Section A-Research paper

Pathophysiologic effects of Diabetes Mellitus on Cardiac Remodeling

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Abstract

Background: Cardiac remodeling is defined as a group of molecular, cellular and interstitial changes that manifest clinically as changes in size, mass, geometry and function of the heart after injury. The process results in poor prognosis because of its association with ventricular dysfunction and malignant arrhythmias After MI, may predispose to ventricular rupture and aneurysm formation. Despite therapeutic advances, mortality rates related to cardiac remodeling/dysfunction remain HIGH. The term "remodeling" was used for the first time in 1982 by Hockman and Buckey, in a myocardial infarction (MI) model. This term was aimed to characterize the replacement of infarcted tissue with scar tissue. Postinfarct ventricular remodeling represents a prevailing cause of heart failure (HF), and it occurs in almost 30% of patients with a previous anterior myocardial infarction (MI) and in only approximately 17% of patients with non-anterior infarct. Adverse cardiac remodeling is an important contributor to heart failure severity. This includes the development of cardiac hypertrophy, fibrosis, inflammation, and cardiomyocyte cell death. Several experimental and human studies have demonstrated beneficial effects of SGLT2 inhibition on cardiac remodeling

Keywords: Diabetes Mellitus, Cardiac Remodeling

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Introduction

Diabetes mellitus is defined as a syndrome, a group of disorders characterized by hyperglycemia and glucose intolerance, caused by either insulin deficiency or impaired insulin function, or a combination of the two **(1).** It is associated with a shorter life expectancy, major morbidity from diabetes-related microvascular complications, an increased risk of macrovascular consequences (ischemic heart disease, stroke, and peripheral vascular disease), and a worse quality of life. Type IIdiabetes is caused by a combination of pathogenetic mechanisms. These include mechanisms that damage pancreatic beta cells, resulting in insulin deficiency, and others that result in insulin resistance **(2).**

Diabetes mellitus, a common metabolic condition, affected 537 million individuals worldwide in 2021 (10.5% prevalence), and this is expected to rise to 783 million cases by 2045 (12.2% prevalence) **(2)**

Diabetes is a serious and quickly expanding global health problem. Diabetes is expected to affect 463 million people in 2019, with 578 million by 2030 and 700 million by 2045, according to the IDF. Two-thirds of persons with diabetes live in cities, and three out of every four are of working age **(3).**

Age, obesity, and a lack of physical exercise all increase the chance of having this type of diabetes. It is more common in women with past GDM and in people with hypertension or dyslipidemia, and its prevalence varies by racial/ethnic grouping. It is more frequently linked to a significant genetic susceptibility than the

autoimmune variant of type 1 diabetes. However, the genetics of this kind of diabetes are complicated and not completely understood **(4).**

Prediabetes is a risk factor for developing type 2 diabetes and is often accompanied by the same co-morbidities associated with type 2 diabetes. Prevalence of prediabetes in adults is reported to be 35–40% in the US and China. While not everyone with prediabetes will develop type 2 diabetes, longitudinal studies suggest annual progression rate between 11 and 13%, depending on the population studied and the definition used to diagnose prediabetes **(5)**.

n resistance and affects 3-14 percent of pregnancies, with higher rates in certain ethnic groups (African American, Latino, Native American, Asian American, Asian Australian, Pacific Islander, Australian Aboriginal, and Middle Eastern) **(6).**

Maternal obesity, elder childbearing (>35 years of age), sedentary lifestyle, a history of polycystic ovarian syndrome, insulin resistance, and prediabetes are all risk factors for gestational diabetes (Denney and Quinn, 2018). This kind of diabetes is managed by diet, exercise, and, if required, medication. Because gestational diabetes mellitus is a high-risk factor for type 2 diabetes, it also increases the risk of several long-term health consequences such as metabolic syndrome and cardiovascular disease **(7).**

Risk factors of T2DM are combination of genetic, metabolic, and environmental factors that interact with each other to lead to its prevalence. Although individual susceptibility to T2DM due to non-modifiable risk variables (ethnicity and family history/genetic predisposition) has a strong genetic base, data from epidemiological research shows that many cases of T2DM can be avoided by changing the main modifiable risk factors (obesity, low physical activity and an unhealthy diet) **(8).**

