentration, these hematologic changes are now understood to reflect a more complex biological response involving stimulation of erythropoiesis.[6,7]

Although several reviews have discussed erythrocytosis associated with SGLT2 inhibitor therapy and its relevance in patients with CKD, HF and diabetes,[8,9] recent observational studies, systematic reviews and meta-analyses, together with new insights from the hematology literature, have refined our understanding of its incidence,

Received: 02/09/2026 **Accepted:** 26/10/2026 **Published Online:** 02/11/2026 **Published:** -
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biological mechanisms, thrombotic risk and clinical management.[6,10-13]

This narrative review examines the current evidence regarding the incidence, pathophysiological mechanisms, clinical significance, diagnostic evaluation and management of SGLT2 inhibitor-associated erythrocytosis. Where appropriate, we critically discuss the available evidence, distinguish well-supported findings from emerging hypotheses, and highlight areas in which uncertainty remains. We also present four real-world clinical cases illustrating common diagnostic challenges and demonstrate how a structured diagnostic algorithm can be applied in routine clinical practice.

EFFECTS OF SGLT2 INHIBITORS ON HEMOGLOBIN AND HEMATOCRIT

Randomized controlled trials have consistently demonstrated modest but reproducible increases in hemoglobin and hematocrit after initiation of SGLT2 inhibitor therapy.[3-5] In CREDENCE, canagliflozin increased mean hemoglobin by 7.1 g/L and hematocrit by 2.4% compared with placebo.[3] Similarly, DAPA-CKD showed a sustained increase in hematocrit of approximately 2.3%, with correction of baseline anemia in more than half of affected patients, regardless of diabetes status.[4]

Comparable findings have been reported in cardiovascular outcome trials. In EMPA-REG OUTCOME, both empagliflozin doses produced sustained increases in hematocrit that were significantly greater than those observed with placebo.[14] Mediation analyses identified changes in hemoglobin and hematocrit as the strongest statistical mediators of the reduction in cardiovascular mortality.[15] However, these analyses cannot establish causality, and the observed association may reflect underlying biological processes triggered by SGLT2 inhibition rather than a direct protective effect of increased hemoglobin or hematocrit per se.[15]

The temporal profile of this response further supports a biological mechanism beyond simple volume contraction. Hemoglobin levels increase after initiation of therapy and remain elevated during follow-up, a temporal pattern difficult to explain by persistent hemoconcentration alone.[6,10] In a recent multicenter real-world cohort of patients with heart failure, among patients without erythrocytosis at baseline who subsequently developed erythrocytosis, the median time to its development was 7 months.[16] This prolonged temporal pattern further supports an erythropoietic response and suggests that assessment limited to the early weeks after treatment initiation may underestimate the long-term hematologic effect.[6,10,16]

Overall, available evidence supports a class effect of SGLT2 inhibitors on hemoglobin and hematocrit.[17] Although modest differences between individual agents have been described, comparative evidence remains limited, relying predominantly on observational studies and indirect comparisons rather than head-to-head randomized trials.[6]

INCIDENCE, ASSOCIATED FACTORS AND CLINICAL SIGNIFICANCE OF ERYTHROCYTOSIS

Although modest increases in hemoglobin and hematocrit are consistently observed with SGLT2 inhibitor therapy, the incidence of clinically significant erythrocytosis varies considerably across studies, ranging from about 2% to over 20%, depending on the population studied, follow-up duration, diagnostic thresholds, and frequency of laboratory monitoring.[11]

Large randomized trials have reported mean increases in hemoglobin of about 0.5-1.0 g/dL and hematocrit of 2%-5%.[3,4,7,14] Smaller observational series have occasionally described more pronounced increases.[18] However, these findings should be interpreted in the context of substantial heterogeneity in study populations, diagnostic thresholds, follow-up duration, and ascertainment methods, as highlighted in a recent systematic review.[11]

Several factors have been associated with an increased likelihood of developing erythrocytosis, including male sex, higher body mass index, smoking and hypertension.[6,10] Disease-specific differences have also been described. Patients with heart failure tend to exhibit a more pronounced increase in hemoglobin, whereas those with chronic kidney disease exhibit a more modest increase.[10] These findings suggest that the hematologic response to SGLT2 inhibitors may be influenced by both patient-specific characteristics and underlying disease states.

Erythrocytosis associated with SGLT2 inhibitors appears to be reversible upon discontinuation of therapy,[11,18] supporting a drug-related secondary mechanism.[9] However, its clinical significance remains uncertain, particularly regarding thromboembolic risk.

