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Research paper

Preventative effects of dapagliflozin on early ventricular dysfunction and remodeling in patients with acute anterior STEMI - The PREDOMINACE trial

Xiaoyan Liu [a,1], Shiying Zhang [a,1], Kangyin Chen [a], Jingjin Che [a,*], Chunjie Li [b,c,**]

[a] Tianjin Key Laboratory of Ionic-Molecular Function of Cardiovascular Disease, Department of Cardiology, Tianjin Institute of Cardiology, The Second Hospital of Tianjin Medical University, Tianjin 300211, People's Republic of China
[b] Department of Cardiology, Tianjin Chest Hospital, Tianjin 300222, People's Republic of China
[c] School of Electrical and Information Engineering, Tianjin University, Tianjin 300072, People's Republic of China

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ABSTRACT

Background: Sodium glucose cotransporter 2 inhibitors (SGLT-2i) are oral hypoglycemic drugs that can reduce the risk of deteriorating heart failure (HF) or cardiovascular death in patients with HF. Although some animal models have shown that SGLT-2i can effectively inhibit reperfusion injury after acute myocardial infarction (AMI), there is no clinical evidence to prove that SGLT-2i can also play a significant role in improving reperfusion injury in patients with AMI. Therefore, PREDOMINACE study enrolled patients with acute anterior large ST-segment elevation myocardial infarction, who are at high risk of developing HF in the future. The aim of this trial is to study the prevention effects of dapagliflozin on early ventricular dysfunction and remodeling in patients with acute anterior ST-segment elevation myocardial infarction (STEMI), and to explore the efficacy and safety of dapagliflozin in the treatment of patients with diabetes and without diabetes after acute anterior STEMI.
Methods: Within a multi-center, randomized, single-blind, controlled trial we will recruit patients with acute anterior STEMI from the Second Hospital of Tianjin Medical University and Tianjin Chest Hospital, who are randomly divided into intervention group or control group in a 1:1 ratio. The intervention group was given dapagliflozin (10 mg once daily) before primary percutaneous coronary intervention (PPCI) and 30 days after PPCI, while the control group is not given SGLT-2i. The primary endpoint is the impact of dapagliflozin on changes of NT-proBNP levels in 30 days of acute anterior STEMI. Secondary endpoints include changes in echocardiographic left ventricular remodeling parameters (LVESV, LVEDV, EF), and the changes of ECG (Q wave leads 30 days after PPCI/ST-segment elevation leads at baseline,ST-segment decline degree 24 h and 7 days after PPCI). Hospitalization rate due to HF or other causes, incidence of malignant arrhythmias, and all-cause mortality will be assessed as exploratory secondary endpoints.
Discussion: The PREDOMINACE trial will test dapagliflozin in patients with acute anterior STEMI, regardless of the presence or absence of diabetes. Therefore, the PREDOMINACE trial may support that the effects of SGLT-2i on improving cardiac remodeling, reducing cardiac pre and after load and improving cardiac metabolism are independent of its antidiabetic effects. Results will provide the clinical rationale for SGLT-2i to improve prognosis in patients with AMI.
Trial registration: Chinese Clinical Trial Registry. Identifier: ChiCTR2100048157. Registered 23 September 2021.

1. Background

SGLT-2i has become part of the quadruple therapy for HF [1]. A number of large international trials have confirmed that SGLT-2i are beneficial to cardiovascular outcomes in patients with atherosclerotic cardiovascular disease (atherosclerotic CVD, ASCVD). The EMPA-REG

* Corresponding author.
** Correspondence to: C. Li, Department of Cardiology, Tianjin Chest Hospital, Tianjin 300222, People's Republic of China.
E-mail addresses: jingjinche@163.com (J. Che), lichunjie0227@126.com (C. Li).
[1] These authors contributed equally to this work as co-first authors.

