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Red Blood Cell Concentration Parameters and Gliflozins

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Introduction

The use of sodium glucose cotransporter 2 inhibitors (SGLT2i), or gliflozins, is recommended to reduce the risk of a major adverse cardiovascular events, particularly hospitalization for heart failure (HF), in patients with or without diabetes [1, 2]. The change in parameters of erythrocyte concentration in blood induced by these drugs, expressed as erythrocyte count per volume, hemoglobin in weight/ volume or hematocrit as percentage or decimal fraction, appear to be the main mediators of their favorable cardiovascular and kidney effects [3-7]. Thus, it should probably be considered an accessible and reliable biomarker of their benefit. Beyond their proven cardiovascular benefit in patients with diabetes type 2, heart failure is an important prescription code of these drugs, for patients with or without diabetes, and its use is projected to increase as guidelines support its use in this condition [6, 7].

An Increment of RBC Parameters should be Pursued in Heart Failure

Reported increments in red cell parameters may vary depending on the statistical approach. Considering hematocrit, a target increment of +2.5 (0.2 SE) [1, 2] to +5 (4 SD) [8] should be desired, to ascertain a net benefit for cardiovascular outcomes. Other changes in biomarkers, like uric acid, creatinine or glucose control, and effects, like lowering blood pressure and some weight loss, will also add advantage to patients with this condition.

Anemia is common in patients with diabetes, heart failure and compromised kidney function, and is generally viewed as an adverse prognostic factor [9]. It is often considered multifactorial, although therapy targets like iron or other vitamin deficiencies should be assessed. About 34% of diabetes male patients were anemic in the trial of dapagliflozin use in heart failure, [10] and an overall increment of + 2.32 ± 3.9%, (HR: 2.4, P< 0.001) was observed in this trial. Anemic patients will have the greatest benefit of these drugs, and changes should be monitored, but generally no flag will appear in the laboratory report.

Normal thresholds of a biomarker in laboratory reports should be adapted to the definition of disease and therefore "*laboratory flags*" may appear with hematocrit values higher than 0.49 in males and 0.46 in females, as defined diagnostic criteria by the World Health Organization in Polycythemia Vera [11]. These thresholds are sensitive to detect this condition but poorly specific of a myeloproliferative neoplasia.

How should we Manage Patients with Hematocrit Beyond Higher Limit Flags?

Erythrocytosis, as defined by these thresholds, is differently managed depending on clinical context, permissive hematocrits (up to 0.65) are considered safe in cyanotic heart disease, [12] and there is no robust evidence about the best management of hypoxic erythrocytosis, which should probably be guided by symptoms and manifestations [13].

There is some evidence that low and high hemoglobin, or hematocrit, may present a U-shaped curve for cardiovascular mortality [14]. Erythropoietin use is considered harmful in patients with anemia and heart failure, [6,7] and hemoglobin targets are lower when used in patients with compromised kidney function [9]. Thrombotic outcomes were the main reason for these limitations, although not clearly related to hematocrit [15].

With the widespread use of gliflozins, we must get used to observe important increments in some patients and flags in the laboratory report (Figure 1). Their link to these changes is evident. Frequently, delta check in the laboratory indicate a need of analyzer recalibration and repeated measurement, however relevant and true changes may be observed.