Ethnicity and family history/genetic predisposition:

T2DM incidence and prevalence vary greatly according to ethnicity and geographical area, with Japanese, Hispanics, and Native Americans having the highest risks. It has been demonstrated that Asians have a greater incidence rate than the White American population and the white population in the United Kingdom, where the biggest risk is among the black population. While no obvious cause has been identified, contributing factors such as modern lifestyle characteristics (which encourage obesity), socioeconomic and direct genetic predisposition, or gene-environment interactions have been proposed **(9).**

T2DM risk is greatly influenced by genetic predisposition. Several T2DM genome-wide association studies have revealed the complicated polygenic basis of T2DM, with most of these loci increasing T2DM risk through primary effects on insulin production and a minority acting through lowering insulin action **(10).**

It was classified trhat these variants according to their possible mechanisms in T2DM pathophysiology, with four fitting a clear IR pattern, two lowering insulin secretion with fasting hyperglycemia, nine lowering insulin secretion with normal fasting glycemia, and one altering insulin processing **(10).**

According to these findings, the genetic architecture of T2DM is extremely polygenic. Interactions between susceptibility loci and environmental variables may explain the missing heritability of T2DM, suggesting that the influence of a specific genetic variation can be modified by environmental factors (and vice versa) **(9).**

Impaired insulin secretion is characterized by a decrease in glucose responsiveness that occurs before the clinical onset of disease. IGT is caused by a decrease in glucose-responsive early-phase insulin secretion, and a decrease in additional insulin secretion after meals causes postprandial hyperglycemia. An oral glucose tolerance test (OGTT) in IGT cases generally shows an over-response in Western and Hispanic individuals with markedly high insulin resistance.Japanese patients, on the other hand, frequently respond to this test with lower insulin secretion.Even when there is an over-reaction in those with obesity or other variables, there is a reduction in early-phase secretory response.The reduction in early-phase secretion is a critical component of this illness and is very significant as a fundamental pathophysiological event during disease initiation in all ethnic groups **(11).**

Impaired insulin secretion is often progressive and involves glucose toxicity and lipotoxicity. In animal tests, they are known to induce a reduction in pancreatic β cell mass when left untreated. The evolution of pancreatic β cell function deterioration has a significant impact on long-term blood glucose regulation **(11).**

Insulin resistance is a condition in which insulin in the body does not respond in proportion to its blood content.Impairment of insulin action in major target organs such as the liver and muscles is a frequent

pathophysiologic characteristic of type 2 diabetes.Insulin resistance develops and spreads before illness onset.The study of the molecular mechanism of insulin action has revealed how insulin resistance is linked to hereditary and environmental variables (hyperglycemia, free fatty acids, inflammatory mechanism, and so on) **(11).**

types of ORAL Hypoglycemic Medications

Sulfonylureas (glipizide, glyburide, gliclazide, glimepiride) Meglitinides (repaglinide and nateglinide)Biguanides (metformin) Thiazolidinediones (rosiglitazone, pioglitazone) α-Glucosidase inhibitors (acarbose, miglitol, voglibose) DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin) SGLT2 inhibitors (dapagliflozin and canagliflozin)

Cycloset (bromocriptine)

Mechanism of Action

-Sulfonylureas bind to adenosine triphosphate-sensitive potassium channels (K-ATP channels) in the beta cells of the pancreas; this leads to the inhibition of those channels and alters the resting membrane potential of the cell, causing an influx of calcium and the stimulation of insulin secretion.

-Meglitinides exert their effects via different pancreatic beta-cell receptors, but they act similarly to sulfonylureas by regulating adenosine triphosphate-sensitive potassium channels in pancreatic beta cells, thereby causing an increase in insulin secretion.

-Metformin increases hepatic adenosine monophosphate-activated protein kinase activity, thus reducing hepatic gluconeogenesis and lipogenesis and increasing insulin-mediated uptake of glucose in muscles.

