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Case Report

Antiarrhythmic Effect of SGLT-2 Inhibitors in High-degree AV Block Caused by Heart Failure: A Case Report

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ABSTRACT

Background: According to WHO's Top 10 Global Health Threats, non-communicable diseases such as heart failure contribute to more than 70% of all deaths worldwide. Several studies have shown that SGLT-2 inhibitors can considerably reduce HF. As research progresses, SGLT-2 inhibitors may lessen the risk of arrhythmias in HF patients. **Case summary:** A 57-year-old female with uncontrolled hypertension came to the ED after collapsing at home. The vital signs and physical examination are normal. The preliminary ECG showed a high degree AV Block with multiple multifocal PVC. Early laboratory revealed mild hypokalemia. The patient experienced a seizure the next day, and an ECG showed total AV block with a non-sustained VT episode with PVC R on T. Following critical cardiac care and stabilization, the patient underwent echocardiography, which showed mild MR and AR with a reduced ejection fraction (47.7%). Once the patient's condition has stabilized, the patient is given 1x10mg Empagliflozin PO. **Discussion:** SGLT-2 inhibitors are beneficial in the treatment of heart failure and arrhythmia. SGLT-2 inhibitors have antiarrhythmic effects through a variety of pathways, such as lowering preload and afterload, inhibition of sodium-hydrogen exchange in myocardial cells, and suppression of the sympathetic nervous system.

Highlights:

1. The antiarrhythmic effect of SGLT-2 inhibitors, particularly empagliflozin, is a very interesting topic to discuss further.
2. In patients with high-degree AV block due to HF in rural areas, the use of SGLT-2 inhibitors is quite rare in Indonesia.

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Introduction

Heart failure (HF) is a major health issue in both developed and developing countries, including Indonesia. The prevalence of HF in Asian countries is generally similar to that reported in European countries (1-3%), but the prevalence rate in Indonesia is reported to be greater than 5%. Heart failure is becoming more common, as patients with acute HF can progress to chronic HF. Guidelines-Directed Medical Therapy (GDMT) at recommended doses is still underutilized in patients with HF. As a result, patients with poorly controlled HF are more likely to develop arrhythmias. Arrhythmias increase the risk of mortality and morbidity in patients with HF, resulting in a significant global healthcare burden. Bradyarrhythmia, which includes sinus node dysfunction, tachy-brady syndrome, and atrioventricular (AV) conduction disturbance, is common in HF. Heart failure can cause a type of bradyarrhythmia, which is known as a high-grade AV block.[1]

High-grade AV block is particularly dangerous since it may cause complete heart block, and syncope is a common symptom [1,2]. Syncope is defined as a transient loss of consciousness (TLOC) due to cerebral hypoperfusion, with a rapid onset, brief duration, and spontaneous complete recovery. Because it can be caused by various conditions, it's easily misunderstood. Syncope in AV block can be caused by sudden ventricular asystole or bradycardia-induced long QT syndrome and torsade de pointes. Meanwhile, effort intolerance results from a failure to adequately raise cardiac output (CO) (chronotropic incompetence) [1]. Some textbooks provide limited information on the mechanisms that induce HF-related AV block, such as "rate-dependent sodium retention," "rate-dependent reduction in cardiac output," and "AV dyssynchrony." Some of these possible mechanisms are based on studies that only included a small number of patients and are of dubious validity.[1,3]

The goal of HF treatment is to reduce morbidity and mortality. Sodium-glucose co-transporter-2 (SGLT2) inhibitors are a new class of drugs recommended for the treatment of HF patients with or without diabetes mellitus (DM). It is now being utilized as an additional therapy for HF in Indonesia, and it has been proven to have antiarrhythmic features as well. The first SGLT-2 inhibitor cohort study in Indonesia was reported in DISCOVER study, where it was used in 1.2% of patients [4,5]. Despite promising data on SGLT-2 inhibitors as potential HF medication with antiarrhythmic properties, the molecular and electrophysiologic mechanism remains unknown. Classical cell receptor-based signaling cascades in myocytes appear unlikely because in vivo and in vitro results remain

inconsistent [6–9]. As a result, in this case report, we are interested in discussing the antiarrhythmic effect of SGLT-2 inhibitors, particularly empagliflozin, in patients with high degree AV block due to HF in rural settings.