In a large retrospective cohort study including 6787 patients, Lee ***et al*** reported an erythrocytosis incidence of 16.9%, whereas thrombotic events occurred in only 0.5% of treated patients.[10] Importantly, only five patients had erythrocytosis at the time of the thrombotic event, and all events were arterial, occurring in individuals with substantial baseline cardiovascular comorbidity.[10] Together with the association between thrombosis and baseline antithrombotic therapy, these findings suggest that the observed risk was more likely driven by underlying patient characteristics than by erythrocytosis itself.[10]

Smaller, highly selected cohorts have reported higher thrombotic event rates. In a series of 100 patients with JAK2-unmutated erythrocytosis, Gangat ***et al*** observed a thrombotic event rate of about 10%, although they found no association with hemoglobin or hematocrit levels.[18] Thrombosis was more frequent among patients undergoing phlebotomy, a finding that likely reflects confounding by indication rather than a harmful effect of phlebotomy itself.[18]

Large comparative analyses have not demonstrated a consistent association between SGLT2 inhibitor-associated

erythrocytosis and thrombotic risk.[6,16,19,20] In propensity score-matched studies, erythrocytosis was more frequent among patients treated with SGLT2 inhibitors compared with other antidiabetic agents, yet no increase in myocardial infarction, stroke, or venous thromboembolism was observed.[6] Similarly, pooled analyses of randomized trials have demonstrated increased rates of erythrocytosis without a corresponding rise in thrombotic events,[19] findings that have been replicated in real-world cohorts of patients with heart failure.[16,20] In a post hoc analysis of the EMPEROR-Preserved trial, empagliflozin increased the incidence of erythrocytosis, but this was not associated with an increased risk of atherothrombotic events, and neither baseline nor incident erythrocytosis was linked to adverse outcomes.[21]

However, more recent studies suggest that this relationship may be more nuanced in selected patient subgroups. A pooled analysis of the CREDENCE and CANVAS trials demonstrated that in males, the effect of canagliflozin varied according to baseline hematocrit, shifting from benefit at lower levels to a signal toward increased myocardial infarction risk at higher levels, particularly in those with erythrocytosis at baseline.[22] Similarly, Chen ***et al*** found that although overall thromboembolic risk was not uniformly increased with SGLT2 inhibitor use, patients who developed erythrocytosis had a higher incidence of arterial and venous thrombotic events.[13] These findings should nevertheless be interpreted cautiously. The CREDENCE/CANVAS findings derive from a subgroup analysis and should be considered hypothesis-generating, whereas the observational nature of the study by Chen ***et al*** leaves it susceptible to residual confounding.[13,22]

Taken together, the available evidence suggests that while erythrocytosis is an increasingly recognized and reproducible effect of SGLT2 inhibitor therapy, its relationship with thromboembolic risk remains complex and incompletely understood. Current evidence does not support a consistent causal association between SGLT2 inhibitor-associated erythrocytosis and thromboembolic events, although a potential increase in risk in selected subgroups cannot be excluded. Nevertheless, careful clinical assessment remains appropriate, particularly in patients with additional thrombotic risk factors or pre-existing erythrocytosis.

PATHOPHYSIOLOGICAL MECHANISMS

The mechanisms underlying SGLT2 inhibitor-associated erythrocytosis are complex and multifactorial. Initially, the increase in hemoglobin and hematocrit observed with these agents was attributed to hemoconcentration.[9] However, this explanation alone is insufficient, as increases in hemoglobin and hematocrit persist for weeks to months.[8,9,23] In addition, increases in reticulocyte count and changes in iron metabolism support enhanced erythropoiesis rather than a simple reduction in plasma volume.[9]

The best-supported mechanism involves stimulation of erythropoiesis through increased erythropoietin production.[9,24,25] By inhibiting sodium and glucose reabsorption in the proximal tubule, SGLT2 inhibitors reduce cortical oxygen consumption and may facilitate recovery of erythropoietin-producing interstitial fibroblasts, which are often dysfunctional in CKD, particularly diabetic kidney disease.[23,26] In parallel, increased distal sodium delivery increases oxygen consumption in the outer medulla,[27] a physiological change proposed to promote HIF-2α activation, a key regulator of erythropoietin gene transcription.[9,25,26] Together, these mechanisms provide the most plausible explanation for the sustained increase in erythropoiesis observed during SGLT2 inhibitor therapy.[9,25]