-Thiazolidinediones activate peroxisome proliferator-activated receptor gamma (PPAR-γ), a nuclear receptor, which increases insulin sensitivity and resultant peripheral uptake of glucose and increases the level of adiponectin, a fat tissue-secreted cytokine, that increases not only the number of insulin-sensitive adipocytes but also stimulates fatty acid oxidation.

- Alpha-glucosidase inhibitors competitively inhibit alpha-glucosidase enzymes in the intestinal brush border cells that digest the dietary starch, thus inhibiting the polysaccharide reabsorption and the metabolism of sucrose to glucose and fructose.

-DPP-4 inhibitors inhibit the enzyme dipeptidyl peptidase 4 (DPP- 4). These deactivate glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), among others. Therefore, these influence glucose control through multiple effects, such as decreasing glucagon release and increasing glucose-dependent insulin release, decreasing gastric emptying, and increasing satiety. SGLT2 inhibitors inhibit sodium-glucose co-transporter 2 (SGLT-2) in proximal tubules of renal glomeruli, causing inhibition of 90% glucose reabsorption and resulting in glycosuria in people with diabetes which in turn lowers the plasma glucose levels.

Cycloset, a sympatholytic dopamine D2 receptor agonist, resets the hypothalamic circadian rhythm, which might have been altered by obesity. This action results in the reversal of insulin resistance and a decrease in glucose production.

cardio vascular benefits of oral anti-diabetics SGLT2 inhibitors: SGLT2-I, also called gliflozins (empagliflozin, canagliflozin and dapagliflozin), is another novel therapy that nowadays represents a cornerstone in the management of HF, given the outstanding results firstly showed by the landmark cardiovascular outcome trials EMPA-REG, CANVAS and DECLARE-TIMI, in which SGLT2-I significantly reduced cardiovascular mortality, all-cause mortality and HF hospitalization **(12)**

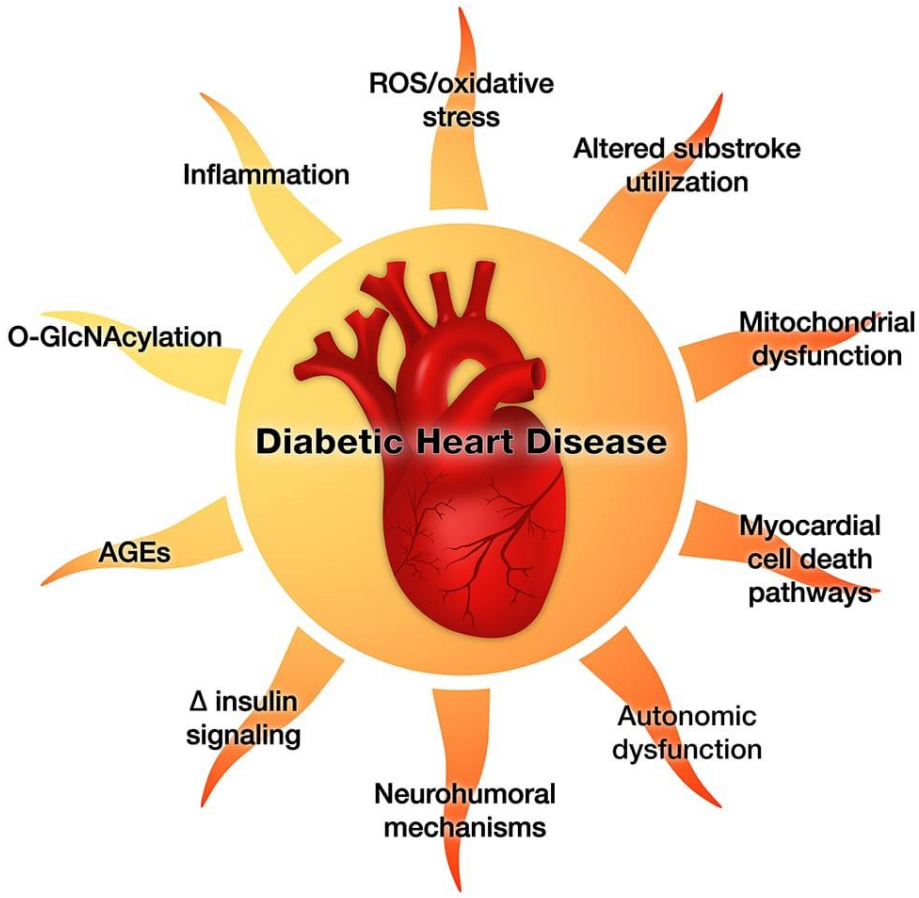
The relative risks of ACS with SGLT2 inhibitor use was consistent with that of all-cause mortality. SGLT2 inhibitor use was associated with a lower risk of ACS than the other OADs and **(13).** One group of drugs that could be characterized as a class effect is the blood glucose co-transporter (SGLT2) or SGLT2 inhibitors. This group of drugs has a hypoglycemic action against hyperglycemia, by increasing the blood glucose ejections into the urine through the kidney. This mechanism of reaction categorizes SGLT2 inhibitors into antidiabetic drugs and makes them suitable for the treatment of diabetes type 2. A number of pharmaceutical substances are classified into the SGLT2 inhibitors class, such as empagliflozin, canagliflozin, dapagliflozin Diabetes is not the only disease that can be treated through SGLT2 inhibitors,

