

## The Effect of SGLT2 Inhibitors on Antianginal Therapy Dynamics in Diabetic CABG Patients

### Diyabetik KABG Hastalarında SGLT2 İnhibitörlerinin Antianjinal Tedavi Dinamiklerine Etkisi

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#### ABSTRACT

**Aim:** Although SGLT2 inhibitors offer cardiovascular benefits in type 2 diabetes, their impact on antianginal therapy needs after CABG remains unclear. This study investigates the potential association between SGLT2i use and alterations in the frequency and intensity of antianginal regimens in these patients.

**Methods:** This retrospective study included 125 diabetic patients  $\geq 1$  year post-CABG, divided into SGLT2i users (n=70) and non-users (n=55). Demographic characteristics, laboratory findings, comorbidities, and antianginal medication profiles were retrospectively analyzed. The primary outcomes were changes in the number and intensity of antianginal medications during follow-up. One-way analysis of covariance (ANCOVA) was performed to assess the independent effect of SGLT2i use after adjustment for potential confounders.

**Results:** Baseline antianginal medication burden and treatment intensity were similar between groups (p>0.05). During follow-up, SGLT2i users demonstrated significantly greater reductions in ivabradine and ranolazine use compared with controls (p=0.035 and p=0.001, respectively). Patients receiving SGLT2i experienced a significantly greater reduction in both the total number of antianginal medications ( $-0.371 \pm 0.66$  vs.  $-0.036 \pm 0.57$ ; p=0.001) and overall treatment intensity ( $-0.52 \pm 0.89$  vs.  $-0.07 \pm 0.79$ ; p=0.001). After adjustment for age, sex, glomerular filtration rate, neutrophil count, and baseline medication burden, SGLT2i use remained independently associated with reduced antianginal medication number (F=7.175; p=0.009) and treatment intensity (F=8.106; p=0.005).

**Conclusion:** SGLT2 inhibitor therapy was independently associated with a reduced antianginal treatment burden in diabetic CABG patients. These findings indicate a potential association between SGLT2i use and additional anti-ischemic benefits beyond glycemic control in chronic coronary syndrome management.

**Key Words:** Chronic coronary syndrome, diabetes, SGLT2i, coronary artery bypass surgery, antianginal

#### ÖZ

**Amaç:** SGLT2 inhibitörleri tip 2 diyabet hastalarında kardiyovasküler faydalar sağlasa da, koroner arter baypas cerrahisi (KABG) sonrası anjina tedavisi ihtiyaçları üzerindeki etkileri belirsizliğini korumaktadır. Bu çalışma, SGLT2i'nin bu hastalarda antianginal tedavilerin sıklığını ve yoğunluğunu değiştirip değiştirmediği ile olan potansiyel ilişkisini araştırmaktadır.

**Yöntem:** Bu retrospektif çalışma, KABG sonrası en az 1 yıl geçmiş olan 125 diyabet hastasını içermekte olup, bu hastalar SGLT2i kullananlar (n=70) ve kullanmayanlar (n=55) olarak iki gruba ayrılmıştır. Demografik özellikler, laboratuvar bulguları, eşlik eden hastalıklar ve antianginal ilaç profilleri retrospektif olarak analiz edildi. Birincil sonuçlar, takip süresi boyunca antianginal ilaçların sayısı ve yoğunluğundaki değişikliklerdir. Potansiyel karıştırıcı faktörler için ayarlama yapıldıktan sonra SGLT2i kullanımının bağımsız etkisini değerlendirmek için tek yönlü kovaryans analizi (ANCOVA) yapıldı.

**Bulgular:** Başlangıçtaki antianginal ilaç yükü ve tedavi yoğunluğu gruplar arasında benzerdi (p>0,05). SGLT2i kullananlarda ivabradin ve ranolazin kullanımında kontrollere kıyasla anlamlı derecede daha büyük azalmalar gözlemlendi (sırasıyla p=0,035 ve p=0,001). Kontrol grubuna kıyasla, SGLT2i alan hastalarda hem toplam antianginal ilaç sayısında ( $-0,371 \pm 0,66$ 'ya karşı  $-0,036 \pm 0,57$ ; p=0,001) hem de genel tedavi yoğunluğunda ( $-0,52 \pm 0,89$ 'a karşı  $-0,07 \pm 0,79$ ; p=0,001) anlamlı derecede daha büyük bir azalma görüldü. Yaş, cinsiyet, glomerüler filtrasyon hızı, nötrofil sayısı ve başlangıçtaki ilaç yükü dikkate alındıktan sonra, SGLT2i kullanımı, antianginal ilaç sayısında (F=7,175; p=0,009) ve tedavi yoğunluğunda (F=8,106; p=0,005) azalma ile bağımsız olarak ilişkili kalmıştır.

**Sonuç:** SGLT2 inhibitör tedavisi, diyabetik KABG hastalarında antianginal tedavi yükünde azalma ile bağımsız olarak ilişkilidir. Bu bulgular, SGLT2i'nin kronik koroner sendrom yönetiminde glisemik kontrolün ötesinde ek anti-iskemik faydalar sağlayabileceğine dair potansiyel bir ilişkiye işaret etmektedir.