Case Presentation

A 57-year-old female patient presented at the emergency department complaining of syncope 30 minutes before admission. She fainted for around 5 minutes. Following that, the patient quickly regained consciousness. The patient then felt ill, with weakness and dizziness. Prior to admission, the patient complained of dizziness, spinning, and palpitations. The patient did not report any chest pain, tightness, nausea, or vomiting. Her appetite and drinking were still fine. The patient had an uncontrolled history of hypertensive heart disease. There was no prior history of diabetes, syncope, or other heart problems. The patient also didn't regularly take her anti-hypertension medication. No history of syncope in first-degree relatives.

Physical examination revealed a blood pressure 120/80 mmHg, a pulse rate 61 BPM irregularly, a respiratory rate of 20x/m, a temperature 36.2°C, and an oxygen saturation 98%. There is no chest wall retraction. Normal vesicular breath sounds without rales or wheezing. Single S1 and S2 sounds were normal without any murmurs. There was no limb edema. Preliminary laboratory examination was within normal limits with slightly elevated serum transaminase levels. Chest X-ray revealed cardiomegaly, interstitial lung edema, and bilateral pleural effusions (Figure 1). Furthermore, 12 lead electrocardiogram (ECG) examination revealed sinus rhythm with atrial rate 105 BPM and ventricular rate 38 BPM; normoaxis; AV Block 3:1 (high degree) with multiple multifocal premature ventricular contraction (PVC) (Figure 2).

The patient was given IVFD NaCl 0.9% 20 drops per minute, Dopamine 5 mcg/kgBW per minute via syringe pump, Furosemide 3x20mg IV, Pantoprazole 2x40mg IV, Enoxaparin Sodium 2x0.6 ml SC, Candesartan 1x8mg PO, Spironolactone 1x25mg PO, Aspirin 1x80mg PO, Clopidogrel 1x75mg PO, Atorvastatin 1x40mg PO, and Salbutamol 3x4mg PO. Then, the patient was admitted to the intensive care unit for further monitoring.

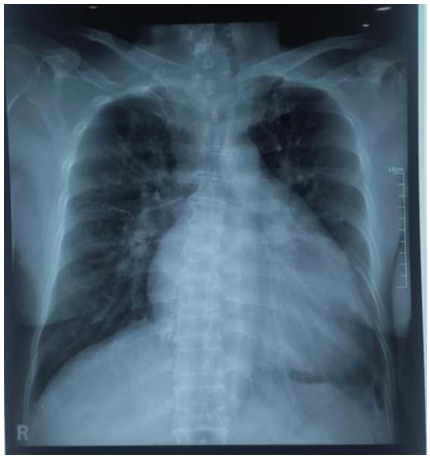

Figure 1. Chest X-Ray show cardiomegaly, interstitial lung edema, and bilateral pleural effusions

