# SGLT2 INHIBITOR-ASSOCIATED POLYCYTHAEMIA

## A HAEMATOLOGY PERSPECTIVE FROM A RETROSPECTIVE CASE SERIES

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## Introduction

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are increasingly prescribed for **type 2 diabetes mellitus (T2DM)** and **heart failure with reduced ejection fraction (HFrEF)**, owing to their proven benefits in **glycaemic control**, **cardiovascular outcomes**, and **renal protection**. Their widespread adoption means clinicians across specialities are encountering patients on these agents.

In recent years, there have been emerging reports of **polycythaemia** occurring in patients receiving SGLT2 inhibitors. The underlying mechanism is not fully established. Proposed mechanisms include **increased erythropoietin (EPO) production**, **haemoconcentration**, or **metabolic changes** influencing red cell mass. However, existing evidence is limited and often derived from **endocrine or cardiology cohorts**, rather than from patients referred specifically to haematology for investigation of polycythaemia.

Polycythaemia is clinically important because it may mimic **myeloproliferative neoplasms (MPNs)** such as **polycythaemia vera (PV)**. This can lead to unnecessary investigations, anxiety, and in some cases invasive testing such as bone marrow biopsy. Distinguishing **drug-induced secondary causes** from clonal haematological disorders is therefore vital to ensure patients receive appropriate and proportionate management.

**Aim:** We undertook a retrospective review of patients referred to haematology with suspected polycythaemia while on SGLT2 inhibitors, in order to describe their clinical features, laboratory findings, and outcomes.

## Results

### Cohort Characterestics:

Between the period of period of February 2019 and December 2024, 18 patients were referred to the haematology department for investigation of polycythaemia. 10 of these were new-onset (6M, 4F), with a median age of 58.

**Figure 1. Flow of haematology referrals**

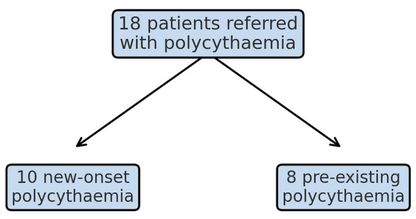
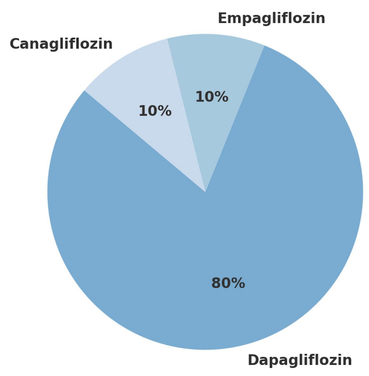


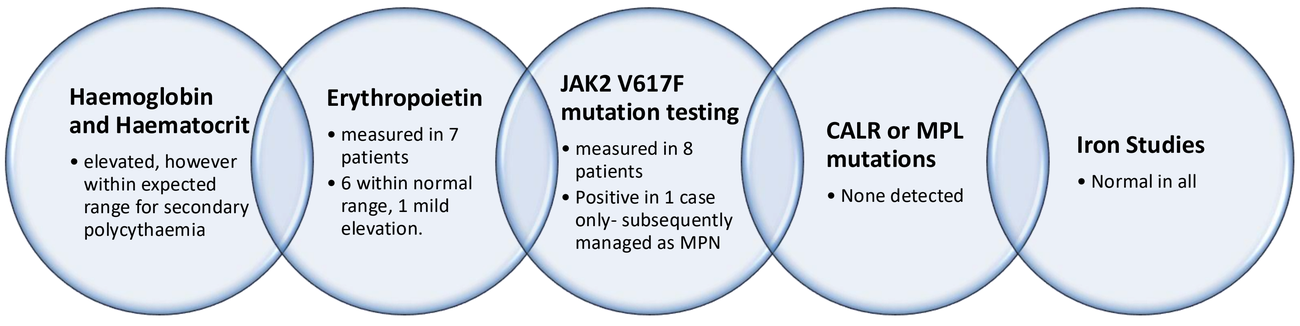

**Figure 2. SGLT2 inhibitors prescribed in new-onset cases (n=10)**
**Distribution reflects local prescribing patterns**




### Onset and Drug Exposure

The time interval for drug initiation to identification of polycythemia ranged from 1 to 18 months, with a median time period of 6 months.

### Laboratory Evaluation




### Comorbidities and potential confounders

Comorbidities in the new-onset group included **heart failure (n=3)**, **chronic obstructive pulmonary disease (n=2)**, and **obstructive sleep apnoea (n=1)**.