**Anahtar Sözcükler:** Kronik koroner sendrom, diyabet, SGLT2i, koroner arter bypass cerrahisi, antianginal

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## Introduction

**C**oronary artery bypass graft (CABG) surgery remains the gold standard for the treatment of advanced coronary artery disease. However, medical management following surgical revascularization is of critical importance for maintaining graft patency, controlling ischemic symptoms, and preventing secondary cardiovascular events [1]. Antiplatelet agents are currently continued for an indefinite period in the vast majority of patients to prevent graft occlusion [2]. Current guidelines recommend beta-blockers and calcium channel blockers (CCBs) as the primary pharmacotherapy for the management of post-operative ischemic symptoms [3]. Particularly in cases involving radial artery grafts, the use of CCB is of strategic importance due to its vital role in preventing graft spasm [3]. Nitrates increase blood flow by dilating the coronary arteries and have long been among the first-line medications of choice. Both short-acting and long-acting forms are available. In addition, ranolazine, trimetazidine, and ivabradine are agents that can be considered alongside standard anti-ischemic therapy [4].

Approximately 20–30% of CABG patients have diabetes, and this condition poses a significant burden on mortality and morbidity during the perioperative period [5]. Achieving glycemic control in patients with diabetes not only reduces surgical site infections but also directly affects long-term vascular healing [6]. In particular, intravenous or subcutaneous insulin administration is preferred to rapidly stabilize blood sugar levels in the early postoperative period (during the intensive care phase) [7]. Oral antidiabetic medications are particularly widely used, and in patients in a stable phase, metformin (a biguanide), sulfonylureas, and next-generation SGLT-2 inhibitors are prescribed.

In recent years, there has been a revolutionary shift in the treatment of type 2 diabetes; sodium-glucose cotransporter-2 (SGLT2) inhibitors have become central to treatment algorithms due to their glucose-lowering effects as well as their proven benefits in heart failure and major adverse cardiovascular events (MACE) [8]. The multifaceted mechanisms of SGLT2 inhibitors—such as optimizing myocardial energy

metabolism, reducing preload and afterload, alleviating interstitial edema, and suppressing inflammation—have also brought to light the potential “anti-ischemic” effects of these agents. These agents suggest that their cardiovascular protective effects may reduce patients’ need for antianginal medications (e.g., nitrates, ranolazine) [4]. Given the growing cardiovascular efficacy of SGLT-2 inhibitors, we anticipate that they may also lead to changes in the patterns of their use for antianginal purposes [9].

Although the effects of SGLT2 inhibitors on major adverse cardiovascular events (MACE) and hospitalizations due to heart failure have been extensively documented in the literature, the direct impact of these agents on the burden of antianginal medication (polypharmacy) in the post-CABG period has not yet been sufficiently elucidated. Agents such as nitrates and trimetazidine, which are the cornerstones of traditional antianginal therapy, have begun to be replaced by more specific molecules in current clinical practice, particularly as the risks associated with polypharmacy and the side effect profile are taken into account [10]. Although nitrates are still the treatment of choice—particularly due to their hemodynamic benefits in cases of heart failure as well as their role in managing ischemic symptoms—it remains to be seen to what extent agents that provide systemic protection, such as SGLT2 inhibitors, can alleviate this traditional treatment burden.

Patients’ participation in post-discharge cardiopulmonary rehabilitation programs and their follow-up via telehealth services improves their medication adherence [11]. These improvements will be particularly correlated with strict control of risk factors and the vascular improvements resulting from antidiabetic therapy.

There are very few studies on this topic in the literature, and the sample size is relatively small for a randomized controlled trial [9]. This study aims to retrospectively investigate the effect of SGLT2 inhibitor use on the number of antianginal medications required and the intensity of treatment in a population of diabetic patients who have undergone CABG. The data obtained are intended to guide clinicians in determining the potential role of SGLT2 inhibitors in the

management of postoperative ischemic symptoms and in optimizing medical treatment.

## Materials and Methods

This study was designed as a retrospective observational case-control study. Ethical approval for this study was obtained from the Alanya Alaaddin Keykubat Clinical Research Ethics Committee via Decision No. 08-02 dated May 13, 2026. The study was conducted in accordance with the principles of the Declaration of Helsinki. Medical records of patients who were admitted to the hospital for any reason within the past year and underwent coronary artery bypass graft (CABG) surgery were retrieved from the Hospital Information Management System (HIMS). The inclusion criteria for the study were: being 18 years of age or older, having a history of CABG for at least one year, having a diagnosis of type 2 diabetes mellitus, currently receiving active antidiabetic treatment, and having complete records of the medications used in the system. Patients without adequate medical records or those who had changed their antidiabetic medication within the past year were excluded from the analysis.