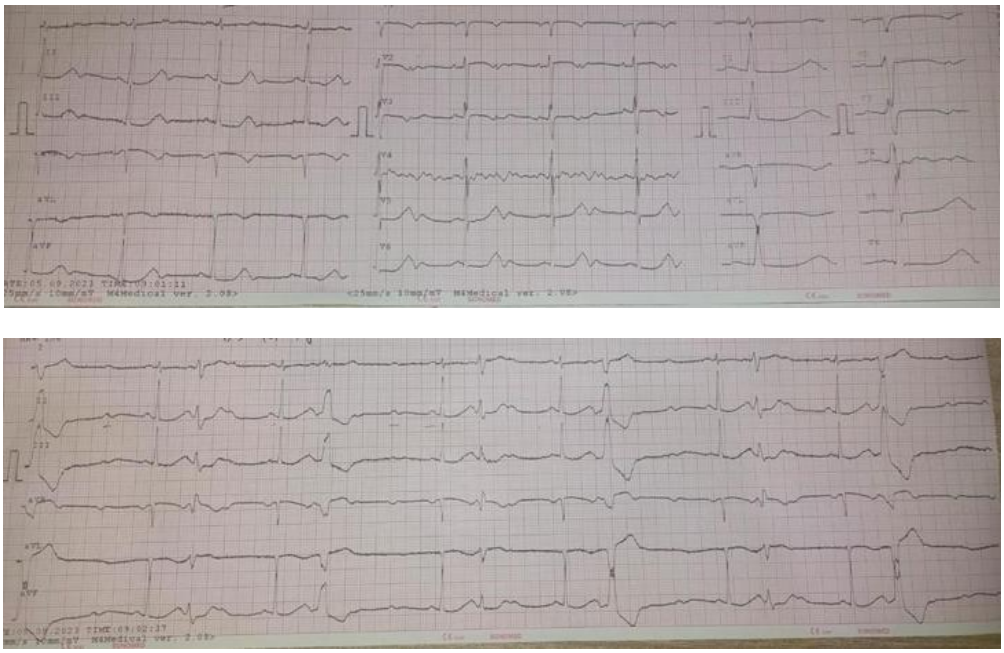

Figure 2. Early ECG in Emergency Room

On the next day, suddenly the patient had a seizure. She had one tonic clonic seizure that went on two minutes. After that, the patient regained consciousness, but she complained of weakness, chest discomfort, and dizziness. The patient's vital signs after the seizure were: blood pressure 140/70 mmHg; heart rate 35 BPM irregularly; respiratory rate 22x/m; temperature 36 C; oxygen saturation 97% with 2lpm nasal cannula. Subsequently, the patient had an immediate serum electrolyte and ECG examination. Laboratory results suggested mild hypokalemia (K : 3.48 mmol/L), hypochloride (Cl: 97.07), and hypocalcemia (Ca: 4.21). Furthermore, a 12-lead ECG revealed sinus rhythm; ventricular rate 38 BPM; normoaxis; total AV block with non-sustained VT episode; and PVC R on T (Figure 3).