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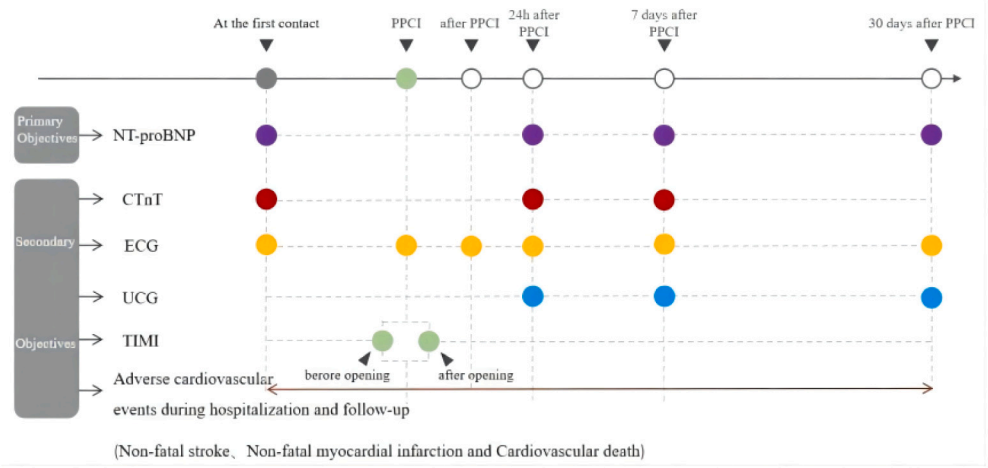

Fig. 1. Study flow chart.

study showed major cardiovascular outcomes and all-cause mortality decreased significantly in T2DM patients with high-risk cardiovascular events treated with empagliflozin [2]. The DAPA-HF study further confirmed that patients with HF treated with dapagliflozin had a lower risk of worsening HF or cardiovascular death, regardless of their diabetic status, suggesting that the cardiovascular benefits of SGLT-2i are independent of its antidiabetic mechanism [3,4].

ST elevated myocardial infarction (STEMI) is a leading cause of morbitdy and morality, which is often associated with high mortality, while percutaneous coronary stenting (PCI) is the most effective intervention to limit cardiac ischemic injury and reduce the incidence of adverse cardiac events [5]. However, revascularization therapy can induce malignant arrhythmias, myocardial stunning, and even increase initial infarct size and accelerate cardiomyocyte death, that is, cardiac ischemia-reperfusion injury [6]. In the DECLARE-MI 58 trial, dapagliflozin significantly reduced the risk of myocardial infarction (MI) complicated with diabetic MACE by 16% [7]. In animal trials, SGLT-2i were applied to heart ischemia-reperfusion models in rats, rabbits and pigs, and the results showed that SGLT-2i before ischemia could improve left ventricular function during myocardial ischemia-reperfusion injury by reducing arrhythmia, reducing infarct size, reducing cardiomyocyte apoptosis and improving myocardial mitochondrial function, thus achieving maximum myocardial protection [8–10].

Although some animal models have shown that SGLT-2i can effectively inhibit reperfusion injury after acute myocardial infarction (AMI), there is no clinical evidence to prove that SGLT-2i can also play a significant role in improving reperfusion injury in patients with AMI. Therefore, PREDOMINACE study enrolled patients with acute anterior large ST-segment elevation myocardial infarction, who are at high risk of developing HF in the future. Our goal is to verify the hypothesis that dapagliflozin is beneficial to cardiac function and left ventricular remodeling in patients with acute anterior STEMI regardless of their diabetic status.

2. Methods/design

2.1. Study design and intervention

PREDOMINACE is a multi-center, randomized, single-blind, controlled trial. We will enroll 360 patients with acute anterior STEMI who meet inclusion criteria to monitor the effect of dapagliflozin 10 mg qd (p.o.) for 30 days on cardiac function and left ventricular remodeling index for these patients and the whole study hypothesis (Fig. 1).

Table 1
Trial objectives

Primary objective
• Changes of NT-proBNP levels in 30 days of acute anterior STEMI
Secondary objectives
• Hospitalization for HF or hospital left ventricular heart failure • Left ventricular remodeling (LVESV, LVEDV, EF) • Q wave leads 30 days after PPCI/ST segment elevation leads at baseline • ST-segment decline degree 24 h and 7 days after PPCI • All adverse cardiovascular events within 30 days (Acute or Non) • New-onset AF
Safety objectives
• number of severe hypotension events • number of severe hypoglycemic events • number of severe hypoglycemic events • number of ketoacidotic events • changes in liver function parameters (AST, ALT, GGT) • changes in renal function parameters (creatinine, eGFR)
Clinical outcomes
• AHF occurred during hospitalization • Recurrent AMI • Readmission for AHF • In-stent thrombosis • Acute stroke • Cardiac death • All cause of death

