The Effect of Empagliflozin on Platelet Function Profiles in Patients with Stable Coronary Artery Disease in Trinidad: The EFFECT Pilot Study

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ABSTRACT

Introduction: This prospective pharmacodynamic (PD) study aimed to assess the effect of the sodium–glucose cotransporter 2 inhibitor (SGLT2i) empagliflozin on platelet reactivity.

Methods: Patients with stable coronary artery disease (CAD) and type 2 diabetes mellitus (T2DM) (n = 20) who were actively treated with dual antiplatelet therapy (DAPT) of aspirin 81 mg daily and clopidogrel 75 mg daily were recruited. Platelet function was measured with the VerifyNow™ P2Y12 assay (Instrumentation Laboratory, Massachusetts, USA) and assessed before the initiation of and after 10 days of treatment with empagliflozin 25 mg once daily maintenance dose regimen. Results were compared with a paired t test.

Results: The mean P2Y12 reaction units (PRU) on empagliflozin was significantly less than without empagliflozin at baseline (187.35, 95% confidence interval (CI) 155.38–219.32 vs. 217.25, CI 180.60–253.90; p < 0.030). The mean difference in PRU was 29.90 (95% CI 3.17–56.63). No patients experienced any serious adverse events (SAEs).

Conclusions: Significantly attenuated platelet reactivity was observed on empagliflozin as compared to without empagliflozin. This dedicated pharmacodynamic study could be clinically pertinent for Trinidadian patients with stable CAD and T2DM on DAPT. Further studies are required to confirm these exploratory findings. (Funded by the University of the West Indies, St. Augustine; EFFECT).

Clinical Trial Registration: ClinicalTrials.gov number NCT04342819.

Keywords: Empagliflozin; Platelet reactivity; Platelet function; Sodium–glucose cotransporter 2 inhibitor (SGLT2i); VerifyNow™
Key Summary Points

Why carry out this study?

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have emerged as pivotal therapies for patients with type 2 diabetes mellitus (T2DM). Several large-scale randomized clinical trials, such as the EMPA-REG OUTCOME and DAPA-HF, have demonstrated a considerable reduction in major adverse cardiovascular events (MACE) [2, 3].

Several putative mechanisms to explain these cardioprotective effects have been proffered but not yet formally proven nor refuted. To our knowledge, the question of whether SGLT2 inhibition also resulted in pleiotropic antiplatelet effects remained unanswered.

What was learned from the study?

Empagliflozin achieved a greater antiplatelet effect and led to significantly lower platelet reactivity than in Trinidadian patients with CAD and T2DM without empagliflozin. This mechanistic pilot study can be clinically relevant because of an improved efficacy and safety profile.

INTRODUCTION

Sodium–glucose cotransporter 2 inhibitors (SGLT2i) have emerged as pivotal therapies for patients with type 2 diabetes mellitus (T2DM) [1]. Several large-scale randomized clinical trials, such as EMPA-REG OUTCOME and DAPA-HF, have demonstrated a considerable reduction in major adverse cardiovascular events (MACE) [2, 3].

SGLT2 inhibition decreases hyperglycemia by inducing glucosuria [1]. Additionally, diuresis, natriuresis, weight loss, and antihypertensive effects also occur [4]. The mechanistic effects of SGLT2 inhibition have not been fully elucidated, and other postulated mechanisms include alterations in myocardial energetics and prevention of cardiac fibrosis, among others [5].

To our knowledge, the question of whether SGLT2 inhibition also resulted in pleiotropic antiplatelet effects remained unanswered. Therefore, we conducted this exploratory pilot study to assess the antiplatelet pharmacodynamic (PD) effect of empagliflozin in a Trinidadian subpopulation with stable coronary artery disease (CAD) and T2DM.