Accumulating evidence also supports an important role for altered iron metabolism in the erythropoietic response to SGLT2 inhibitors.[9,25] Treatment is associated with suppression of hepcidin, increasing iron availability through enhanced intestinal absorption and mobilization from macrophage and hepatic stores.[25,28] These changes are accompanied by reductions in ferritin and increases in transferrin and soluble transferrin receptor levels, consistent with increased iron mobilization and utilization for erythropoiesis.[24,25,28] This coordinated regulation of iron homeostasis may explain why SGLT2 inhibitors can sustain erythropoiesis even in patients with functional iron deficiency.[9,25]

Additional mechanisms have been proposed but remain less well established. Experimental and mechanistic studies suggest that SGLT2 inhibitors activate nutrient deprivation signaling pathways involving SIRT1 and AMPK, which may enhance HIF-2α activity and suppress hepcidin production.[25] Similarly, increased ketone body production has been hypothesized to stimulate erythropoietin synthesis, although direct clinical evidence supporting this mechanism remains limited.[24,26]

Overall, current evidence supports a multifactorial model in which stimulation of erythropoietin production and coordinated changes in iron metabolism represent the principal mechanisms underlying SGLT2 inhibitor-associated erythrocytosis, whereas the contribution of nutrient-sensing pathways and ketone metabolism remains less certain.

DIFFERENTIAL DIAGNOSIS AND CLINICAL EVALUATION

As erythrocytosis associated with SGLT2 inhibitors has become increasingly recognized, referrals to hematology have also increased, often prompted by hemoglobin or hematocrit values exceeding diagnostic thresholds for polycythemia vera (PV).[12] From a clinical standpoint, SGLT2 inhibitor-associated erythrocytosis is thought to represent an erythropoietin-driven, non-clonal process.[9,12] However, distinguishing drug-induced erythrocytosis from primary or alternative secondary causes is essential, as management and prognostic implications differ substantially.[12,29]

The initial evaluation should confirm persistent erythrocytosis and include a comprehensive clinical assessment

for secondary causes, such as smoking, chronic hypoxic lung disease, obstructive sleep apnea, androgen use, and erythropoietin-producing tumors.[12,29] A detailed medication review is also essential, particularly for agents known to stimulate erythropoiesis, including testosterone and exogenous erythropoietin.[12,29]

Measuring serum erythropoietin levels is a useful part of the diagnostic workup. Elevated or inappropriately normal levels support secondary erythrocytosis, whereas suppressed levels raise suspicion for PV.[12,29] However, serum EPO levels should not be interpreted in isolation, as normal values do not exclude PV and may also be observed in secondary erythrocytosis. Their interpretation should therefore be integrated with clinical findings and molecular testing.[12,29] In the series of 100 patients with JAK2-unmutated erythrocytosis, Gangat *et al* reported normal or increased erythropoietin levels in all informative cases, supporting an erythropoietin-driven mechanism.[18]

JAK2 mutation testing is a central component of the diagnostic evaluation when a clonal myeloproliferative disorder is suspected, particularly because PV may coexist with or be unmasked by secondary erythropoietic stimuli.[8,12,29] In patients with a strong clinical suspicion of PV, serum EPO measurement and *JAK2 V617F* mutation testing should be performed concurrently rather than sequentially based on EPO results.[12,29]

Features warranting further investigation include a history of thrombosis, aquagenic pruritus, splenomegaly, unexplained persistent erythrocytosis, leukocytosis or thrombocytosis.[8,12,29] In contrast, a stepwise diagnostic approach may be appropriate in patients with a low clinical probability of a myeloproliferative neoplasm, guided by the clinical context and hematological findings.[29]

Although uncommon, *JAK2* mutations have been identified in patients presenting with erythrocytosis during SGLT2 inhibitor therapy, likely reflecting previously unrecognized PV rather than a drug-induced process.[8,12] In patients with negative *JAK2 V617F* testing but persistent clinical suspicion of PV, additional evaluation, including *JAK2* exon 12 mutation testing and bone marrow examination, should be considered according to current diagnostic criteria.[12,29]

Overall, evaluating erythrocytosis in patients treated with SGLT2 inhibitors should follow a structured approach that prioritizes excluding primary hematologic disorders and other secondary causes before attributing erythrocytosis to SGLT2 inhibitor therapy alone.[12,29] We propose a pragmatic diagnostic algorithm to guide the evaluation of erythrocytosis during SGLT2 inhibitor therapy (Fig. 1).