Abbreviations: NT-proBNP=N-terminal pro brain natriuretic peptide; STEMI=ST-segment elevation myocardial infarction; LVESV = Left ventricular end-systolic volume; LVEDV = Left ventricular end-diastolic volume; AHF = acute heart failure; HF = heart failure; EF = Ejection fractions; PPCI=Primary percutaneous coronary intervention; MI = Myocardial infarction; AMI = acute myocardial infarction; AF = Atrial fibrillation; AST = Aspartat-Aminotransferase; ALT = Alanin-Aminotransferase; GGT = Gamma-Glutamyl-Transferase; eGFR = Estimated Glomerular Filtration Rate.

2.2. Study hypothesis

Early use of SGLT-2i dapagliflozin after acute anterior STEMI will reduce NT-proBNP more effectively within 30 days after acute anterior STEMI.

Table 2
List of inclusion and exclusion criteria.

Inclusion criteria
• 18–80 years of age • The first acute anterior STEMI, defined as ST-segment elevation ≥0.2 mV in at least 4 adjacent leads within 12 h of onset • Agreed to receive PPCI
Exclusion criteria
• Hemodynamic instability (systolic pressure <90 mmHg or any signs of insufficient organ perfusion, such as oliguria or wet and cold limbs, etc.) • PPCI failed • Patients being treated with any SGLT-2i (dapagliflozin, canagliflozin, empagliflozin) within the 4 weeks prior to the screening visit • Type 1 diabetes patients • Allergic reactions to SGLT-2 inhibitors • Previous history of HF, MI, valvular disease (moderate or more stenosis or regurgitation), congenital heart disease • eGFR<30 ml/min/1.73 m^2 • Acute genitourinary infection • Suffer from malignant tumors • Females that are pregnant, breastfeeding, or preparing for pregnancy

Abbreviations: STEMI=ST-segment elevation myocardial infarction; MI = Myocardial infarction; PPCI=Primary percutaneous coronary intervention; SGLT-2i = SGLT-2 inhibitors; HF = Heart failure; eGFR = Estimated Glomerular Filtration Rate.

2.3. Study endpoints

The primary objective of the PREDOMINACE study is to monitor the changes of NT-proBNP levels in patients with acute anterior STEMI (with or without T2DM) within 30 days after taking dapagliflozin. Secondary objectives, safety objectives and clinical outcomes are shown in Table 1.

2.4. Ethical review

The research protocol, the written informed consent forms, case report forms (CRFs) and the subject recruitment procedure has been approved by the Ethics Committee of the Second Hospital of Tianjin Medical University and Tianjin Chest Hospital. All subjects are required to sign an informed consent form before registration. The protocol was registered on Chinese Clinical Trial Registry (Identifier: ChiCTR2100048157) on September 23th, 2021, before recruiting the first patient.

2.5. Patient recruitment and registration

The PREDOMINACE trail is a single-center, randomized, controlled prospective study. Patients begin taking dapagliflozin as recommended in the guidelines. During the screening process, the requirements of inclusion and exclusion criteria are evaluated and confirmed (Table 2). Patients who were previously treated with dapagliflozin or other SGLT-2i need to be at least 30 days apart before starting to use dapagliflozin to avoid residual effects. In the intervention group, the initial dose of 10 mg is taken orally once at the first contact, and according to the guidelines, dapagliflozin (10 mg qd) is maintained from the second day. The interval time between the first medication and the second medication must be ≥12 h (Fig. 2). Subject name abbreviation, the subject number and group number are recorded in the CRFs. The patients' medical records (clinical records/CRF, laboratory sheets, etc.) will be kept completely in the hospital where you see the doctor. Researchers, ethics committees and drug regulatory authorities will be allowed to access patients' medical records. A summary of all visits and procedures is summarized below (Table 3).