METHODS

Study Design and Patient Population

The study complied with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, and was approved by the Campus Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad [6]. All participants provided written informed consent to participate in this prospective, open-label study that aimed to assess the effect of empagliflozin 25 mg once daily for 10 days. Patients were screened and enrolled between May 2020 and August 2020 at the cardiology outpatient clinic at our institution (Eric Williams Medical Sciences Complex, Trinidad and Tobago). They were considered eligible for the study if they were over 18 years of age and awaiting elective percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) on dual antiplatelet therapy (DAPT) for at least 4 weeks with aspirin 81 mg per day maintenance dose and clopidogrel 75 mg per day maintenance dose with T2DM. Exclusion criteria for this...
study included an acute coronary syndrome (ACS) within 6 months, active bleeding, prior hemorrhagic cerebrovascular event (CVE), clinical instability after an index event, use of an oral anticoagulation agent (warfarin derivative or other anticoagulant therapy such as dabigatran, rivaroxaban, apixaban, edoxaban), platelet count below 100 x 10^9/μL, hemoglobin level below 10 g/dL, serum creatinine level below 1.5 mg/dL, patients on concurrent CYP 2C19 inhibitors, and CYP 3A4 inducers. They were followed up for 28 days post procedure after completing the study to assess whether they experienced any adverse events.

**Blood Sampling and VerifyNow™ P2Y_{12} Testing**

Clopidogrel was held on the morning of their fasting scheduled visit (8:00–9:00 am) (18–24 h before baseline blood sampling), which ensured the determination of trough levels of clopidogrel reactivity. Blood samples were obtained at rest by antecubital puncture using a 21-gauge needle and placed into Vacuette (Greiner Bio-One North America, Monroe, NC, USA) blood collecting tubes containing 3.8% trisodium citrate after discarding the first 5 mL of blood to avoid artifactual platelet activation. Samples were processed by laboratory personnel blinded to ongoing study data. Platelet function assays included the VerifyNow™ P2Y_{12} (VN-P2Y_{12}) assay (Instrumentation Laboratory, Massachusetts, USA). The assays were performed according to standard protocols, as previously described [7–9]. The VN-P2Y_{12} assay reports the results as P2Y_{12} reaction units (PRU). A PRU greater than 208 was considered high on-treatment platelet reactivity (HPR) according to the last consensus [10]. The enrolled patients were then treated with empagliflozin 25 mg once daily for 10 days with pill accountability by the clinical research associate. After 10 days of the empagliflozin regimen, platelet reactivity was assessed a second time with the VN-P2Y_{12} assay using the aforementioned methodology (see Fig. 1).

**Patient Interview and Case Report Form**

The patients’ demographic data were recorded on a case report form (CRF) and included the patient’s medical, procedural history, and any cardiovascular medications.

**Statistical Analysis**

The sample size was calculated as 20 patients on the basis of a paired proportion sample, an alpha (α) value of 0.05, power of 80%, estimated baseline prevalence of 30% of PRU greater than 208, and absolute delta of 20% (expected prevalence of 10% of PRU greater than 208). Continuous variables were expressed as means ± 95% confidence intervals (CI) and categorical variables as frequencies and percentages. Paired t tests were used for comparisons of mean differences in PRU scores and McNemar’s test for paired proportions. No adjustments for multiple comparisons were made. Missing data were not imputed (none). A two-tailed p value of 0.05 was considered to indicate a statistically significant difference for all the analyses performed. Statistical analysis was performed using SPSS version 25.0 software (IBM SPSS Statistics, New York City, NY, USA).