The number of participants to be included in the study was calculated at the outset using the G\*Power software. The use of antianginal medication was used as the primary variable in determining the estimated sample size; based on a calculation using an independent samples t-test with 80% power, a significance level of  $\alpha=0.05$ , and a "moderate" Cohen's effect size, a target of at least 102 cases was set. After applying the exclusion criteria, the study was completed with a total of 125 patients who met the eligibility criteria (n=70 receiving SGLT2i, n=55 not receiving SGLT2i). Specifically, patients in the active treatment arm were prescribed either empagliflozin (n=36) or dapagliflozin (n=34) at standard recommended dosages.

Patients' demographic data, anthropometric measurements from index hospital admissions or outpatient visits, surgical details (CABG duration, use of vein/arterial grafts), and all medications prescribed after discharge were retrospectively reviewed through the system. In particular, the antidiabetic agents (metformin, sulfonylurea, insulin, dipeptidyl peptidase-4 [DPP-4] inhibitors,

etc.) and antianginal medications (beta-blockers, calcium channel blockers, nitrates, ranolazine, trimetazidine, ivabradine) used by patients in the final year prior to the study, as well as any changes in the dosage or use of these medications, were recorded in detail. The follow-up period for evaluating changes in antianginal medications was standardized to a 1-year interval following the index date, and this duration was consistent between both the SGLT2i and control groups. The 'intensity of antianginal therapy' was defined as a composite score calculated by summing the number of antianginal medication classes prescribed and adjusting for their respective dosages (e.g., standard doses received a base score, while maximum tolerated doses or dose increases received proportionally higher scores). In short, each dose increase was counted as a one-point increase in the calculation. During the analysis phase, patients were divided into two main groups based on their SGLT2 inhibitor (SGLT2i) usage status: "SGLT2i users" and "non-SGLT2i users."

The detailed medical histories of all study participants were reviewed, and any accompanying cardiovascular, renal, and endocrine diseases were recorded. In this context, hypertension, hyperlipidemia, coronary artery disease, heart failure, chronic obstructive pulmonary disease (COPD), stroke, peripheral artery disease, and alcohol and tobacco use were noted. In individuals receiving medical treatment for hypertension and hyperlipidemia, the presence of these conditions was assumed.

Patients' routine biochemical tests (urea, creatinine, liver function tests, electrolytes, CRP, amylase), glycemic parameters (glucose, HbA1c), lipid profiles, and complete blood count (CBC) data were recorded. Glomerular filtration rate (GFR) was calculated using the e-GFR formula. Additionally, 12-lead resting ECG recordings (presence of sinus rhythm or atrial fibrillation/flutter), transthoracic echocardiographic evaluation results (left ventricular ejection fraction), and, if available, postoperative angiography reports indicating graft dysfunction were included in the analysis.

## Statistical Analysis

IBM SPSS Statistics for Windows, Version 20.0

(IBM Corp., Armonk, NY) was used for statistical analyses. The normality of continuous variables was assessed by visually examining histograms and Q-Q plots, as well as using the Shapiro-Wilk test. Continuous variables that followed a normal distribution were presented as mean  $\pm$  standard deviation, while those that did not follow a normal distribution were presented as median (interquartile range). Categorical variables were expressed as frequency (n) and percentage (%).

The Student's t-test was used to compare continuous variables following a normal distribution between the two groups, while the Mann-Whitney U test was used for data that did not follow a normal distribution. Categorical data were compared using the chi-square test or Fisher's exact test. To evaluate the independent effect of SGLT2i use on the number of antianginal medications and the intensity of antianginal treatment, a one-way analysis of covariance (ANCOVA) was performed, incorporating potential confounding factors (baseline number of medications, age, sex, GFR, and neutrophil count, etc.) into the analysis. In all comparisons, a two-sided p-value of  $<0.05$  was considered statistically significant.

## Results

The study included a total of 125 patients, comprising those receiving SGLT2 inhibitor (SGLT2i) therapy (n=70) and those not receiving it (n=55). The mean age in the SGLT2i group was significantly lower ( $65.58 \pm 9.19$  vs.  $71.35 \pm 8.35$ ;  $p=0.001$ ), and a higher proportion of males was observed in this group (87.1% vs. 70.9%;  $p=0.021$ ). No statistically significant differences were observed between the groups regarding the prevalence of comorbidities (hyperlipidemia, chronic obstructive pulmonary disease, heart failure, hypertension, stroke, peripheral artery disease) or the rates of other cardiovascular/diabetic medication use ( $p>0.05$ ). Furthermore, the groups were found to be similar in terms of left ventricular ejection fractions, duration of coronary artery bypass graft (CABG) (mean 10.5 years), and CABG surgical details ( $p>0.05$ ) (Table 1).

Upon evaluation of laboratory findings, the glomerular filtration rate (GFR) was found to be statistically significantly higher in the group using SGLT2 inhibitors ( $75.81 \pm 18.71$  mL/min/1.73 m<sup>2</sup>

vs.  $84.04 \pm 19.07$  mL/min/1.73 m<sup>2</sup>;  $p=0.019$ ), and the neutrophil count was found to be marginally significantly higher ( $5.10 \pm 1.87$  vs.  $4.48 \pm 1.52 \times 10^3/\mu\text{L}$ ;  $p=0.050$ ). However, no statistically significant differences were observed between the two groups regarding urea, creatinine, glycemic parameters (glucose, HbA1c), lipid profile, liver function tests, electrolytes, and inflammation markers (CRP) ( $p > 0.05$ ) (Table 2).

