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Incidental changes in hemoglobin levels in patients with myelofibrosis receiving treatment with sodium-glucose co-transporter-2 inhibitors

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Running title: SGLT-2 inhibitor use in myelofibrosis

Key words: Anemia, Thrombosis, *JAK2*, myeloproliferative

Data sharing: please email the corresponding author.

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Sodium-glucose co-transporter-2 inhibitors (SGLT-2I) (also known as gliflozins or flozins) are increasingly prescribed for diabetes mellitus, heart failure and chronic kidney disease.[1] Food and Drug Administration (FDA)-approved drugs within the SGLT-2I class, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugloflozin, and sotagliflozin offer cardioprotection and enhance erythropoiesis through interrelated mechanisms.[2] The physiology of SGLT2-I induced erythrocytosis is multifactorial, potential mechanisms include i) increased erythropoietin (Epo) production, ii) suppression of hepcidin and modulation of iron metabolism and iii) hemoconcentration.[3] In placebo-controlled studies, empagliflozin demonstrated a dose-dependent increase in hemoglobin (Hgb) and hematocrit (Hct) levels, with median increase in Hct of 4.8% ± 5.5% and 5.0% ± 5.3% with empagliflozin 10 mg and 25 mg, respectively, versus 0.9% ± 4.7% with placebo.[4] SGLT-2I have also been shown to ameliorate anemia in patients with chronic kidney disease; in a post-hoc analysis of the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE)[5] and Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trials,[6] respective increase in Hct was 2.4% and 2.3% higher in the canagliflozin and dapagliflozin arms compared to placebo. Moreover, resolution of anemia was noted in a higher proportion of patients on dapagliflozin than placebo (53.3% vs 29.4%). In light of these observations, we postulate that SGLT-2I might stimulate erythropoiesis and improve anemia in chronic myeloid malignancies such as myelofibrosis (MF).[7-9] Accordingly, in the current study, our primary objective was to evaluate the impact of SGLT-2I therapy on Hgb levels and anemia-related outcomes in patients with MF.

After approval by the institutional review board for minimal risk research protocol, the Mayo Clinic myeloproliferative neoplasm (MPN) clinical database was queried to identify patients with primary or secondary MF, prescribed SGLT2-I for diabetes mellitus, heart failure or chronic kidney disease, following established diagnosis of MF.[10] The time of SGLT-2I initiation was considered baseline and for each patient, baseline Hgb, changes in Hgb and thrombotic events during SGLT-2I treatment were

recorded. Therapeutic interventions for MF including timing of initiation and discontinuation of cytoreductive agents were carefully documented.

A total of 16 patients with MF (primary MF (PMF) (*n*=12), post-essential thrombocythemia MF (post-ET MF) (*n*=4); median age; 74 years, 56% males) received treatment with empagliflozin (*n*=10), dapagliflozin (*n*=4), or canagliflozin (*n*=2) between July 2019 and March 2024. *JAK2V617F* mutation was detected in 8 (50%); *CALR* mutation in 5 (31%), *MPL* in 2 (13%) cases, while 1 (6%) case was triple-negative. A history of thrombosis before SGLT-2I use was documented in 8 (50%) of patients which included four arterial (25%) and four venous (25%) events. 7 (44%) of patients received cytoreductive therapy, including hydroxyurea (*n*=2), ruxolitinib (*n*=4), and momelotinib (*n*=1); 11 (69%) and 6 (38%) of patients were also on antiplatelet therapy and systemic anticoagulation, respectively.

Table 1 provides detailed clinical and laboratory characteristics of 16 patients with MF started on SGLT-2I at a median of 12 months (range; 2-73 months) following MF diagnosis. Baseline median (range) Hgb value at the time of initiation of SGLT-2I was 11 g/dL (8–15), 6 (38%) patients displayed Hgb <10 g/dl including one case (6%) with transfusion-dependent anemia. At a median treatment duration of 11.5 months (2-73), two (13%) patients experienced venous thrombosis while receiving SGLT-2I therapy; both events were chronic pulmonary thromboembolism secondary to pulmonary hypertension. Median follow-up from MF diagnosis and SGLT-2I initiation was 4 years (1-18 years) and 1.2 (0.3-6.1 years), respectively, during which 4 deaths and no leukemic transformations were recorded.