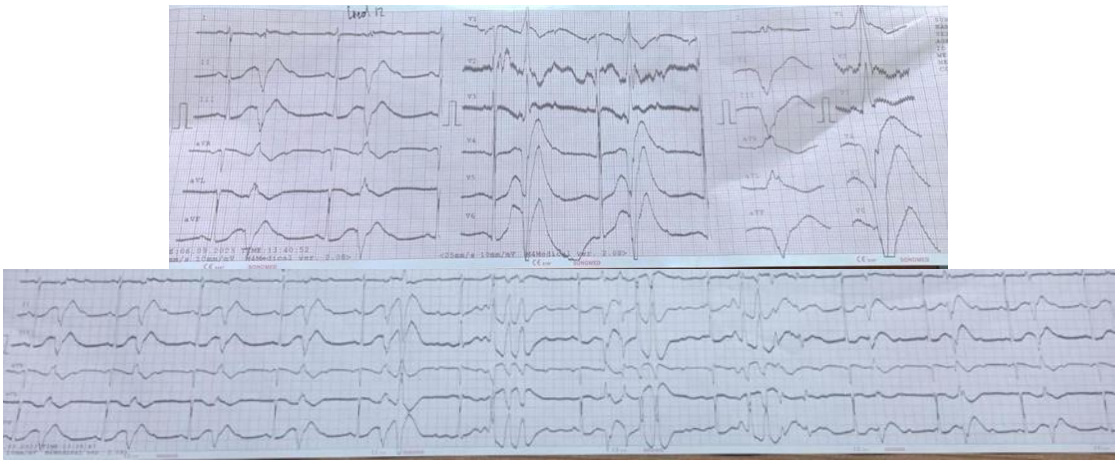

Figure 3. ECG after a seizure in the ICU

Furthermore, the patient was given adjunctive therapy such as Drip KCl 25 mcg (1 flash) slowly drops accompanied by Dopamine 5 mcg/kgBW per minute via syringe pump, MgSO4 20% 2x1 gr IV, Furosemide 3x20mg IV, Pantoprazole 2x40mg IV, Enoxaparin Sodium 2x0.6 ml SC, Candesartan 1x8mg PO, Spironolactone 1x25mg PO, Aspirin 1x80mg PO, Clopidogrel 1x75mg PO, Atorvastatin 1x40mg PO, and Salbutamol 3x4mg PO. On the next day, the monitor displayed an ECG monitor as below (Figure 4). Serum electrolyte testing was repeated and the results is within normal limit.

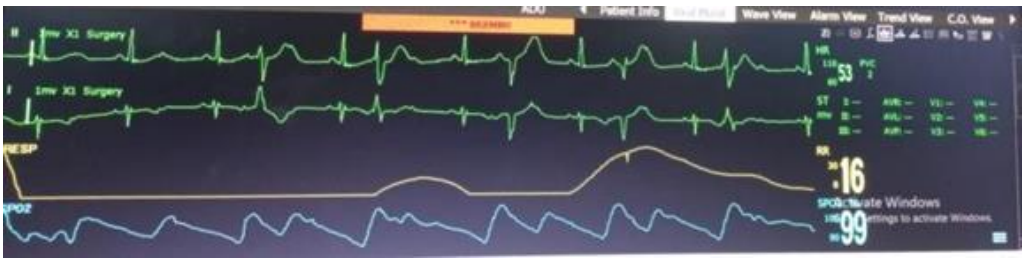

Figure 4. ECG monitor in ICU

The patient was hospitalized in the intensive care unit for 5 days. After the patient's condition had stabilized, an echocardiographic examination was performed and revealed valvular heart disease [moderate mitral regurgitation (MR) and atrial regurgitation AR)] with decreased left ventricular function [ejection fraction (EF) 40.65%] (Figure 5).

Once the patient's condition has stabilized, the patient is given 1x10mg Empagliflozin PO. The patient was diagnosed by HF mid-range Ejection Fraction (HFmrEF) with High Degree AV Block (3:1).