**RESULTS**

A total of 20 patients with stable CAD and T2DM on DAPT with aspirin and clopidogrel were enrolled in the study. Table 1 shows the demographics of the study participants. The mean age was 64.2 years. Just less than half of the patients were female and all bar one patient was South Asian in ethnicity. The prevalence of prior myocardial infarction (MI) was 10%, that of hypertension (HTN) was 95%, that of dyslipidemia (HLD) was 70%, and that of cerebrovascular events (CVE) was 55%. No patient had a recorded history of chronic kidney (CKD), lung, and peripheral artery disease (PAD). The mean body mass index (BMI) was 26.7 kg/m². There was also a prevalence of at least 80% use of angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB),
and neprilysin inhibitors (Ni), and over 60% for beta-blockers and 90% for high-intensity statins. Slightly more than one-third of patients were on calcium channel blockers (CCB), with 50% also being on nitrates and trimetazidine, and one-fifth on ivabradine. No patients were on mineralocorticoid receptor antagonists (MRA). Nearly one-third of patients were on insulin therapy, while half were on metformin and sulfonlyureas. No patients were on glucagon-like peptide 1 receptor agonists (GLP-1RA) or dipeptidyl peptidase 4 (DPP4i) inhibitors. No
| Characteristics                              | Frequency (%) |
|---------------------------------------------|---------------|
| **Age**                                     |               |
| Mean                                        | 64.2 years    |
| Range                                       | 46–80 years   |
| **Gender**                                  |               |
| Female                                      | 9 (45)        |
| Male                                        | 11 (55)       |
| **Ethnicity**                               |               |
| South Asian                                 | 19 (95)       |
| Caribbean Black                             | 1 (5)         |
| Interracial                                 | 0 (0)         |
| **Body mass index (BMI)**                   |               |
| Mean                                        | 26.7 kg/m²    |
| Range                                       | 14.7–34.5 kg/m²|
| Normal                                      | 18.5–24.9 kg/m²|
| **Weight**                                  | 72.9 kg       |
| **Systolic blood pressure**                 | 153 mmHg      |
| Normal                                      | < 120 mmHg    |
| **Diastolic blood pressure**                | 87 mmHg       |
| Normal                                      | < 80 mmHg     |
| **Comorbidities**                           |               |
| Prior myocardial infarction (MI)            | 2 (10)        |
| Diabetes mellitus (DM)                      | 20 (100)      |
| Glycosylated hemoglobin (HbA₁c)             | 8.29 (mean)   |
| Range                                       | 5.6–12.5      |
| Normal                                      | < 6%          |
| Fasting blood glucose (FBG)                 | 188 mg/dL     |
| Normal                                      | < 126 mg/dL   |
| Hypertension (HTN)                          | 19 (95)       |
| Dyslipidemia                                | 14 (70)       |
| Chronic kidney disease (CKD)                | 0 (0)         |
| Cerebrovascular events (CVE)                | 11 (55)       |
| Chronic obstructive pulmonary disease (COPD)| 0 (0)         |
| Peripheral artery disease (PAD)             | 0 (0)         |
| Cardiovascular medications                 |               |
| Aspirin                                     | 20 (100)      |
| Characteristics                                                                 | Frequency (%) |
|---------------------------------------------------------------------------------|---------------|
| Clopidogrel                                                                      | 20 (100)      |
| Angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, neprilysin inhibitor (ACEi, ARB, Ni) | 16 (80)       |
| Beta-blocker (BB)                                                                | 13 (65)       |
| Statin                                                                           | 19 (95)       |
| Mineralocorticoid receptor antagonist (MRA)                                      | 0 (0)         |
| Calcium channel blocker (CCB)                                                   | 7 (35)        |
| Nitrates                                                                        | 10 (50)       |
| Ivabradine                                                                       | 10 (50)       |
| Trimetazidine                                                                    | 10 (50)       |
| Diabetic medications                                                             |               |
| Insulins                                                                         | 6 (30)        |
| Oral hypoglycemics                                                               |               |
| Metformin                                                                        | 10 (50)       |
| Sulfonylureas                                                                   | 10 (50)       |
| Glucagon-like peptide 1 receptor agonists (GLP-1RA)                              | 0 (0)         |
| Dipeptidyl peptidase 4 inhibitors (DPP4i)                                        | 0 (0)         |
| Cardiovascular procedures                                                       |               |
| Percutaneous coronary intervention (PCI)                                         | 0 (0)         |
| Coronary artery bypass grafting (CABG)                                          | 0 (0)         |
| P2Y12 reaction units (PRU)                                                       |               |
| PRU > 208                                                                        | 15 (75)       |
| PRU < 208                                                                        | 5 (15)        |
| Basic laboratory values                                                          |               |
| Serum hemoglobin (Hb)                                                            | 14.3 (normal 13.2–17.6 g/dL) |
| Serum creatinine (sCr)                                                           | 0.78 (normal 0.81–1.21 mg/dL) |
| Serum triglycerides (TG)                                                         | 187 (normal < 150 mg/dL) |
| Serum total cholesterol (TC)                                                     | 192 (normal < 170 mg/dL) |
| Serum low-density lipoprotein (LDL)                                              | 157 (normal < 130 mg/dL) |
| Serum high-density lipoprotein (HDL)                                             | 34 (normal > 50 mg/dL) |
patients received either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). The patients’ hemoglobin and serum creatinine levels were normal, whereas the mean glycosylated hemoglobin (HbA1c) was 8.29%, mean triglycerides, total cholesterol, and low-density lipoprotein were 187 mg/dL, 192 mg/dL, and 157 mg/dL, respectively. The mean PRU on empagliflozin was significantly less than that without empagliflozin at baseline (187.35, 95% confidence interval (CI) 155.38–219.32 vs. 217.25, 95% CI 180.60–253.90; \( p \) < 0.030) (Table 2, Fig. 2). The mean difference in PRU was 29.90 (95% CI 3.17–56.63). Seventy-five percent of patients had high on-treatment platelet reactivity (HPR) with a PRU greater than 208 which decreased to half (\( p \) < 0.06) with near-significance. No patients experienced any serious adverse events.