Considering the initial use of antianginal medications, the rates of ivabradine, ranolazine, trimetazidine, and nitrate use, the average number of antianginal medications ( $0.89 \pm 1.01$  vs.  $1.05 \pm 1.03$ ;  $p=0.370$ ) and the intensity of antianginal therapy ( $1.47 \pm 1.50$  vs.  $1.07 \pm 1.23$ ;  $p=0.114$ ) were similar between the groups. However, a significant reduction in the need for antianginal medications was observed in the group receiving SGLT2i during the follow-up period. In this group, the rates of dose reduction or discontinuation of ivabradine (0.0% vs. 11.4%;  $p=0.035$ ) and ranolazine (3.6% vs. 22.9%;  $p=0.001$ ) were significantly higher than in the control group. Consequently, the reduction in the total number of antianginal medications ( $-0.371 \pm 0.66$  vs.  $-0.036 \pm 0.57$ ;  $p=0.001$ ) and the decrease in the intensity of antianginal therapy ( $-0.52 \pm 0.89$  vs.  $-0.07 \pm 0.79$ ;  $p=0.001$ ) was statistically significantly more pronounced in those using SGLT2i. There were no significant differences between the groups based on the type of SGLT2i agent used ( $p>0.05$ ) (Table 3).

To assess the independent effect of SGLT2i use on antianginal therapy, a one-way analysis of covariance (ANCOVA) was performed while controlling for potential confounding factors (age, sex, GFR, and neutrophil count). The analysis revealed that even after adjusting for clinical variables and the number of baseline antianginal medications included as covariates, SGLT2i use was shown to reduce the number of antianginal medications in a statistically significant and independent manner ( $F=7.175$ ;  $p=0.009$ , Mean Difference: 0.326, 95% Confidence Interval: 0.085 – 0.567) (Table 4). Similarly, in the ANCOVA model established for the intensity of antianginal therapy, it was confirmed that SGLT2i use independently reduced the intensity of antianginal therapy, independent of baseline medication load

Table 1. Baseline Characteristics and Medicine History

| Parameter                               | Total (N=125) | Non-SGLT2i (N=55) | SGLT2i (N=70) | p     |
|-----------------------------------------|---------------|-------------------|---------------|-------|
| Age, mean±SD                            | 68,14 (±9,25) | 71,35 (±8,35)     | 65,58 (±9,19) | 0,001 |
| Gender (Male), n (%)                    | 100 (80,0%)   | 39 (70,9%)        | 61 (87,1%)    | 0,021 |
| Hyperlipidemia, n (%)                   | 112 (89,6%)   | 52 (94,5%)        | 60 (85,7%)    | 0,508 |
| COPD, n (%)                             | 15 (12,0%)    | 8 (14,5%)         | 7 (10,0%)     | 0,585 |
| Heart Failure, n (%)                    | 22 (17,6%)    | 8 (14,5%)         | 14 (20,0%)    | 0,477 |
| Hypertension, n (%)                     | 119 (95,2%)   | 54 (98,2%)        | 65 (92,9%)    | 0,896 |
| Stroke, n (%)                           | 12 (9,6%)     | 5 (9,1%)          | 7 (10,0%)     | 0,807 |
| Peripheral Arterial Disease, n (%)      | 15 (12,0%)    | 7 (12,7%)         | 8 (11,4%)     | 0,915 |
| RAA Blocker, n (%)                      | 86 (68,8%)    | 37 (67,3%)        | 49 (70,0%)    | 0,427 |
| Calcium Channel Blocker, n (%)          | 38 (30,4%)    | 16 (29,1%)        | 22 (31,4%)    | 0,696 |
| Betablocker, n (%)                      | 97 (77,6%)    | 40 (72,7%)        | 57 (81,4%)    | 0,720 |
| MRA, n (%)                              | 24 (19,2%)    | 10 (18,2%)        | 14 (20,0%)    | 0,820 |
| Lipid Lowering Agent, n (%)             | 105 (84,0%)   | 46 (83,6%)        | 59 (84,3%)    | 0,327 |
| Anticoagulant, n (%)                    | 17 (13,6%)    | 9 (16,4%)         | 8 (11,4%)     | 0,602 |
| Antiplatelet, n (%)                     | 77 (61,6%)    | 36 (65,5%)        | 41 (58,6%)    | 0,850 |
| Dipeptidyl peptidase-4 Inhibitor, n (%) | 67 (53,6%)    | 26 (47,3%)        | 41 (58,6%)    | 0,278 |
| Acetylsalicylic Acid, n (%)             | 79 (63,2%)    | 32 (58,2%)        | 47 (67,1%)    | 0,179 |
| Metformin, n (%)                        | 65 (52,0%)    | 29 (52,7%)        | 36 (51,4%)    | 0,514 |
| Sulfonylurea, n (%)                     | 18 (14,4%)    | 9 (16,4%)         | 9 (12,9%)     | 0,681 |
| Thiazolidinedione, n (%)                | 2 (1,6%)      | 1 (1,8%)          | 1 (1,4%)      | 0,863 |
| Insulin, n (%)                          | 28 (22,4%)    | 10 (18,2%)        | 18 (25,7%)    | 0,389 |
| Ejection Fraction, mean±SD              | 51,12 (±9,32) | 53,07 (±8,69)     | 49,51 (±9,61) | 0,062 |
| CABG Duration, mean±SD                  | 10,56 (±4,40) | 10,51 (±3,98)     | 10,59 (±4,76) | 0,938 |
| Vein Graft, n (%)                       | 111 (88,8%)   | 47 (85,5%)        | 64 (91,4%)    | 0,242 |
| Arterial Graft, n (%)                   | 97 (77,6%)    | 43 (78,2%)        | 54 (77,1%)    | 0,868 |
| Angiography after CABG, n (%)           | 75 (60,0%)    | 32 (58,2%)        | 43 (61,4%)    | 0,713 |
| Graft Dysfunction, n (%)                | 58 (46,4%)    | 27 (49,1%)        | 31 (44,3%)    | 0,718 |