Figure 1 and Table 2 highlight Hgb changes from baseline to post treatment Hgb levels in all 16 patients with MF receiving SGLT-2I. 14 (88%) patients displayed increase in Hgb levels after initiation of SGLT-2I, with Hgb improvement of ≥1 g/dl in 9 (54%) patients. Hgb increase of 1.5g/dl or greater was documented in 6 (38%) of cases (Patients 2, 5, 8, 9, 11 and 15), and 3 (19%) patients displayed Hgb increase between 1-1.4 g/dl (Patients 4, 7 and 13). Among 6 anemic patients with baseline Hgb < 10 g/dl (Patients 2, 4, 9, 11, 13, 14), 3 (50%) showed Hgb improvement of ≥ 1.5 g/dl, and 2 (33%) displayed Hgb increase of 1 g/dl. On the other hand, two patients (12%) did not experience Hgb improvements; Patient 3

had a decline in Hgb and Patient 14 remained transfusion-dependent during SGLT-2I therapy. Details on hematological parameters and clinical course for patients with Hgb improvement of ≥1 g/dl are provided below.

Patient 2, a 77-year-old female with *JAK2*V167F mutated post-ET MF without history of thrombosis and not on cytoreductive therapy, received canagliflozin 100 mg daily for diabetes mellitus and chronic kidney disease. Baseline Hgb/Hct was 8.2 g/dL/27.5%, and one month after initiation of SGLT-2I, peak Hgb/Hct level of 10.2 g/dL/33.5% was observed. Shortly thereafter, two weeks after achieving peak Hgb/Hct, canagliflozin was discontinued due to pancreatic cysts and Hgb after stopping SGLT-2I was recorded at 9.3 g/dl.

Patient 4, a 79-year-old male with *JAK2*V167F mutated PMF and history of venous thrombosis, received empagliflozin 10 mg daily for heart failure with reduced ejection fraction (HFrEF) and diabetes mellitus. Baseline Hgb/Hct was 9.4 g/dL/28%; four months after initiation of SGLT-2I, peak Hgb/Hct level of 10.4 g/dL/31.8% was achieved, which was sustained for 25 months.

Patient 5, a 72-year-old male with *JAK2*V167F mutated PMF received dapagliflozin 5 mg daily for diabetes mellitus and chronic kidney disease.. Baseline Hgb/Hct was 10.9 g/dL/34.7%; and fifteen months after initiation of SGLT-2I, peak Hgb/Hct level of 13.1 g/dL/42.2% was recorded which was sustained for nine months. Dapagliflozin was discontinued due to acute kidney injury and Hgb within one month of stopping the drug was at 9.5 g/dl. It is to be noted that he had received intravenous iron two weeks prior to peak Hgb/Hct. Also, he was started on ruxolitinib 5 mg twice daily three days prior to peak Hgb.

Patient 7, a 60-year-old female with *JAK2*V167F mutated PMF, on hydroxyurea 1000 mg daily, received dapagliflozin 10 mg daily for HFrEF. Baseline Hgb/Hct was 14.7 g/dL/45.9%, and one month after initiation of SGLT-2I, peak Hgb/Hct level of 16.1 g/dL/49.4% was observed. Thereafter, eight weeks after achieving peak Hgb/Hct, dapagliflozin was discontinued due to unclear reasons.

Patient 8, a 65-year-old male with *MPL* mutated PMF received empagliflozin 25 mg daily for diabetes mellitus. Baseline Hgb/Hct was 10.3 g/dL/30.9%; and six months after initiation of SGLT-2I, peak Hgb/Hct level of 11.9 g/dL/35.2% was observed which was sustained for six months. He was started on ruxolitinib 5 mg twice daily, ten days prior to peak Hgb.

Patient 9, a 75-year-old male with *JAK2*V167F mutated PMF and history of venous thrombosis before and during SGLT-2I, received empagliflozin 10 mg daily for HFrEF. Baseline Hgb/Hct was 8.7 g/dL/27.7%; and, eight months after initiation of SGLT-2I, peak Hgb/Hct level of 11.6 g/dL/38.4% was observed. Notably, ruxolitinib 20 mg twice daily had been discontinued and he was started on momelotinib 200 mg daily three months prior to peak Hgb.