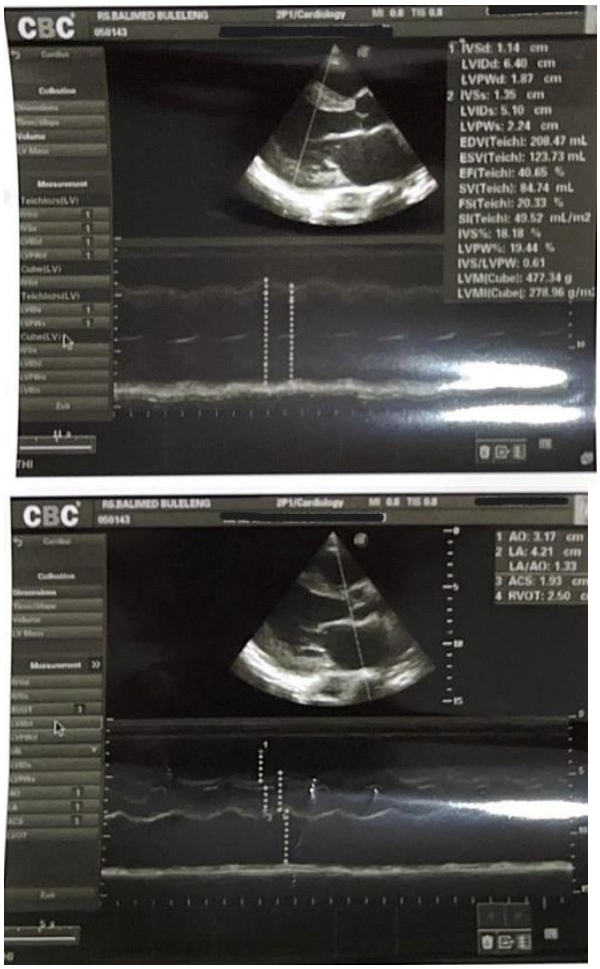

Figure 5. Echocardiography examination

The patient was transferred to the wards when the condition and vital signs were stable. Further therapy for 4 days in the wards was given such as Empagliflozin 1x10mg PO, Furosemide 2x20mg IV, Pantoprazole 2x40mg IV, Candesartan 1x8mg PO, Spironolactone 1x25mg PO, Aspirin 1x80mg PO, Clopidogrel 1x75mg PO, Atorvastatin 1x40mg PO, Ramipril 1x2.5 mg PO, and Salbutamol 3x4mg PO. Following the treatment, the patient no more complained of breathlessness, no seizures, and felt better. The latest ECG results revealed sinus bradycardia with 50 BPM, normoaxis, and T inversion in lead V1-V4 (Figure 6). The patient's condition improved, and she was discharged.

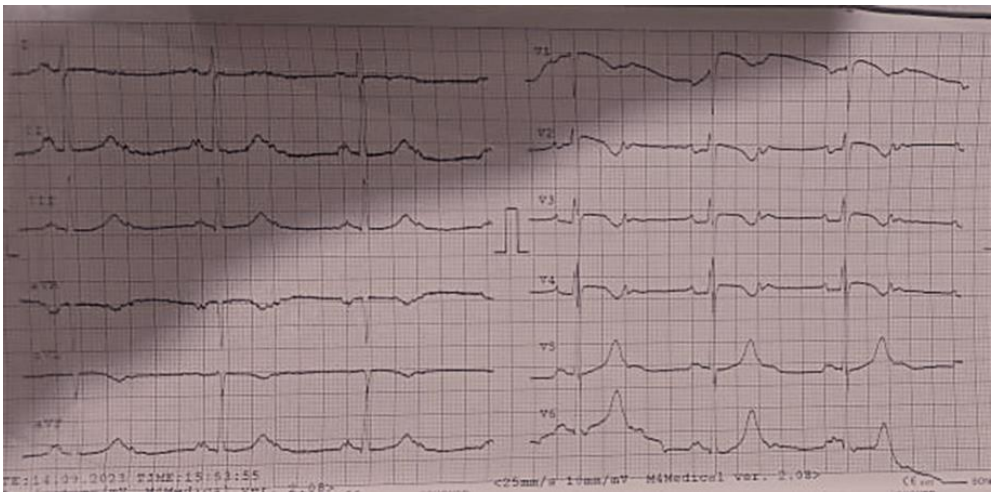

Figure 6. Latest ECG results in ward.

Discussion

This case discusses a patient who experienced sudden syncope. Cardiac syncope is caused by abnormal conditions in the cardiovascular system, which include bradyarrhythmias. High-grade AV block (P: QRS ratio of 3:1 or above) is a bradyarrhythmia characterized by a very slow ventricular rate and is frequently mistaken with third-degree (complete) heart block [2,10]. Heart failure has been linked to an increased risk of AV block, which may be related to a low ventricular rate. If bradyarrhythmia-related syncope is suspected, ECG monitoring should begin immediately and this become gold standard for diagnosing arrhythmic syncope (Class I; LoE B) [3]. This patient's ECG indicates AV Block 3:1 (high degree) with multiple multifocal PVC. This arrhythmia is frequent in HF and has been linked to left ventricular hypertrophy (LVH), which involves systolic and diastolic LV dysfunction [11]. In this case, a chest x-ray also revealed cardiomegaly.