Table 2. Laboratory Parameters

| Parameter                        | Total (N=125)    | Non-SGLT2i (N=55) | SGLT2i (N=70)    | p     |
|----------------------------------|------------------|-------------------|------------------|-------|
| Glucose (mg/dL)                  | 165,66 (±65,40)  | 163,62 (±71,33)   | 167,25 (±60,91)  | 0,765 |
| Urea (mg/dL)                     | 42,37 (±17,54)   | 44,98 (±17,28)    | 40,22 (±17,59)   | 0,148 |
| Creatinine (mg/dL)               | 0,96 (±0,29)     | 0,98 (±0,27)      | 0,94 (±0,30)     | 0,512 |
| GFR (mL/min/1.73m <sup>2</sup> ) | 80,32 (±19,27)   | 75,81 (±18,71)    | 84,04 (±19,07)   | 0,019 |
| ALT (U/L)                        | 23,11 (±17,58)   | 20,40 (±10,01)    | 25,24 (±21,62)   | 0,138 |
| AST (U/L)                        | 23,28 (±18,25)   | 21,73 (±9,76)     | 24,50 (±22,83)   | 0,416 |
| Albumin (g/dL)                   | 42,21 (±3,96)    | 41,98 (±3,52)     | 42,42 (±4,34)    | 0,559 |
| Sodium (mEq/L)                   | 139,58 (±2,87)   | 139,93 (±2,75)    | 139,29 (±2,95)   | 0,232 |
| Potassium (mEq/L)                | 4,42 (±0,50)     | 4,47 (±0,52)      | 4,38 (±0,48)     | 0,319 |
| Amylase (U/L)                    | 68,14 (±28,70)   | 70,51 (±30,67)    | 66,02 (±26,98)   | 0,470 |
| CRP (mg/L)                       | 9,20 (±11,31)    | 13,17 (±27,80)    | 11,33 (±21,78)   | 0,352 |
| HbA1c (%)                        | 7,22 (±1,02)     | 7,88 (±1,62)      | 7,55 (±1,37)     | 0,190 |
| Triglyceride (mg/dL)             | 173,76 (±102,95) | 170,02 (±98,66)   | 176,68 (±106,93) | 0,744 |
| Total Cholesterol (mg/dL)        | 173,02 (±48,58)  | 179,89 (±46,53)   | 167,87 (±49,82)  | 0,211 |
| LDL Cholesterol (mg/dL)          | 102,87 (±40,77)  | 109,30 (±41,74)   | 97,84 (±39,60)   | 0,137 |
| HDL Cholesterol (mg/dL)          | 42,05 (±9,46)    | 42,69 (±9,18)     | 41,56 (±9,71)    | 0,549 |
| Hemoglobin (g/dL)                | 13,01 (±1,86)    | 12,79 (±1,71)     | 13,17 (±1,96)    | 0,274 |
| WBC (10 <sup>3</sup> /μL)        | 7,68 (±2,22)     | 7,30 (±2,05)      | 7,98 (±2,32)     | 0,100 |

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Table 2. Continue...

|                                   |                        |                        |                        |       |
|-----------------------------------|------------------------|------------------------|------------------------|-------|
| Neutrophil ( $10^3/\mu\text{L}$ ) | 4,83 ( $\pm 1,74$ )    | 4,48 ( $\pm 1,52$ )    | 5,10 ( $\pm 1,87$ )    | 0,050 |
| Lymphocyte ( $10^3/\mu\text{L}$ ) | 1,94 ( $\pm 0,65$ )    | 1,89 ( $\pm 0,61$ )    | 1,98 ( $\pm 0,68$ )    | 0,498 |
| Platelet ( $10^3/\mu\text{L}$ )   | 209,92 ( $\pm 53,58$ ) | 213,38 ( $\pm 50,13$ ) | 207,18 ( $\pm 56,85$ ) | 0,534 |
| PDW (%)                           | 16,39 ( $\pm 2,46$ )   | 16,16 ( $\pm 2,44$ )   | 16,58 ( $\pm 2,48$ )   | 0,358 |
| PCT (%)                           | 0,19 ( $\pm 0,048$ )   | 0,19 ( $\pm 0,046$ )   | 0,19 ( $\pm 0,050$ )   | 0,688 |
| RDW (%)                           | 15,25 ( $\pm 2,01$ )   | 15,16 ( $\pm 1,58$ )   | 15,32 ( $\pm 2,28$ )   | 0,662 |