2.6. Study medication

Dapagliflozin, a kind of SGLT2i, is a hypoglycemic drug that inhibits glucose reabsorption in proximal tubules. The study dose is 10 mg qd, whole tablets swallowed with water. The prescription drug, sponsored by AstraZeneca Pharmaceutical, is 7 tablets per box, and subjects are given 4 boxes of 28 tablets in 30 days. If you miss a dose, you should take it as soon as you remember. You should not take double dose on the same day. It is recommended that subjects should follow the study protocol and give maintenance dose treatment on the premise of ensuring overall safety and tolerance. If necessary, adjust other hypoglycemic drugs in patients with T2DM to avoid hypoglycemia. If there are serious adverse reactions or the combination cannot be adjusted, the use of dapagliflozin will be suspended temporarily. Then the patient can be reevaluated and closely observed clinically, if possible, the patient will receive dapagliflozin again. If the patient stops taking the study drug, we will instruct the patient to conduct the end-of-study survey.

2.7. Study statistics

2.7.1. Sample size

Previous data showed that NT-proBNP levels of patients with acute STEMI after PPCI were 713.68 ± 398.42 pg/ml, and NT-proBNP levels decreased by about 55.5 % after using dapagliflozin for 6 months in patients with acute STEMI after PPCI. If it is expected that NT-proBNP

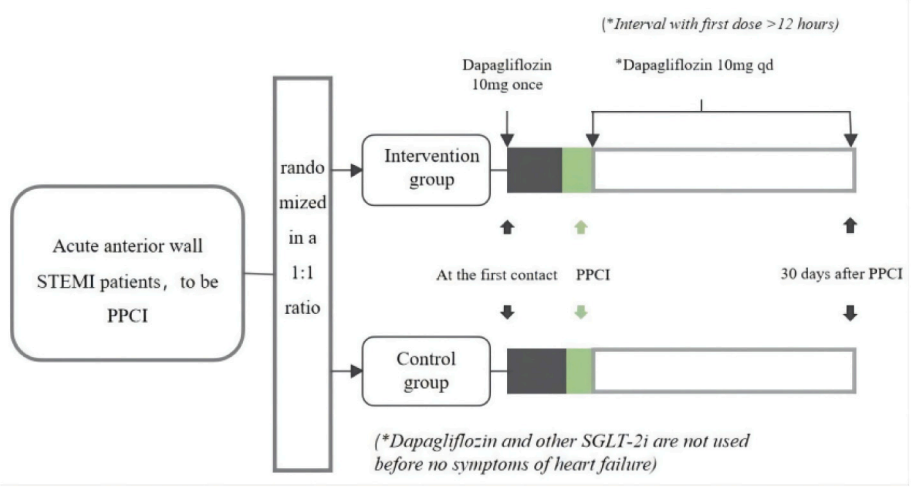

Fig. 2. Overview of the study timeline.

Table 3
SPIRIT flow diagram.

RCT	STUDY PERIOD				
	Baseline (visit 1)	Visit 2	Visit 3	Visit 4	Follow-up (visit 5)
TIMEPOINT	0	After PPCI	24h after PPCI	7 days after PPCI	30 ± 5 days after PPCI
ENROLLMENT					
Eligibility screen	√				
Informed consent	√				
Randomization	√				
Allocation	√				
INTERVENTIONS					
Dapagliflozin (intervention group)	←	—	—	→	
Control group	←	—	—	→	
ASSESSMENTS					
Anthropometric measurements	√				
Vital signs (blood pressure, heart rate)	√				
Medical history	√				
Concomitant medication	√			√	√
Adverse events					√
Laboratory					
NT-proBNP (local)	√		√	√	√
CTnT (local)	√		√	√	
Liver function parameters (AST, ACT, GGT)			√		
Renal function parameters (creatinine, eGFR)			√		
Investigations					
Echocardiogram (UCG)			√	√	√
Electrocardiogram (ECG))	√	√	√	√	√

Abbreviations: PPCI=Primary percutaneous coronary intervention; NT-proBNP = N-terminal pro brain natriuretic peptide; CTnT = Troponin T; AST = Aspartat-Aminotransferase; ALT = Alanin-

Aminotransferase; GGT = Gamma-Glutamyl-Transferase; eGFR = Estimated Glomerular Filtration Rate; UCG = Echocardiogram; ECG = Electrocardiogram.

levels of patients with acute anterior STEMI can be reduced by 20 % 30 days after PPCI, $\alpha = 0.05$, $1\text{-}\beta = 0.9$, the sample size intervention group = control group = 163 subjects. The lost-to-follow-up data will be replaced up to a maximum of 10 % of the calculated sample size, so 180 subjects are needed in each group.