since cardiovascular (CV) disease is the main cause of mortality in patients with diabetes mellitus type 2 (T2DM) and SGLT2 inhibitors have an effect on it too.
SGLT2 protein is located in the kidneys. It is a glucose transporter protein in humans and it is responsible for the reabsorption of glucose by the kidney. SGLT2 inhibitors inhibit the SGLT2 protein and therefore lower blood glucose levels by blocking glucose resorption in the kidney, due to an increase in renal urinary glucose (glycosuria). Further glucose control can be accomplished **(14)**
Empagliflozin, being one of the SGLT2 inhibitors, is responsible for the inhibition of the renal sodium-glucose cotransporter-2 (SGLT-2 inhibitor) **(15).**

Cardiac remodeling is defined as a group of molecular, cellular and interstitial changes that manifest clinically as changes in size, mass, geometry and function of the heart after injury. The process results in poor prognosis because of its association with ventricular dysfunction and malignant arrhythmias After MI, may predispose to ventricular rupture and aneurysm formation. Despite therapeutic advances, mortality rates related to cardiac remodeling/dysfunction remain HIGH. The term "remodeling" was used for the first time in 1982 by Hockman and Buckey, in a myocardial infarction (MI) model. This term was aimed to characterize the replacement of infarcted tissue with scar tissue. **(16)**
Postinfarct ventricular remodeling represents a prevailing cause of heart failure (HF), and it occurs in almost 30% of patients with a previous anterior myocardial infarction (MI) and in only approximately 17% of patients with non-anterior infarct **(17)**
Adverse cardiac remodeling is an important contributor to heart failure severity. This includes the development of cardiac hypertrophy, fibrosis, inflammation, and cardiomyocyte cell death. Several experimental and human studies have demonstrated beneficial effects of SGLT2 inhibition on cardiac remodeling **(17)**
SGLT2 INHIBITORS In a randomized trial, people with type 2 diabetes and a history of coronary artery disease were treated with empagliflozin versus placebo for 6 months . The primary outcome—change in LV mass index (evaluated by cardiac magnetic resonance imaging) was significantly lower in those treated with empagliflozin versus in those who received placebo. Although these data do not provide insight about the exact mechanism of action, they do suggest that even short-term exposure to SGLT2 inhibitors can promote cardiac reverse remodeling **(16)**
SGLT2 INHIBITORS ROLE against cardiac remodling
In a randomized trial, people with type 2 diabetes and a history of coronary artery disease were treated with empagliflozin versus placebo for 6 months . The primary outcome—change in LV mass index (evaluated by cardiac magnetic resonance imaging) was significantly lower in those treated with empagliflozin versus in those who received placebo. Although these data do not provide insight about the exact mechanism of action, they do suggest that even short-term exposure to SGLT2 inhibitors can promote cardiac reverse remodeling **(16)**
In the EMMY (Impact of EMpagliflozin
on cardiac function and biomarkers of heart failure in patients with acute
MYocardial infarction) trial, 467 patients were randomized to empagliflozin 10 mg or placebo within 72 h of PCI for acute MI.429 The study The drug was associated with a significantly greater N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction over 26 weeks (primary outcome) and a significant improvement in echocardiographic LV parameters, without demonstrating any difference in adverse events of special interest including metabolic acidosis and diabetic ketoacidosis **(18)**
mechanisms:
a) A key role of the SGLT2 pathway is an increased myocardial uptake of ketone bodies resulting in an improved myocardial energy supply and thus impacts the energetic state of the myocardial cells leading to a decrease in cardiac necrosis and cardiac dysfunction
B) experimental studies showed potential beneficial myocardial effects of SGLT2-inhibition through upregulation of cardioprotective proteins. **(18)**
C) an increased uptake of the GTP enzyme cyclohydrolase1 for empagliflozin independent of diabetic status affecting the cGCH1-BH4/NO-pathway and resulting in a reduction of cardiac dysfunction by its anti-remodeling effect **(18)**
D) SGLT2-inhibitors ameliorates left ventricular remodeling in heart failure by the adenosine monophosphate-activated protein kinase (AMPK)-pathway with reduction in myocardial necrosis and cardiac inflammatory processes through enhancing myocardial energetics and attenuating ischemia and reperfusion injury **(19)**
E) mechanism of SGLT2-inhibition is the reduction of oxidate stress levels mediating anti-inflammatory effects by the BCL2as well as Signal transducer and activator of transcription 3/januskinase2(STAT3/JAK2)-pathway and thus,decreasing myocardial necrosis and cardiac dysfunction **(13).**