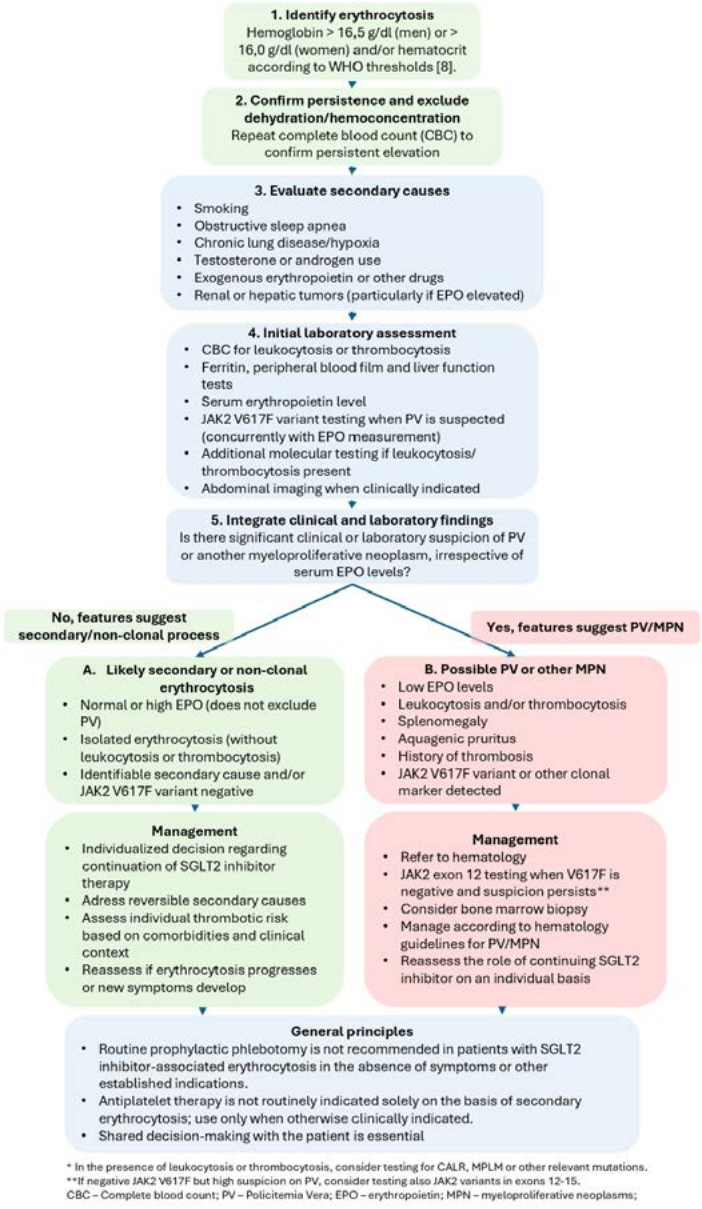


Figure 1. Suggested approach to erythrocytosis during SGLT2 inhibitor therapy.

CLINICAL MANAGEMENT AND UNCERTAINTIES

The optimal management of SGLT2 inhibitor-associated erythrocytosis remains uncertain, reflecting the limited and heterogeneous nature of the available evidence. Current data suggest that thrombotic risk is generally low and often attributable to underlying cardiovascular comorbidities rather than erythrocytosis itself.[6,10,21] Large observational studies and analyses of randomized trials have not demonstrated a consistent increase in thromboembolic events, although some studies suggest a potential increase in risk in selected subgroups.[6,13,21,22] However, most available studies were not specifically designed to assess thrombotic risk associated with SGLT2 inhibitor-induced erythrocytosis, and the evidence should therefore be interpreted cautiously.

Given the well-established cardiovascular and renal benefits of SGLT2 inhibitors, current evidence and expert recommendations do not support routine discontinuation of therapy solely due to erythrocytosis.[1,2,8,12] The recent update on JAK2-unmutated erythrocytosis emphasizes that thrombotic risk is not clearly increased in most forms of secondary erythrocytosis and that management should focus on the underlying cause rather than routine therapeutic interventions.[12] Accordingly, the decision to continue or discontinue SGLT2 inhibitor therapy should be individualized, taking into account the underlying indication, the degree of erythrocytosis, alternative causes, and the overall clinical context.