Electrolyte imbalances are also common in HF patients. In this case, the arrhythmia recurred, resulting in total AV block with non-sustained VT episode and PVC R on T. Laboratory results suggested mild hypokalemia (K : 3.48 mmol/L). As a result, the patient was given a slow bolus of 25 mcg KCl IV and MgSO4 20% 2x1 gr IV. Hypokalemic states are common too in HF patients and may be caused by increased renin angiotensin system (RAS) activity. Hypomagnesemia is also common, but the link between hypomagnesemia and ventricular arrhythmias is not as strong as it is with potassium abnormalities. However, disruptions in serum magnesium are common in cases of refractory arrhythmia. Na/K-ATPas activity is reduced in hypomagnesemia. The intracellular potassium concentration is therefore reduced. It causes the resting membrane potential to be closer to the threshold potential, encouraging hyperexcitability.[12]

Furthermore, an echocardiogram revealed eccentric LV with a decreased EF (47.7%), moderate MR and AR with calcification in three leaflets. Left ventricular hypertrophy is known to be caused by pro-arrhythmic electrophysiological changes, such as reduced cell-cell coupling, decreased membrane potential, and sub-endocardial ischemia. Increased preload and afterload, which reduce the repolarization phase of the action potential, and high LV filling pressures favor the incidence of arrhythmias in HF [11,13]. A new study by Viskin et al proposes a possible role for diastolic MR, lower cardiac output (CO), and decreased LV compliance in the pathophysiology of HF and AV blocks [1]. This diastolic MR can be suggest caused by three mechanisms, such as LV asynchrony, an excessive increase in LV end-diastolic pressure, or delayed LV systole (most common). Patients with moderate-severe acute AR also might develop an increase in

LV end-diastolic pressure that exceeds left atrial pressure. As a result, end-diastolic MR may occur, which increases LA volume and causes pulmonary edema [14]. Recent studies also revealed that even mild MR in HF patients can result in significant elevation of LA and dyspnea [15]. The novel concept of "stiff left atrium syndrome" explains this. Due to aging, scarring, or adverse remodeling, these patients have decreased LA compliance. Excessive atrial distension caused by even a minor regurgitant volume overload can cause the atrium to shift into the steeper part of the pressure-volume relationship, further reducing compliance. As a result, the pressures in the LA and pulmonary arteries rise significantly and disproportionately. However, this important understanding may be missed without a comprehensive hemodynamic catheterization.[1,15]

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors target SGLT-2 proteins expressed in the proximal convoluted tubules and have been rethought beyond their glucosuria effects [16]. SGLT-2 inhibitors have been reported to be beneficial in the treatment of HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF), and HF with preserved ejection fraction (HFpEF). The American College of Cardiologists (ACC) and the European Society of Cardiology (ESC) recently recommended these as an adjuvant therapy to RAAS inhibitors and beta-blockers in patients with NYHA grade II-IV, HFrEF, HFmrEF, and HFpEF [9,17–19]. Two trials, EMPEROR-Preserved and DELIVER, studied the use of SGLT2 inhibitors (empagliflozin and dapagliflozin) in HF patients with LVEF>40%, justifying an update in the recommendations for HFmrEF and HFpEF. Based on these two trials, the following recommendations for HFmrEF and HFpEF have been made.[19]

SGLT-2 inhibitors have been shown to have several important metabolic effects on the myocardium, including increased ketone bodies, free fatty acids, and branched-chain amino acid utilization; increased cellular pathways that counteract adverse cellular pathways caused by myocardial damage; anti-inflammatory effects; changes in cellular calcium homeostasis; and cardiac sympathetic modulators [9]. Arrhythmias and sudden cardiac death are thought to be promoted by a disrupted metabolic pathway. This could be a mechanism of action for SGLT-2 inhibitors, which have been shown to stabilize an impaired state of energy consumption in the heart. Classical cell receptor-based signaling cascades in myocytes appear unlikely because in vivo and in vitro results are still inconsistent.