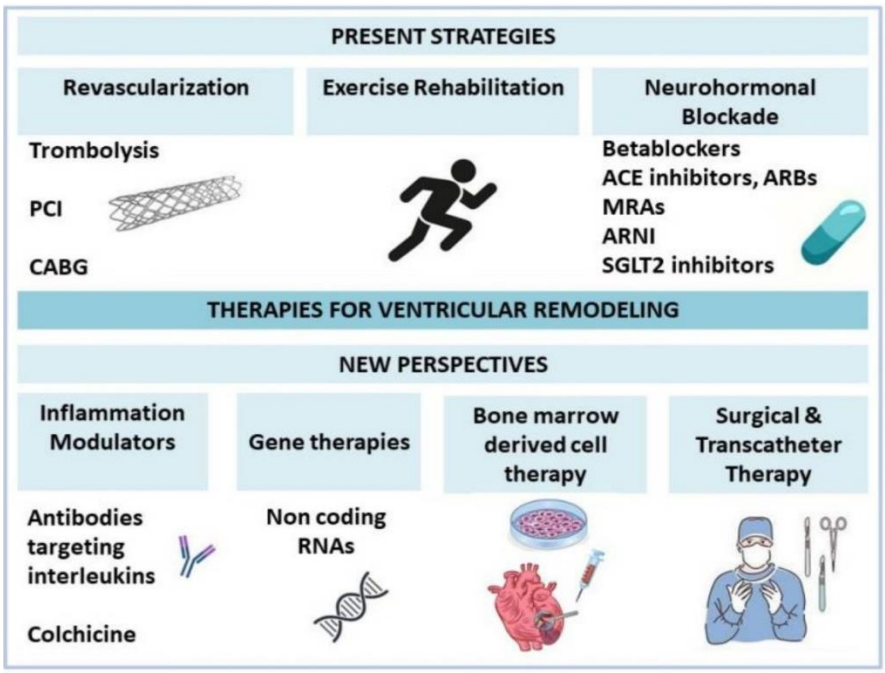
All these preclinical molecular effects ameliorates inflammatory response and necrosis of cardiomyocytes resulting in smaller infarct size, less reperfusion injury and anti-remodeling effects