In patients with marked or progressive erythrocytosis, temporary treatment interruption may be considered

following individualized assessment, particularly when additional thrombotic risk factors are present or the underlying etiology remains uncertain. Such decisions should balance the established cardiorenal benefits of SGLT2 inhibitors against potential risks, recognizing that evidence regarding the clinical consequences of marked erythrocytosis remains limited. Reintroduction may be considered in selected patients with compelling cardiorenal indications, provided that close hematological monitoring is maintained. However, recurrence of erythrocytosis following rechallenge should prompt reassessment of the risk–benefit balance, as illustrated by one of our clinical cases.

In clinical practice, management should begin with confirmation of persistent erythrocytosis and exclusion of alternative secondary and primary causes, as outlined above.[12,29] Referral to hematology is appropriate when a *JAK2* mutation is detected or when the etiology remains unclear.[8]

Based on expert opinion, treatment with an SGLT2 inhibitor is not necessarily contraindicated in patients with an underlying myeloproliferative neoplasm. In patients with a clear cardiorenal indication, therapy may be continued provided that close hematologic monitoring is maintained and the underlying myeloproliferative neoplasm is appropriately managed.[8]

Current evidence does not demonstrate a consistent benefit of phlebotomy in reducing thrombotic risk in this population, and some studies have reported higher event rates among patients undergoing phlebotomy, likely reflecting confounding by indication.[18] Accordingly, routine or prophylactic phlebotomy is not recommended in SGLT2 inhibitor-associated erythrocytosis.[8,29] Therapeutic phlebotomy may nevertheless be considered on an individual basis for symptom control in selected patients.[12]

In contrast to polycythemia vera, where antiplatelet therapy is routinely recommended, no evidence supports routine antiplatelet therapy specifically for SGLT2 inhibitor-associated erythrocytosis.[29] Decisions regarding these interventions should therefore be individualized, taking into account the patient's overall thrombotic risk profile and clinical context.[12]

Patients should be informed about the possibility of erythrocytosis during SGLT2 inhibitor therapy and the current uncertainty regarding its thrombotic implications. Shared decision-making and appropriate hematological monitoring remain essential, particularly when treatment continuation or reintroduction is being considered.

REAL LIFE CLINICAL CASES

Case 1

An 80-year-old man with chronic kidney disease, type 2 diabetes mellitus, and ischemic heart disease developed erythrocytosis several years after initiation of SGLT2 inhibitor therapy, with a further rise in hemoglobin following the switch from dapagliflozin to empagliflozin, reaching a peak hemoglobin level of 17.9 g/dL. Hematologic investigation showed negative *JAK2* mutation testing and normal erythropoietin levels. During the diagnostic workup, obstructive sleep apnea was also identified, representing a potential alternative contributor to secondary erythrocytosis. After discontinuation of the SGLT2 inhibitor, hemoglobin levels returned to the normal range within two months, supporting an association between SGLT2 inhibitor therapy and erythrocytosis. Dapagliflozin therapy was not reintroduced during the reported follow-up period.

Case 2

A 43-year-old man with IgA nephropathy (Oxford classification M0 E0 S1 T0 C0) was started on dapagliflozin in August 2024. At treatment initiation, hemoglobin was 14.1 g/dL. Following dapagliflozin initiation, progressive erythrocytosis was observed, with hemoglobin increasing to 16.2 g/dL in November 2024, 17.0 g/dL in February 2025, and peaking at 18.0 g/dL with hematocrit >50% in October 2025. Dapagliflozin was subsequently discontinued and the patient was referred to Hematology for further evaluation. Investigation showed erythropoietin levels within the normal range. After withdrawal of dapagliflozin, hemoglobin levels gradually improved, decreasing to 17.6 g/dL in December 2025, 16.8 g/dL in January 2026, and 16.4 g/dL in May 2026. Renal function remained stable throughout follow-up, supporting a likely contributory role of SGLT2 inhibitor therapy in the development of erythrocytosis. Dapagliflozin was not reintroduced during follow-up.