Patient 11, a 78-year-old male with *JAK2*V167F mutated PMF and history of arterial thrombosis was started on empagliflozin 10 mg daily for HFrEF. He was also receiving darbepoetin alfa 200 mcg every 2 weeks. Baseline Hgb/Hct was 9.9 g/dL/33.6%, and six months after initiation of SGLT-2I, peak Hgb/Hct level of 11.9 g/dL/37% was achieved and was maintained for five months. At that time, empagliflozin was discontinued due to gastrointestinal intolerance and Hgb level one month after stopping drug was at 9.9 g/dl.

Patient 13, an 82-year-old female with *MPL* mutated post-ET MF, received dapagliflozin 5 mg daily for diabetes mellitus. Baseline Hgb/Hct was 9.2 g/dL/30.6%; and, fourteen months after initiation of SGLT-2I, peak Hgb/Hct level of 10.2 g/dL/31.3% was recorded.

Patient 15, a 75-year-old male with *JAK2*V167F mutated PMF and history of arterial thrombosis, received empagliflozin 12.5 mg daily for diabetes mellitus. Baseline Hgb/Hct was 13.7 g/dL/43.4% and twenty-eight months after initiation of SGLT-2I, peak Hgb/Hct level of 15.9 g/dL/48.4% was observed and sustained for thirty months. Thereafter, empagliflozin was discontinued due to gastrointestinal intolerance and Hgb after stopping the drug was at 13.5 g/dl.

SGLT-2I use in patients with MPN is understudied; a recent report on 11 patients with ET receiving SGLT-2I therapy, showed consistent increments in Hgb/Hct levels with baseline median (range) increase in Hgb and Hct of 1.5 g/dL (1-4) and 5.1% (2.6-13.8), respectively.[11] A separate study described unmasking of underlying *JAK2*-mutated MPN in nine patients on SGLT-2I and highlighted four incidents of thrombotic complications.[12] The current series is the foremost to underline the erythropoietic activity of SGLT-2I in MF patients and suggests therapeutic value of SGLT-2I for management of MF-related anemia. Hepcidin is upregulated in MF, and SGLT-2I induced suppression of hepcidin and modulation of iron metabolism likely contributes to the observed increase in Hgb levels.[13] The majority of patients experienced increase in Hgb levels after initiation of SGLT-2I; five patients had sustained Hgb improvement of $\geq$ 1.5 g/dl for at least 12 weeks including two patients not receiving concurrent therapy; mostly (80%) males and all were *JAK2* mutated. Moreover, among six patients with baseline anemia (Hgb < 10 g/dl), 5 (83%) showed improvement in Hgb of atleast 1 g/dl. In regard to drug safety, two venous thrombotic events occurred during SGLT2-1 use and both were unrelated to therapy and none of the patients experienced leukemic transformation. Incidentally, SGLT-2I use was associated with a lower incidence of acute myeloid leukemia in a population-based analysis of patients with diabetes mellitus receiving SGLT-2I (n=718,276) compared to dipeptidyl peptidase 4 inhibitors (n=1,159,112) (HR 0.67, $p<0.01$).[14] Furthermore, several preclinical studies have provided evidence for potential anticancer effects of SGLT-2I. [15] Taken together, the current study suggests salutary effects of SGLT-2I on Hgb levels in patients with MF, however, additional studies are required to better characterize the improvements in Hgb level in the context of JAK inhibitors, and other cytoreductive therapies.

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Table 1. Clinical and laboratory characteristics of 16 patients with myelofibrosis (MF) at initiation of sodium glucose co-transporter-2 inhibitors (SGLT-2I)