Table 3. Antianginal Medication Preferences

| Parameter                            | Total (N=125)       | Non-SGLT2i (N=55)     | SGLT2i (N=70)        |
|--------------------------------------|---------------------|-----------------------|----------------------|
| <b>Before SGLT2i</b>                 |                     |                       |                      |
| Ivabradine                           |                     |                       |                      |
| 5 mg BID                             | 12 (9,6%)           | 3 (5,5%)              | 9 (12,9%)            |
| 7.5 mg BID                           | 3 (2,4%)            | 1 (1,8%)              | 2 (2,9%)             |
| Ranolazine                           |                     |                       |                      |
| 375 mg BID                           | 22 (17,6%)          | 10 (18,2%)            | 12 (17,1%)           |
| 500 mg BID                           | 27 (21,6%)          | 10 (18,2%)            | 17 (24,3%)           |
| 750 mg BID                           | 6 (4,8%)            | 0 (0,0%)              | 6 (8,6%)             |
| Trimetazidine (35 mg BID)            | 21 (16,8%)          | 10 (18,2%)            | 11 (15,7%)           |
| Nitrate (50/60 mg OD)                | 32 (25,6%)          | 15 (27,3%)            | 17 (24,3%)           |
| Antianginal Count, mean $\pm$ SD     | 0,98 ( $\pm 1,02$ ) | 0,89 ( $\pm 1,01$ )   | 1,05 ( $\pm 1,03$ )  |
| Antianginal Intensity, mean $\pm$ SD | 1,30 ( $\pm 1,39$ ) | 1,07 ( $\pm 1,23$ )   | 1,47 ( $\pm 1,50$ )  |
| <b>After SGLT2i</b>                  |                     |                       |                      |
| Ivabradine                           |                     |                       |                      |
| 5 mg BID                             | 8 (6,4%)            | 4 (7,3%)              | 4 (5,7%)             |
| 7.5 mg BID                           | 2 (1,6%)            | 1 (1,8%)              | 1 (1,4%)             |
| Ranolazine                           |                     |                       |                      |
| 375 mg BID                           | 13 (10,4%)          | 9 (16,4%)             | 4 (5,7%)             |
| 500 mg BID                           | 24 (19,2%)          | 7 (12,7%)             | 17 (24,3%)           |
| 750 mg BID                           | 4 (3,2%)            | 3 (5,5%)              | 1 (1,4%)             |
| Trimetazidine (35 mg BID)            | 18 (14,4%)          | 10 (18,2%)            | 8 (11,4%)            |
| Nitrate (50/60 mg OD)                | 30 (24,0%)          | 17 (30,9%)            | 13 (18,6%)           |
| Antianginal Count, mean $\pm$ SD     | 0,79 ( $\pm 0,99$ ) | 0,92 ( $\pm 1,01$ )   | 0,68 ( $\pm 0,97$ )  |
| Antianginal Intensity, mean $\pm$ SD | 1,03 ( $\pm 1,33$ ) | 1,15 ( $\pm 1,35$ )   | 0,94 ( $\pm 1,32$ )  |
| <b>Change Status</b>                 |                     |                       |                      |
| Ivabradine                           |                     |                       |                      |
| No Change                            | 115 (92,0%)         | 54 (98,2%)            | 61 (87,1%)           |
| Decrease                             | 8 (6,4%)            | 0 (0,0%)              | 8 (11,4%)            |
| Increase                             | 2 (1,6%)            | 1 (1,8%)              | 1 (1,4%)             |
| Ranolazine                           |                     |                       |                      |
| No Change                            | 97 (77,6%)          | 44 (80,0%)            | 53 (75,7%)           |
| Decrease                             | 18 (14,4%)          | 2 (3,6%)              | 16 (22,9%)           |
| Increase                             | 10 (8,0%)           | 9 (16,4%)             | 1 (1,4%)             |
| Trimetazidine                        |                     |                       |                      |
| No Change                            | 118 (94,4%)         | 51 (92,7%)            | 67 (95,7%)           |
| Decrease                             | 5 (4,0%)            | 2 (3,6%)              | 3 (4,3%)             |
| Increase                             | 2 (1,6%)            | 2 (3,6%)              | 0 (0,0%)             |
| Nitrate                              |                     |                       |                      |
| No Change                            | 113 (90,4%)         | 51 (92,7%)            | 62 (88,6%)           |
| Decrease                             | 7 (5,6%)            | 1 (1,8%)              | 6 (8,6%)             |
| Increase                             | 5 (4,0%)            | 3 (5,5%)              | 2 (2,9%)             |
| $\Delta$ Antianginal Count           | 0,19 ( $\pm 0,65$ ) | -0,036 ( $\pm 0,57$ ) | 0,371 ( $\pm 0,66$ ) |
| $\Delta$ Antianginal Intensity       | 0,26 ( $\pm 0,89$ ) | -0,07 ( $\pm 0,79$ )  | 0,52 ( $\pm 0,89$ )  |