### Summary of findings

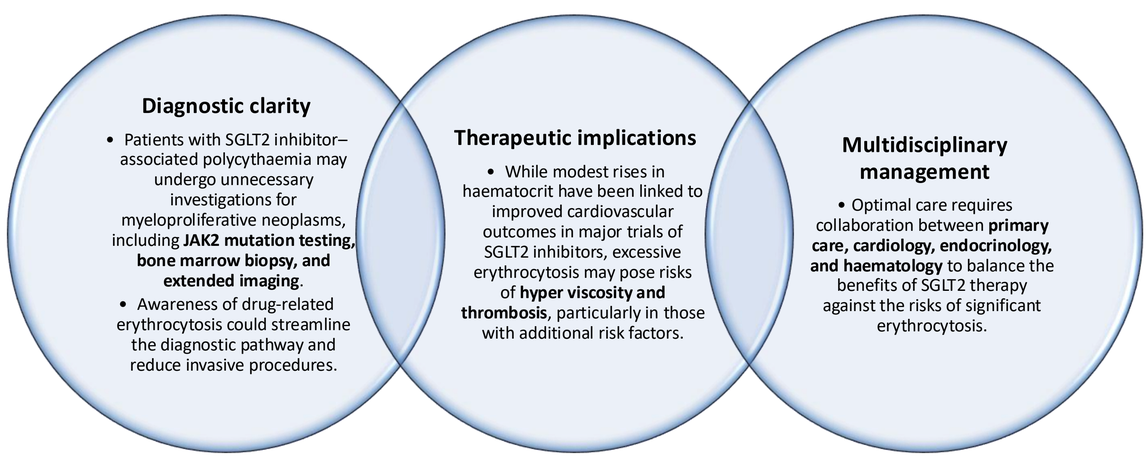
Taken together, these findings demonstrate that a subset of patients exposed to SGLT2 inhibitors developed **new-onset secondary polycythaemia** within months of treatment initiation. The lack of consistent EPO elevation, the rarity of clonal mutations, and the timing of onset all support a **drug-associated mechanism**. Nonetheless, comorbidities such as cardiopulmonary disease may act as cofactors in susceptible individuals.

## Conclusion

In this single-centre cohort, **10 out of 18 patients** referred to haematology were identified as having **new-onset polycythaemia temporally associated with SGLT2 inhibitor initiation**. The **latency period of 1–18 months**, coupled with **normal erythropoietin levels in the majority** and **lack of clonal markers in most cases**, supports a **secondary, drug-associated mechanism** rather than primary polycythaemia.

These findings add to the growing but limited body of evidence linking SGLT2 inhibitors with erythrocytosis[2,3]. Mechanistic hypotheses include modulation of **renal hypoxia-inducible factor (HIF) pathways**, restoration of **renal erythropoietin-producing cell function**, and attenuation of **tubulointerstitial glucotoxicity**, thereby enabling enhanced erythropoiesis [1,4,5]

### Relevance of Clinical Association




Our series highlights that SGLT2 inhibitors should be **actively considered in the differential diagnosis of new-onset polycythaemia**. Incorporating a focused drug history into the initial haematology work-up could prevent delays, avoidable anxiety, and unnecessary invasive testing.

Further **prospective and mechanistic studies** are needed to define incidence, identify patient subgroups at greatest risk, and clarify whether this effect is a benign biomarker of cardio-renal benefit or a clinically significant adverse effect requiring intervention.

## REFERENCES

1. Aoun, M., Koussa, S. and Daou, R., 2024. Erythrocytosis and chronic kidney disease: A review. *Kidney International Reports*, [online].
2. Liu, Y., et al., 2024. Diagnosis, management, and outcomes of drug-induced erythrocytosis: A systematic review. *British Journal of Haematology*, 207(2), pp.203–215.
3. Gangat, N., Szuber, N., Al-Kali, A., Lasho, T., Finke, C., Pardanani, A. and Tefferi, A., 2021. JAK2 wild-type erythrocytosis associated with sodium-glucose cotransporter-2 inhibitor therapy. *American Journal of Hematology*, 96(8), pp.E285–E288.
4. Marathias, K.P., Lambadiari, V., Raptis, S.A. and Dimitriadis, G.D., 2020. Competing effects of renin–angiotensin system blockade and sodium-glucose cotransporter-2 inhibitors on erythropoietin secretion in diabetes. *Journal of Clinical Medicine*, 9(5), p.1565.
5. Packer, M., 2021. Critical examination of mechanisms underlying the reduction in heart failure events with SGLT2 inhibitors: identification of a molecular link between their actions to stimulate erythrocytosis and to alleviate cellular stress. *Cardiorenal Medicine*, 11(1), pp.1–9.

## CONTACT

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