Variables at time of SGLT-2I	***N=16***
Age in years, median (range)	74 (56-88)
Male gender, *n (%)*	9 (56)
Driver mutation, *n (%)*	
- *JAK2*	8 (50)
- *CALR*	5 (31)
- *MPL*	2 (13)
MPN type, *n (%)*	
- MF	12 (75)
- Post ET MF	4 (25)
Time from Myelofibrosis diagnosis to SGLT-2I in months, median (range)	5 (0-206)
SGLT-2I and dose, *n (%)*	
- Canagliflozin 100 mg	1 (6)
- Canagliflozin 150 mg	1 (6)
- Dapagliflozin 5 mg	2 (13)
- Dapagliflozin 10 mg	2 (13)
- Empagliflozin 10 mg	5 (31)
- Empagliflozin 12.5 mg	1 (6)
- Empagliflozin 25 mg	4 (25)
Additional cause for erythrocytosis, *n (%)*	
- Obstructive sleep apnea (OSA)	6 (38)
Thrombosis history[α], *n* (%)	
- Major arterial thrombosis before SGLT- 2I	4 (25)
- Major venous thrombosis before SGLT-2I	4 (25)
Splenomegaly, *n* (%)	10 (63)
Baseline hemoglobin g/dl, median (range) (n=16)	11 (8-15)
- Baseline Hemoglobin < 10 g/dl, *n (%)*	6 (38)
- Baseline Hemoglobin below reference range, *n (%)*	16 (100)
Reference range; females (11.6 – 15 g/dl), males (13.2-16.6 g/dl)	
Baseline hematocrit %, median (range)	33 (24-46)
- Baseline hematocrit <30% *n (%)*	4 (25)
- Baseline hematocrit below reference range, *n (%)*	16 (100)
Reference range; females (35.5 – 44.9 %), males (38.3-48.6%)	

[α]cerebrovascular accident, myocardial infarction, deep venous thrombosis, pulmonary embolism. ET: Essential Thrombocythemia MPN: Myeloproliferative neoplasms

Table 2. Clinical outcomes of 16 patients with myelofibrosis (MF) after initiation of sodium glucose co-transporter-2 inhibitors (SGLT-2I)

Outcomes after SGLT-2I therapy	
Increase in hemoglobin/hematocrit, *n (%)*	14 (88)
Peak hemoglobin g/dl, median (range)	12 (8-16)
- Male	12 (10-16)
- Female	11 (8-16)
Peak hematocrit %, median (range)	36 (24-50)
- Male	38 (32-48)
- Female	34 (24-50)
Change in hemoglobin/hematocrit	
- Change in hemoglobin g/dl, median (range)	1 (0-3)
- Change in hematocrit %, median (range)	4 (0-11)
- Time to peak hemoglobin/hematocrit in months, median (range)	6 (1-33)
Baseline leukocyte count x 10^9/l, median (range)	8 (5-22)
Leukocyte count at time of peak hemoglobin, x 10^9/l, median (range)	9 (8-24)
Baseline platelet count x 10^9/l, median (range)	361 (12-715)
Platelet count at time of peak hemoglobin, x 10^9/l, median (range)	386 (15-666)
Serum erythropoietin mIU/mL, median (range)	*n=7*
	52 (7-2448)
Pretreatment Serum erythropoietin mIU/mL, median (range)	*n*=3
Reference range (2.6 - 18.5 mIU/mL)	52 (26-55)
Serum ferritin mcg/L, median (range)	*n=16*
Reference range (24 - 336 mcg/L)	111 (20-3266)
Treatment for MF *n* (%)	
- Antiplatelet therapy	11 (69)
- Systemic Anticoagulation	7 (44)
- Cytoreductive therapy$^{\Omega}$	7 (44)
- Darbepoetin alfa	2 (13)
SGLT-2I treatment duration in months, median (range)	12 (2-73)
Thrombosis during SGLT-2I therapy, *n* (%)	
- Major arterial thrombosis, *n* (%)	0
- Major venous thrombosis, *n* (%)	2 (13)

$^{\Omega}$Cytoreductive therapy: Hydrea (n=2), Ruxolitinib (n=4), Momelotinib (n=1)