DISCUSSION

Diabetes is associated with a complex neurohormonal milieu that accentuates platelet reactivity [11]. Several factors contributing to this phenomenon include hyperglycemia, dyslipidemia, insulin resistance with resultant oxidative stress, inflammation, and endothelial dysfunction [11].

Recently, SGLT2is have gained robust traction as a novel class of antidiabetic agents with a unique mechanism of decreasing hyperglycemia by inducing glucosuria [12]. It does this chiefly by inhibiting the sodium–glucose cotransporter 2 proteins, which resorb glucose in the proximal convoluted tubule of the nephron [13]. In addition to its primary effect, natriuresis, weight loss, antihypertensive, and antilipidemic effects also occur [4]. Other postulated extraglycemic mechanisms include alterations in myocardial energetics and attenuation of fibrosis [5].

SGLT2is have been evaluated in several landmark cardiovascular (CV) outcome trials, and specifically, the EMPA-REG OUTCOME trial indicated an essential signal with reduced MACE mediated by lower rates of CV death (hazard ratio (HR) 0.62, 95% CI 0.49–0.77;
Several putative mechanisms to explain these cardioprotective effects have been proffered but not yet formally proven nor refuted. For example, glycemic control with a similar reduction in HbA1c with other pharmacotherapies such as DPP4is does not necessarily equate to comparable CV benefit. Additionally, glycemic control usually requires protracted administration, as evidenced by the ADVANCE study to clinically translate into a reduction of MACE [14]. This is in contrast to SGLT2i CV outcome trials in which there is an early and clear-cut divergence of the event-free survival curves. The DAPA-HF trial, which evaluated another SGLT2i, dapagliflozin, also demonstrated similar CV benefits even in patients without diabetes.

To the authors’ knowledge, it has not yet been described that SGLT2 inhibition attenuates platelet reactivity either directly or indirectly via pleiotropic mechanisms. We suggest several critical pathways that could contribute to an antiplatelet effect of SGLT2is, as evidenced by our study’s findings [15].