Table 4. ANCOVA Analysis for Antianginal Count

| Parameter         | Type III Sum of Squares | df  | Mean Square | F      | P Value |
|-------------------|-------------------------|-----|-------------|--------|---------|
| Corrected Model   | 12,824                  | 6   | 2,137       | 5,888  | 0,000   |
| Intercept         | 0,551                   | 1   | 0,551       | 1,518  | 0,221   |
| Antianginal Count | 6,903                   | 1   | 6,903       | 19,015 | 0,000   |
| Age               | 0,388                   | 1   | 0,388       | 1,068  | 0,304   |
| GFR               | 0,343                   | 1   | 0,343       | 0,946  | 0,333   |
| Gender            | 0,553                   | 1   | 0,553       | 1,524  | 0,220   |
| Neutrophil        | 0,259                   | 1   | 0,259       | 0,713  | 0,400   |
| SGLT2i Usage      | 2,604                   | 1   | 2,604       | 7,175  | 0,009*  |
| Error             | 40,294                  | 111 | 0,363       |        |         |
| Total             | 58,000                  | 118 |             |        |         |
| Corrected Total   | 53,119                  | 117 |             |        |         |

<sup>a</sup>R Squared = 0,241 (Adjusted R Squared = 0,200)

\*Mean difference: 0,326 95% Confidence Interval: 0,085 - 0,567

df: degrees of freedom

Table 5. ANCOVA Analysis for Antianginal Intensity

| Parameter         | Type III Sum of Squares | df  | Mean Square | F      | P value |
|-------------------|-------------------------|-----|-------------|--------|---------|
| Corrected Model   | 25,114a                 | 6   | 4,186       | 6,357  | 0,000   |
| Intercept         | 1,053                   | 1   | 1,053       | 1,599  | 0,209   |
| Antianginal Count | 12,368                  | 1   | 12,368      | 18,783 | 0,001   |
| Age               | 0,824                   | 1   | 0,824       | 1,251  | 0,266   |
| GFR               | 0,430                   | 1   | 0,430       | 0,654  | 0,421   |
| Gender            | 1,678                   | 1   | 1,678       | 2,548  | 0,113   |
| Neutrophile       | 0,889                   | 1   | 0,889       | 1,350  | 0,248   |
| SGLT2i Usage      | 5,337                   | 1   | 5,337       | 8,106  | 0,005*  |
| Error             | 73,089                  | 111 | 0,658       |        |         |
| Total             | 108,000                 | 118 |             |        |         |
| Corrected Total   | 98,203                  | 117 |             |        |         |

<sup>a</sup>R Squared = 0,256 (Adjusted R Squared = 0,216)

\*Mean difference: 0,466 95% Confidence Interval: 0,142 - 0,791

df: degrees of freedom

and other covariates ( $F=8.106$ ;  $p=0.005$ , Mean Difference: 0.466, 95% Confidence Interval: 0.142–0.791) (Table 5).

## Discussion

This study provides important data examining the effect of SGLT2 inhibitor use on the antianginal medication burden in a population of diabetic patients who have undergone coronary artery bypass graft (CABG) surgery. The key finding of our study is that SGLT2 inhibitor use resulted in a significant reduction in both the number of antianginal medications and the intensity of treatment during the follow-up period, independent of age, sex, renal function, and baseline medication burden. In particular, a reduction in the doses of

or discontinuation of “second-line” antianginal agents, such as ivabradine and ranolazine, was found to be significantly higher in the group using SGLT2 inhibitors.

SGLT2 inhibitors may have beneficial effects on coronary microcirculation function, exercise capacity, quality of life, and survival in patients with coronary heart disease and type 2 diabetes. This provides new evidence that SGLT2 inhibitors improve coronary microcirculation function [12]. The beneficial effects of SGLT2 inhibitors on the cardiovascular system have been clearly demonstrated in large-scale clinical trials such as EMPA-REG OUTCOME, CANVAS, and DECLARE-TIMI 58 [13-15]. However, these studies typically

focus on MACE and hospitalizations due to heart failure. The anti-ischemic effects of SGLT2 inhibitors and how these effects translate into the use of antianginal medications, however, represent a relatively new and emerging area in the literature.

While our investigation encompassed patients with diabetic coronary artery disease, the specific rationale for the absence of SGLT-2 inhibitor prescription among patients in the control group could not be definitively established due to the retrospective design. This omission might be attributed to individual physician preferences, potential contraindications, patient intolerances, or specific reimbursement criteria at the time of treatment.