Figure Legend

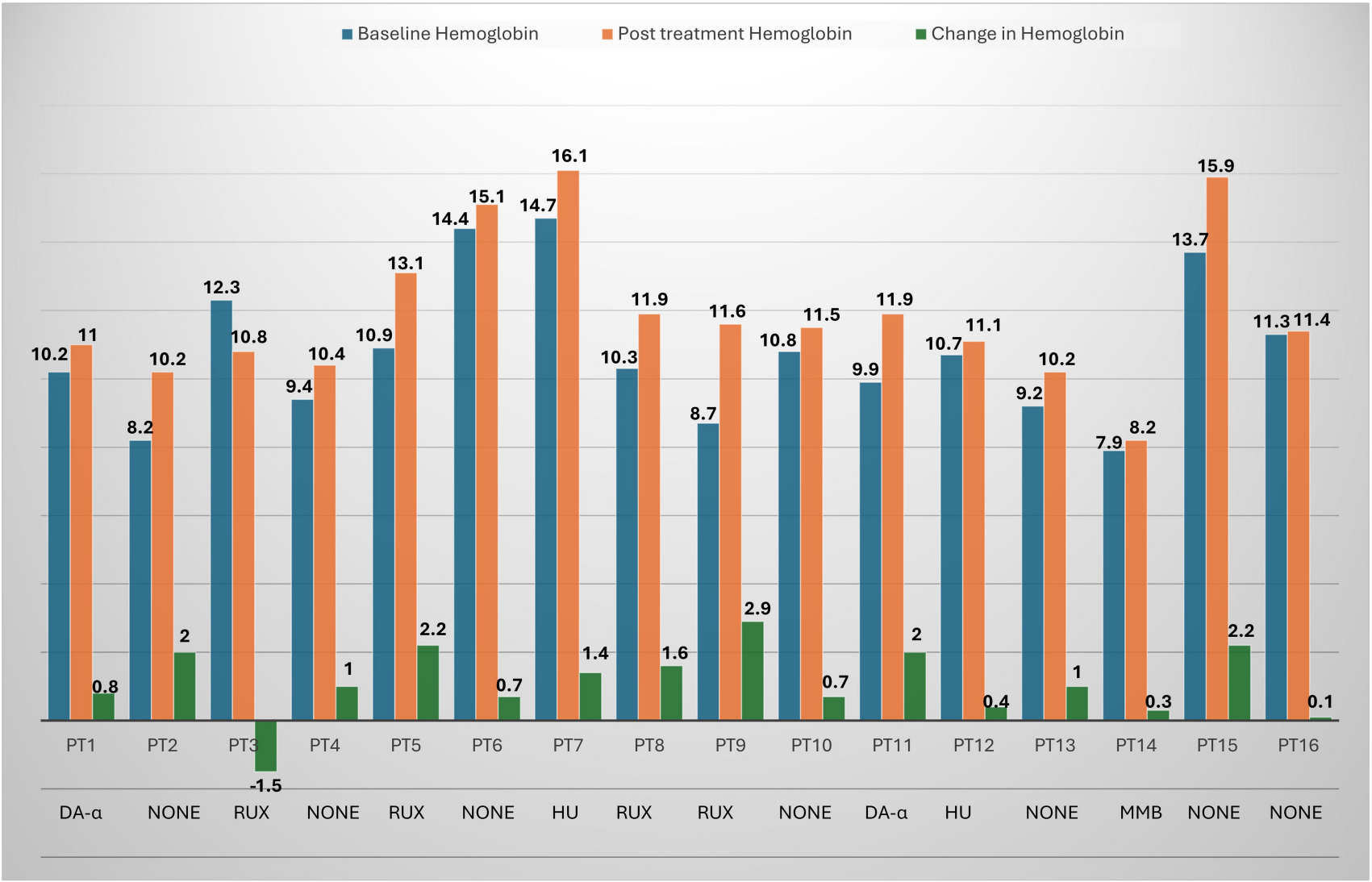
Baseline hemoglobin, hemoglobin post-treatment and change in hemoglobin in 16 patients with myelofibrosis (MF) receiving sodium glucose co-transporter-2 inhibitors (SGLT-2I)

DA-α = Darbepoetin alfa

HU= Hydroxyurea

RUX= Ruxolitinib

MMB= Momelotinib


Baseline Hemoglobin
Post treatment Hemoglobin
Change in Hemoglobin
10.2
11
0.8
8.2
10.2
2
12.3
10.8
-1.5
9.4
10.4
1
10.9
13.1
2.2
14.4
15.1
0.7
14.7
16.1
1.4
10.3
11.9
1.6
8.7
11.6
2.9
10.8
11.5
0.7
9.9
11.9
2
10.7
11.1
0.4
9.2
10.2
1
7.9
8.2
0.3
13.7
15.9
2.2
11.3
11.4
0.1
PT1
PT2
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PT15
PT16
DA-α
NONE
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DA-α
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