Case 3

A 51-year-old man with hypertension, hyperuricemia, psoriatic arthritis, obesity, and a previous smoking history was referred to Nephrology for evaluation of proteinuria, and dapagliflozin was initiated in June 2025 as an antiproteinuric measure. Hemoglobin levels progressively increased from 16.8 g/dL in 2019 to 18.2 g/dL in May 2025 and 20 g/dL in November 2025 following SGLT2 inhibitor initiation. He was subsequently referred to Hematology for evaluation of erythrocytosis. At presentation to the Hematology clinic, hemoglobin was 18.1 g/dL and hematocrit 53.7%. Investigation showed elevated erythropoietin levels (24 mU/mL) and negative *JAK2* mutation testing, consistent with secondary erythrocytosis. Obesity and snoring also raised suspicion for obstructive sleep apnea as a potential contributing factor. Hematology initiated low-dose aspirin and therapeutic phlebotomy. Dapagliflozin was discontinued, and follow-up showed improvement in blood counts, with hemoglobin decreasing to 16.9 g/dL and remaining stable at 17.3 g/dL in May 2026. Given the presence of erythrocytosis before treatment initiation, these findings

suggest that dapagliflozin may have contributed to the worsening of a pre-existing erythrocytosis rather than being its sole cause. Dapagliflozin was not reintroduced during follow-up.

Case 4

A 54-year-old man with hypertension, dyslipidemia, gout, and CKD due to biopsy-proven secondary focal segmental glomerulosclerosis associated with hypertension developed erythrocytosis during dapagliflozin therapy, with hemoglobin increasing from 16.2 g/dL in January 2021 to 18.2 g/dL in May 2022. Hematological evaluation showed normal erythropoietin levels (8.4 mIU/mL) and negative *JAK2* mutation testing, and Hematology initiated therapeutic phlebotomies in July 2022. Mild obstructive sleep apnea was also diagnosed. Dapagliflozin was temporarily discontinued in February 2024, with hemoglobin decreasing to 16.5 g/dL in April, although intermittent erythrocytosis persisted. Following reintroduction in December 2024, and despite positive airway pressure therapy initiated in February 2025 and repeated therapeutic phlebotomies, hemoglobin increased to 18.4 g/dL (hematocrit 53.9%) in October 2025. Definitive discontinuation of dapagliflozin was decided in March 2026, followed by a decrease in hemoglobin to 16.3 g/dL in May 2026. This clinical course supports a contributory role of dapagliflozin in a likely multifactorial erythrocytosis.

Collectively, these four cases illustrate the heterogeneous clinical presentation of SGLT2 inhibitor-associated erythrocytosis. Despite differences in underlying kidney disease, baseline hemoglobin levels, and concomitant risk factors such as obstructive sleep apnea, all patients underwent clinical evaluation for alternative causes, and hemoglobin levels improved following SGLT2 inhibitor discontinuation. *JAK2 V617F* testing was negative in the patients in whom it was performed.

Importantly, treatment discontinuation in these cases reflected individualized clinical decisions made in the context of substantial erythrocytosis and evolving evidence regarding its clinical implications, and should not be interpreted as a recommendation for routine withdrawal of SGLT2 inhibitors. In one patient, worsening erythrocytosis following dapagliflozin reintroduction further supported a drug-related contribution, although the persistence of erythrocytosis during the initial treatment interruption suggests a multifactorial etiology.

These observations, summarized in Table 1, highlight the importance of systematically evaluating alternative causes of erythrocytosis and individualizing treatment decisions while acknowledging the temporal association between SGLT2 inhibitor exposure and changes in hemoglobin levels.

Table 1. Summary of real-world cases of erythrocytosis associated with SGLT2 inhibitor therapy.

Case	Age/ Sex	CKD etiology	SGLT2 inhibitor	Baseline Hb, g/dL	Peak Hb, g/dL	EPO, mUI/mL	JAK2	SGLT2i reintroduction	Clinical outcome
1	80/M	Cardiorenal-metabolic syndrome	Empagliflozin	13.9	17.9	12	Negative	No	Hb returned to baseline after empagliflozin suspension.
2	43/M	IgA nephropathy	Dapagliflozin	14.1	18.0	12	Not performed	No	Hb returned to baseline after dapagliflozin suspension.
3	51/M	Isolated proteinuria	Dapagliflozin	18.2	20.0	24	Negative	No	Hb improved after dapagliflozin discontinuation despite initial phlebotomy and aspirin therapy.
4	54/M	Secondary FSGS	Dapagliflozin	16.2	18.2	8.4	Negative	Yes	Erythrocytosis recurred after dapagliflozin reintroduction and resolved following definitive discontinuation.

CONCLUSION

SGLT2 inhibitors are associated with a consistent increase in hemoglobin and hematocrit, reflecting a complex biological response in which enhanced erythropoiesis appears to play a predominant role. As the use of these agents continues to expand, erythrocytosis has become

an increasingly recognized clinical finding that generally represents a secondary and potentially reversible process. Current evidence does not support a consistent association between SGLT2 inhibitor-associated erythrocytosis and thromboembolic events, although available data remain limited and some uncertainty persists regarding specific patient subgroups. Consequently, erythrocytosis developing during SGLT2 inhibitor therapy should prompt appropriate evaluation to exclude primary hematologic disorders and alternative secondary causes.