Current data indicate that empagliflozin significantly improves angina symptoms and exercise capacity in patients with both type 2 diabetes and chronic refractory angina [9]. These agents alleviate angina pain by shifting myocardial energy metabolism from fatty acids to glucose, suppressing lactate production, and improving myocardial work efficiency [16, 17]. In addition, they are known to reduce inflammation, sympathetic nerve activity, and blood pressure [18]. The reduction in the antianginal burden observed in our study is consistent with the findings reported by Mansouri et al., who demonstrated that empagliflozin reduces angina symptoms by improving microvascular function [9].

The pathophysiological mechanisms underlying the reduction in the need for antianginal therapy with SGLT2 inhibitors are multifaceted. SGLT2 inhibitors enhance “fuel efficiency” by shifting myocardial metabolism toward the use of ketone bodies, which are a more efficient energy source than glucose oxidation [19]. This has been termed the “thrifty substrate hypothesis.” This metabolic shift may have raised the ischemic threshold, particularly in patients with incomplete revascularization or microvascular dysfunction following CABG. Additionally, the mild diuretic and natriuretic effects provided by SGLT2 inhibitors reduce left ventricular wall tension, thereby lowering myocardial oxygen consumption and creating an indirect anti-ischemic effect.

Our findings reveal a notable reduction in the

doses of ivabradine and ranolazine in the group using SGLT2i. In patients following CABG, polypharmacy both increases the risk of side effects and makes treatment adherence more difficult. Our findings suggest that SGLT2i therapy may not only provide glycemic control but also improve quality of life by reducing patients' total medication burden and potentially lowering treatment costs. In particular, the reduction in the use of agents preferred for microvascular angina, such as ranolazine ( $p=0.001$ ), can be interpreted as a clinical reflection of the potential beneficial effects of SGLT2i on microvascular tone and endothelial function.

Agents such as nitrates and trimetazidine, which have traditionally played a key role in anti-ischemic therapy, are now being used less frequently in current clinical practice, particularly in post-CABG (coronary artery bypass graft) patients where the risk of polypharmacy is a concern. Although the metabolic modulatory effect of trimetazidine and the venodilatory properties of nitrates provide symptomatic relief, the fact that the effects of these agents on long-term cardiovascular outcomes remain more limited compared to newer-generation agents such as SGLT2 inhibitors supports this trend. Nevertheless, unlike other antianginal medications, nitrates still hold strategic importance in clinical practice, particularly in cases accompanied by heart failure, due to their preload-reducing effects and ability to alleviate dyspnea symptoms [20]. This situation stems from the fact that nitrates play a functional role not only in controlling ischemic symptoms but also in maintaining hemodynamic balance in the pathophysiology of heart failure. We believe that the differences observed in our study regarding trimetazidine and nitrates are primarily due to the preference for nitrates in the management of heart failure.

The results of the ANCOVA analysis in our study demonstrated that the observed anti-ischemic benefit was independent of clinical confounders. Even after adjusting for variables such as age, GFR, and neutrophil count, the independent reduction in the intensity of antianginal therapy associated with SGLT2i use ( $p=0.005$ ) supports the notion that these agents should be an indispensable part of medical management in the

post-CABG period.

### Limitations

Our study has certain limitations. First, given the single-center, retrospective, observational nature of our study, the generalizability of the findings to the entire CABG population may be limited, and the study design may harbor potential selection biases. Second, the frequency and severity of angina in patients were not prospectively assessed using specific, objective scoring systems based on patient self-report, such as the Canadian Cardiovascular Society (CCS) classification or the Seattle Angina Questionnaire (SAQ). Changes in antianginal medication prescriptions (dose reduction or discontinuation) on the system were used solely as an indirect indicator of symptomatic improvement. Although this reduction in the burden of antianginal medications is a strong clinical reflection of ischemic improvement, it cannot be overlooked that changes in medication doses may have occurred not only due to symptomatic relief but also as a result of physician preference, strategies to avoid polypharmacy, or agent-specific side effects. Furthermore, the lack of data on patients' exercise capacity and quality-of-life questionnaires has limited the ability to fully analyze the clinical benefits provided by SGLT2 inhibitors. Third, the exact duration of SGLT2 inhibitor therapy prior to the evaluation period could not be fully detailed for all participants, which could potentially impact the extent of the observed clinical benefits. Fourth, the retrospective design precludes determining the exact reasons why certain diabetic patients did not receive SGLT2 inhibitor therapy. Finally, although ANCOVA was utilized to adjust for known covariates, baseline imbalances between the study arms—such as the significantly younger age and the potential differences in receiving optimal medical therapy in the SGLT2i cohort—remain a limitation that could introduce residual confounding.

### Conclusion

In summary, this study demonstrated that the use of SGLT2 inhibitors in diabetic patients who have undergone CABG was significantly and independently associated with a lower burden of antianginal medication and treatment intensity. These findings highlight that SGLT2 inhibitors

are not only glucose-lowering agents but also an important option that contributes to anti-ischemic therapy in the management of chronic coronary syndrome. Multicenter, prospective, and randomized controlled trials are needed to definitively establish the causal relationship between the anti-ischemic effects of SGLT2 inhibitors—including their ability to reduce the burden of antianginal medication, improve functional capacity, and elucidate underlying anti-ischemic mechanisms—in the post-CABG period.

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