According to Philippaert et al, empagliflozin works by targeting late sodium channels and reducing late sodium current in murine models of HF. The late sodium current is linked to increased calcium influx

and a prolongation of the action potential's plateau phase. Heart failure and bradycardia can increase late sodium currents, which may be related to electrophysiological and mechanical dysfunction.[6–8]

Despite promising data on SGLT-2 inhibitors with potential antiarrhythmic properties, the mechanism is still unknown. However, Fernandes et al. found that SGLT-2 inhibitors have significant antiarrhythmic mechanisms, such as (1) hemodynamic effects that cause plasma volume contraction, reducing blood pressure, as well as reducing preload and afterload; (2) inhibition of sodium-hydrogen exchange in myocardial cells, which is linked to reductions in myocardial hypertrophy, fibrosis, adverse remodeling, systolic dysfunction; and (3) inhibition of sympathetic nerve system [23,24]. Because SGLT-2 inhibitors are small molecules (< 500 g/mol), it can be easily absorbed and metabolized by cardiomyocytes and exert effects within the cell. SGLT-2 inhibitors also can reverse 59% of all known protein changes in HFpEF via the sodium hydrogen antiporter 1 (NHE1) receptor, as well as influence on oxidative stress, myocardial stiffness, myocardial extracellular matrix remodeling, and systemic inflammation.[9,25]

However, Kolesnik et al recently summarized the complexity of these effects, which involve upregulations of the JAK/STAT3, ERK 1/2, cGCH1-BH4/NO, B-cell lymphoma 2 gene, and AMPK pathways. The PGC-1a/NRF-1/Tfam pathway and alterations in the sodium-calcium exchanger (NCX) protein following SGLT-2 inhibitor treatment are the focus of recent evidence at the atrial level. With regard to all identified and hidden downstream pathways, a multifactorial mechanism of action appears to be the most obvious explanation for the overall beneficial outcomes of clinical trials and the diversity of upregulated proteins following SGLT-2 inhibitor treatment.[9]

Empagliflozin 10 mg was given to the patient in this case. This medication has been shown to improve patient outcomes. A subsequent ECG revealed sinus bradycardia with no recurrence of malignant arrhythmias. The main conclusion of Antwi-Amoabeng et al's study was that HF patients who received a 10 mg dose of empagliflozin revealed a significant increase in QRS duration. Non-enzymatic glycosylation of protein subunits can occur and the extent of glycosylation is directly proportional to the glucose concentration of the protein's environment. Heavy glycosylation is a feature of many sodium channels that may affect their steady-state and function, with the effect differing in vivo from that seen in cell lines.

Furthermore, as with other membrane proteins, heavy glycosylation may affect empagliflozin's docking domain and binding to the human cardiomyocyte late sodium channel. The use of

empagliflozin was linked to decrease in the ventricular arrhythmia. Empagliflozin use is expected to cause reflex tachycardia due to its diuresis effects, but this may be mitigated by empagliflozin's sympathetic attenuation effects.[26] In this case, empagliflozin was shown to enhance the patient's clinical outcome by lowering CV mortality and hospitalization time. The patient was improved with no shortness of breath, recurring seizures, or refractory arrhythmias, as evidenced by an ECG return to sinus rhythm.

This case report has some limitations, including uncertainty about the medication's antiarrhythmic effect. This is because only one patient received the medication. Further studies, e.g. case series and randomized control trials, are needed to prove antiarrhythmic effects of these medication in HF with arrythmia, especially AV block. Also, serial echocardiography and ECG were not performed when the patient came back to clinic, which led to delayed follow-up. This is due to limited national insurance coverage and claims.

Conclusion

As research progresses, it has been discovered that SGLT-2 inhibitors may significantly reduced risk of arrhythmia and HF by inhibiting sodium-hydrogen exchange in myocardial cells and sympathetic nerve system. Clinicians must also understand the electrophysiological effects of these medications. Further study is needed to understand the molecular processes and cardioprotective effects of SGLT-2 inhibitors, which could lead to new therapeutic approaches for patients with cardiovascular risk factors.

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