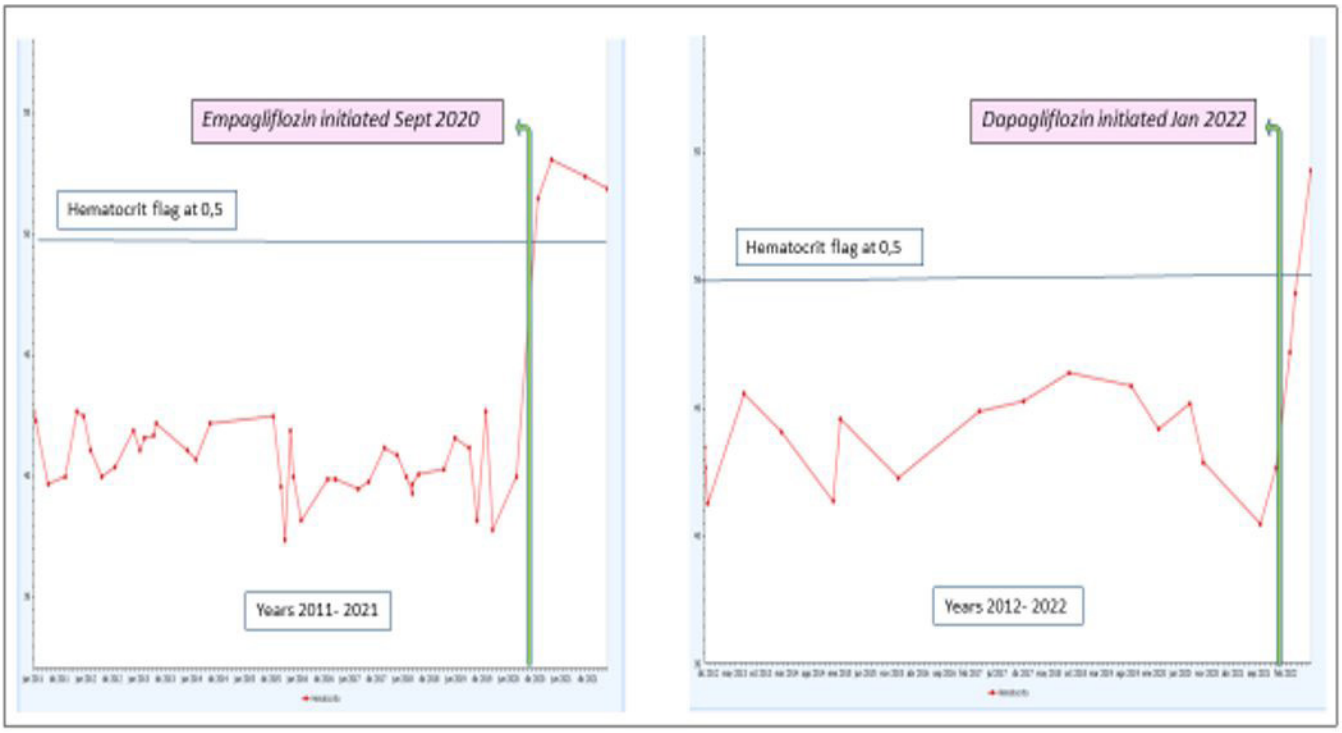

Figure 1. Graphics by our laboratory information system on long term evolution in hematocrit of two male patients, and changes after exposure to gliflozins.

Many patients presenting a normal- high hematocrit before they initiate gliflozins, will achieve cardiovascular benefit at the expense of abnormal flags in the laboratory report. Stroke risk and peripheral arterial disease complications do not seem to be increased with their use, [16, 17] so we should probably define higher limits of normality and be more permissive with abnormally high hematocrits for these drugs. A referral to hematology is frequently advised to these patients, and surely continues to be a reason to assess for JAK 2 mutation status and circulating erythropoietin levels, and some may be categorized as idiopathic erythrocytosis by some consultants. Red cell parameters return to normal after withdrawal of these drugs, but bloodletting is advised for some patients [18]. To our knowledge, no outcomes have been measured attending to (base line Hb???) abnormally high hemoglobin or hematocrit in outcome trials. Therefore, we don´t know how to manage this subset of patients, and what is the individual benefit of this medication, or at what levels we should be confident with patients presenting abnormally high hematocrit.

Clinical interventions supported by evidence are due to be applied to the general population at risk, and gliflozins are among the most sustained evidence-based drugs to obtain favorable cardiovascular outcomes [19] To get the greatest benefit, number needed to treat may be optimized by individually selecting patients to whom apply evidence. Harm should also be documented by subgroup analysis to avoid it in individual patients, and as such an analysis of outcomes in this population subgroup would shed light on how to manage and advice these patients.

Conclusion

Documenting an increment in red blood cell parameters should be pursued in patients receiving gliflozins, as an accessible and reliable biomarker of their cardiovascular and renal benefits. Anemic patients will be most benefitted, but some patients may present abnormally high erythrocyte counts, and no guidance exists to manage this situation beyond avoiding dehydration. A direct temporal relation to gliflozins should be searched, and decisions on whether continue, modulate, or avoid them should be a consensus among hematology and cardiovascular community. High hematocrits have traditionally been considered a thrombotic risk factor, [20] greatly inferred by studies in myeloproliferative neoplasia, however no proven threshold is defined as safe in this population subgroup.

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