Given the substantial cardiovascular and renal benefits of SGLT2 inhibitors, current evidence does not support routine discontinuation of therapy solely on the basis of erythrocytosis. Management should instead rely on individualized risk assessment and shared decision-making, balancing the expected cardiorenal benefits of treatment against potential risks in each patient.

Prospective studies are needed to better define the long-term clinical implications of SGLT2 inhibitor-associated erythrocytosis and to establish evidence-based management strategies. Until then, a pragmatic approach integrating current evidence with clinical judgment remains essential.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Acknowledgments

During the preparation of this work, the authors used ChatGPT (OpenAI) for language editing and text refinement, including improvements in grammar and style. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the article's scientific content, interpretation, and conclusions.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Contributorship Statement

BM: Conceived the review, performed the literature review, and drafted the manuscript. AF, JA and KS: Contributed to the conception of the review and critically revised the manuscript.

FF, JC and KS: Critically revised the manuscript. All authors read and approved the final version of the manuscript.

All authors contributed to this work, approved the final version of the manuscript for publication, and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the data presented.

REFERENCES

1. Braunwald E. Gliflozins in the Management of Cardiovascular Disease. N Engl J Med. 2022;386:2024–34. doi.org/10.1056/nejmra2115011.
2. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The Lancet. 2019;393:31–9. doi:10.1016/S0140-6736(18)32590-X.
3. Oshima M, Neuen BL, Jardine MJ, Bakris G, Edwards R, Levin A, et al. Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. Lancet Diabetes Endocrinol. 2020;8:903-14. doi:10.1016/S2213-8587(20)30300-4.
4. Koshino A, Schechter M, Chertow GM, Vart P, Jongs N, Toto RD, et al. Dapagliflozin and Anemia in Patients with Chronic Kidney Disease. NEJM Evid. 2023;2. doi:10.1056/evidoa2300049.
5. The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023;388:117-27. doi:10.1056/NEJMoa2204233.
6. Lewis M, Burrack N, Heymann A, Grossman A, Neuman T, Abuhasira R. Sodium-glucose cotransporter 2 inhibitors, erythrocytosis, and thrombosis in adults with type 2 diabetes. JAMA Netw Open 2025;8. doi:10.1001/jamanetworkopen.2025.17086.
7. Tian Q, Guo K, Deng J, Zhong Y, Yang L. Effects of SGLT2 inhibitors on haematocrit and haemoglobin levels and the associated cardiorenal benefits in T2DM patients: A meta-analysis. J Cell Mol Med 2022;26:540–7. doi:10.1111/jcmm.17115.
8. Gangat N, Tefferi A. Sodium-glucose co-transporter-2 inhibitor use and erythrocytosis: assessment of risk and need for referral to haematology. Nephrol Dial Transplant. 2023;38:2670-2. doi:10.1093/ndt/gfad171.
9. Aoun M, Jadoul M, Anders HJ. Erythrocytosis and CKD: a review. Am J Kidney Dis. 2024;84:495-506. doi:10.1053/j.ajkd.2024.02.015.
10. Lee JY, Lee JH, Jung EJ, Park W, Seo J, Kang M, et al. Prevalence and thrombotic risk of SGLT-2 inhibitor-associated erythrocytosis: a retrospective cohort study. Cardiovasc Diabetol. 2025;24. doi:10.1186/s12933-025-02805-6.
11. Liu J, Chin-Yee B, Ho J, Lazo-Langner A, Chin-Yee IH, Iansavitchene A, et al. Diagnosis, management, and outcomes of drug-induced erythrocytosis: a systematic review. Blood Adv. 2025;9:2108-18. doi:10.1182/bloodadvances.2024015410.
12. Gangat N, Szuber N, Tefferi A. JAK2 unmutated erythrocytosis: 2026 update on diagnosis and management. Am J Hematol. 2025;100:2333-54. doi:10.1002/ajh.70118