Hyperglycemia can escalate platelet reactivity via several mechanisms, which include surface protein glycation with a resultant decrease in membrane fluidity, an overall osmotic effect, and activation of protein kinase C [16–18]. It is also strongly correlated to dyslipidemia, which can also independently increase platelet reactivity, typically mediated by apolipoprotein E [19]. Interestingly, enhanced glycemic control has been associated with attenuated platelet reactivity [20]. A recent study alluded to a near 1% decrease in HbA1c with SGLT2 inhibition [21]. Additionally, SGLT2i treatment was associated with a small increase in high-density lipoprotein (HDL) cholesterol and a decrease in triglyceride (TG) levels [22].

BMI and specifically overweight and obesity have been associated with increased platelet reactivity [23]. SGLT2i treatment is associated with an average 2-kg to 4-kg reduction of body weight [24]. Also, obesity can induce and exacerbate insulin resistance. Insulin antagonizes the effect of platelet agonists such as collagen, ADP, epinephrine, and platelet-activating factor (PAF) [25]. Thus, resistance by the platelet to the effects of insulin attenuates insulin-mediated antagonism of platelet activation and thereby promotes platelet reactivity. Several small preclinical, animal, and phase 1 studies suggest that SGLT2i ameliorates myocardial insulin resistance and obesity-induced inflammation [26–29].

Oxidative stress accentuates platelet reactivity and induces endothelial dysfunction [30–32]. Superoxide can lead to intracellular calcium release and attenuates the biologic activity of nitric oxide [33, 34]. Impaired endothelial function results in decreased prostacyclin and nitric oxide concentrations [35]. There are also increased endogenous inflammatory, platelet adhesion, and activation markers in diabetes such as surface glycoproteins Ib and IIb/IIIa, PAF, and Fcγ receptor type IIa (FcγRIIa), which are implicated in augmented platelet reactivity [36]. SGLT2is have been recently highlighted to possess antioxidant and anti-inflammatory properties in several small preclinical, animal, and phase 1 studies to reduce interleukin-6 (IL-6), tumor necrosis factor alpha (TNFα), monocyte chemotactic protein 1 (MCP-1), and C-reactive protein (CRP) [37].

We postulate that SGLT2i-mediated attenuation in platelet reactivity occurs via the aforementioned multifaceted pathways of decreased hyperglycemia, dyslipidemia, obesity, insulin resistance, oxidative stress, inflammation, and endothelial dysfunction with the potential clinical sequelae of an overall reduction of MACE.

Study Limitations

This pilot study was adequately powered for PD PRU outcomes and achieved its target enrollment of 20 patients. However, this study was not designed to evaluate clinical endpoints, and therefore, no safety or efficacy conclusions can be affirmed. The patient population comprised almost entirely the South Asian ethnicity (95%) with an HPR of 75%, consistent with previous studies performed by this group, which may allude to an inherent selection bias [7, 38, 39]. The study’s findings cannot be externally applied or generalized to other subpopulations.
such as patients receiving more potent antiplatelet agents such as prasugrel or ticagrelor. Composite testing with other platelet function assessment modalities such as flow cytometry and thromboelastography would have been informative; however, these are not currently available in Trinidad.

CONCLUSIONS

Empagliflozin achieved a greater antiplatelet effect and led to significantly lower platelet reactivity than in Trinidadian patients with CAD and T2DM without empagliflozin. This mechanistic pilot study can be clinically relevant because of an improved efficacy and safety profile.

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**Compliance with Ethics Guidelines.** The study complied with the Declaration of Helsinki, International Conference on Harmonization, Good Clinical Practice, and was approved by the Campus Research Ethics Committee of the University of the West Indies, St. Augustine, Trinidad [6]. All participants provided written informed consent to participate.

**Data Availability.** All available data can be obtained by contacting the corresponding author. EFFECT ClinicalTrials.gov number NCT04342819. All materials, data, code, and associated protocols will be made promptly available to the editor and readers upon request. If requested, there will not be any restrictions on the availability of materials.

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