2.7.2. Statistical analysis

If the data are normally distributed, the summary of continuous variables is represented as mean and standard deviation, for skewed data, the summary is represented as the median and quartile range, while classified variables are presented as frequency and percentage. All statistical tests are double-tailed, with a significance level of 5 %. The primary and selected secondary outcome parameters will be grouped and analyzed, including diabetes history, age and baseline cardiac function indicators.The detailed statistical analysis plan will be finalized before the data collection is completed.

3. Discussion

The aim of this trial is to test the hypothesis that dapagliflozin is beneficial to cardiac function and left ventricular remodeling in patients with acute anterior STEMI regardless of their diabetic status. Cardiac fibrosis is widely regarded as the ultimate common pathway for the occurrence and development of HF, which involves cardiac remodeling. Due to the deposition of extracellular matrix proteins by cardiac fibroblasts, the ventricular compliance is blocked and the development of HF is accelerated, while in the rat MI model, dapagliflozin showed significant cardiac anti-fibrotic effect by increasing the activation of M2 macrophages and inhibiting myofibroblasts differentiation [11]. A meta-analysis evaluating the regulatory effect of SGLT-2i on myocardial infarct size in 16 animal models of myocardial ischemia-reperfusion injury showed that acute administration of SGLT-2i can significantly reduce infarct size compared with placebo, regardless of their diabetic status [12]. In clinical studies (such as the EMPA-REG OUTCOME trial and the CANVAS program), SGLT-2i have produced favorable cardiovascular benefit outcomes through different possible mechanisms [13]. The DAPA-HF study opened a new quadruple therapy for the treatment of HF, and SGLT-2i has become an important part in the treatment of HF [2]. Since MI is the main risk factor for the occurrence and development of HF, we speculate that the use of dapagliflozin immediately after AMI may play an important role in the prevention of ventricular dysfunction and remodeling, independent of its antiglucose effect. Although current guidelines recommend the use of such drugs, so far, SGLT-2i has been used cautiously in cardiovascular events, even in hospital settings [14]. Moreover, due to the lack of research data, there is still uncertainty about whether the drug can be safely used in this environment. The PREDOMINACE trial will provide much-needed safety data in this cohort of patient.

4. Conclusion

The PREDOMINACE trial will test dapagliflozin in patients with acute anterior STEMI, regardless of their diabetic status. Therefore, the PREDOMINACE trial may support that the effects of SGLT-2i on improving cardiac remodeling, reducing cardiac pre and after load and improving cardiac metabolism are independent of its antidiabetic effects. Results will provide the clinical rationale for SGLT-2i to improve prognosis in patients with AMI.

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List of abbreviations

ALT	Alanin-Aminotransferase
AST	Aspartat-Aminotransferase
GGT	Gamma-Glutamyl-Transferase
eGFR	Estimated Glomerular Filtration Rate
STEMI	ST-segment elevation myocardial infarction
LVESV	Left ventricular end-systolic volume
LVEDV	Left ventricular end-diastolic volume
HF	heart failure
AHF	acute heart failure
EF	ejection fractions
PPCI	primary percutaneous coronary intervention
AF	atrial fibrillation
CRF	case report form
AMI	acute myocardial infarction
MI	myocardial infarction
NT-proBNP	N-terminal pro brain natriuretic peptide
CTnT	Troponin T
SGLT2	sodium glucose cotransporter 2
T2DM	type 2 diabetes mellitus
UCG	ultrasonic cardiogram
ECG	electrocardiogram
ASCVD	atherosclerotic cardiovascular disease
ADA	American Diabetes Association
AHA	American Heart Association

Authors' contributions

Designed scheme and wrote the paper: Xiaoyan Liu, Shiying Zhang.

Detailed instruction, edited and reviewed the manuscript: Kangyin Chen, Jingjin Che, Chunjie Li.

Final approval of manuscript: All authors.

Registration of randomized clinical trial

- Title: Prevention effects of dapaglifozin on early ventricular dysfunction and remodeling in patients with acute anterior STEMI (PREDOMINACE).
- ChiCTR (Chinese Clinical Trial Registry) Identifier: ChiCTR2100048157.

Declaration of competing interest

The authors have stated that they have no conflict of interest.

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