13. Chen YH, Hsieh TYJ, Sun AYE, Chen K, Choi E, Rastogi N, et al. Erythrocytosis and thromboembolic risks associated with SGLT2 inhibitors in type 2 diabetes. Sci Rep. 2026;16. doi:10.1038/s41598-025-31726-3.
14. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117-28. doi:10.1056/NEJMoa1504720.
15. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, et al. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA- REG OUTCOME trial. Diabetes Care. 2018;41:356–63. doi:10.2337/dc17-1096.
16. Pherai MS, Jong FEI de, Jansen J, Tukker M, Özoğul S, Lenting S, et al. Secondary Erythrocytosis in Patients With Heart Failure on SGLT2 Inhibitors: Insights from a Multicenter "Real World" Study. Am J Cardiol. 2026;259:71–3. doi:10.1016/j.amjcard.2025.09.011.
17. Wang X, Fu R, Liu H, Ma Y, Qiu X, Dong Z. The effects of sodium glucose co-transporter (Sglt) 2 inhibitors on hematocrit levels: A systematic review and meta-analysis of randomized controlled trials. Ann Palliat Med 2021;10:6467–81. doi:10.21037/apm-21-1022.
18. Gangat N, Abdallah M, Szuber N, Saliba A, Alkhateeb H, Al-Kali A, et al. Sodium-glucose co-transporter-2 inhibitor use and JAK2 unmutated erythrocytosis in 100 consecutive cases. Am J Hematol. 2023;98:E165-E167. https://doi.org/10.1002/ajh.26933.
19. Stefánsson BV, Heerspink HJL, Wheeler DC, Sjöström CD, Greasley PJ, Sartipy P, et al. Correction of anemia by dapagliflozin in patients with type 2 diabetes. J Diabetes Complications 2020;34. doi:10.1016/j.jdiacomp.2020.107729.
20. Mohamed AA, Andersen CF, Christensen DM, Riis-Vestergaard LD, Mohammad M, Elmegaard M, et al. Erythrocytosis incidence and thromboembolic risk in heart failure with reduced ejection fraction treated with SGLT2 inhibitors: a nationwide register-based cohort study. Cardiovasc Diabetol. 2025;24:314. doi :10.1186/s12933-025-02871-w.
21. Ferreira JP, Zannad F, Vasques-Nóvoa F, Neves JS, Filippatos G, Pocok SJ, et al. Anaemia, erythrocytosis, and empagliflozin in heart failure with preserved ejection fraction: the EMPEROR-Preserved trial. Eur Heart J 2025;46(11):1074–7. doi:10.1093/eurheartj/ehae864.
22. Doi Y, Hamano T, Yamaguchi O, Isaka Y. Canagliflozin may increase thromboembolic events in males with erythrocytosis but not in females. Blood Adv. 2025;9:3202–12. doi:10.1182/bloodadvances.2025016320.
23. Sano M, Goto S. Possible mechanism of hematocrit elevation by sodium glucose cotransporter 2 inhibitors and associated beneficial renal and cardiovascular effects. Circulation. 2019;139:1985-7. doi:10.1161/CIRCULATIONAHA.118.038881.
24. Mazer CD, Hare GMT, Connelly PW, Gilbert RE, Shehata N, Quan A, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. Circulation. 2020;141:704-7. doi:10.1161/CIRCULATIONAHA.119.044235.
25. Packer M. How can sodium-glucose cotransporter 2 inhibitors stimulate erythrocytosis in patients who are iron-deficient? Implications for understanding iron homeostasis in heart failure. Eur J Heart Fail. 2022;24:2287-96. doi: 10.1002/ejhf.2731.
26. Bailey CJ, Day C, Bellary S. Renal protection with SGLT2 inhibitors: effects in acute and chronic kidney disease. Curr Diab Rep. 2022;22:39-52. doi:10.1007/s11892-021-01442-z.
27. Sørensen SS, Gullaksen S, Vernstrøm L, Ringgaard S, Laustsen C, Funck KL, et al. Evaluation of renal oxygenation by BOLD-MRI in high-risk patients with type 2 diabetes and matched controls. Nephrol Dial Transplant. 2023;38:691–9. doi:10.1093/ndt/gfac186.
28. Ghanim H, Abuaysheh S, Hejna J, Green K, Batra M, Makdissi A, et al. Dapagliflozin suppresses hepcidin and increases erythropoiesis. J Clin Endocrinol Metab. 2020;105:E1056-63. doi:10.1210/clinem/dgaa057.
29. Mithoowani S, Laureano M, Crowther MA, Hillis CM. Investigation and management of erythrocytosis. CMAJ. 2020;192:E913-8. doi:10.1503/cmaj.191587.