Empagliflozin and dapagliflozin reduced the incidence of recurrent MI, which may be related to the gliflozins capacity to reduce the ischemic-reperfusion injury In MI, SGLT2 inhibitors switch the myocardial substrate utilization from glucose towards ketone bodies, free fatty acids and branched-chain amino acids, thereby improving myocardial energetics. Experimental evidence shows that SGLT2 inhibitors exert cardioprotective effects in animal models with acute MI by improving cardiac function during ischemia, reducing infarction size and subsequently attenuating HF development Patients with acute MI have been relatively understudied in SGLT2 inhibitor outcome trials to date. Currently, there are three trials ongoing, EMPACT-MI, EMMY and DAPA-MI, which will evaluate the efficacy and safety of the early initiation of SGLT2 inhibitors within days of an acute MI. Diabetic cardiomyopathy Background Diabetes mellitus frequently coexists with heart failure (HF), but few studies have compared the associations between diabetes mellitus and cardiac remodeling, quality of life, and clinical outcomes, according to HF phenotype **(18)**
Among patients with HFrEF and HFpEF, type 2 diabetes mellitus is associated with smaller indexed LV diastolic volumes, higher LV filling pressures, poorer QoL, and worse cardiovascular outcomes, with several differences noted between HF phenotypes. **(18)**



Multifactorial contributors to diabetic cardiomyopathy

Diabetes predisposes affected individuals to a significant spectrum of cardiovascular complications, one of the most debilitating in terms of prognosis is heart failure. Indeed, the increasing global prevalence of diabetes and an aging population has given rise to an epidemic of diabetes-induced heart failure. Despite the significant research attention this phenomenon, termed diabetic cardiomyopathy, has received over several decades, understanding of the full spectrum of potential contributing mechanisms **(19)**



How to avoid cardiac remodling

Different existing drugs including β-adrenergic receptor (β-AR) blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor (AR) blockers, mineralocorticoid receptor blockers, hydralazine, nitrates, and cardiac resynchronization therapy have been evaluated for preventing adverse cardiac remodeling **(20)**

a)ANGIOTEN SININHIBITION

The renin-angiotensin system regulates the structural remodeling of the left ventricle for post-MI cardiac healing and long-term prognosis [92]. Interestingly, the renin-angiotensin system is regulated by multiple mechanisms: (1) β-AR blockers inhibit the secretion of renin, (2) renin inhibitors directly diminish the activity of renin, (3) ACE inhibitors block the formation of angiotensin II, and (4) AR blockers dampen the activation of angiotensin II type 1 (AT1) receptor.

b) BETA-RECEPTORS BLOCKING

The activation of β-ARs increases the cAMP synthesis and activates protein kinase A, representing the primary mechanism for acute enhancement of cardiac reserve to maintain heart function. The β-AR blockers suppress the activation of β-ARs and attenuate adverse cardiac remodeling at the molecular and organ levels **(21)**

Indeed, several β-AR blockers exhibit potential for reversing cardiac remodeling,

ACE-inhibitors/angiotensin-receptor blocker as well as betablockers should be early initiated in the acute setting of acute myocardial infarction **(22)**

C) MINIRALOCORTICOID RECEPTORS ANTAGONISM

MRA treatment reduced all-cause mortality and the composite outcome of ventricular arrhythmia, ischemic events, new or worsening HF, cardiovascular deaths, and cardiovascular hospitalizations in post-STEMI patients without LVSD. In addition, post-STEMI patients without LVSD improved ventricular remodeling and cardiac function by MRA. Early administration of MRA within 7 days after AMI resulted in a greater improvement in all-cause mortality and LVEF. **(23)**

D)SGLT2 INHIBITORS ROLE

Imaging Techniques of Adverse Remodeling Ventricular remodeling evaluation relies on assessing ventricular geometry and function, which can be performed with echocardiography or CMR (cardiac magnetic resonance).

Compared with echocardiography, CMR presents better contrast resolution, higher reproducibility, and independence from acoustic windows and may also provide valuable information regarding the presence and extent of myocardial fibrosis in the form of late gadolinium enhancement (LGE) **(23)**

Myocardial infarction and ischemia can lead to myocyte loss, myocardial fibrosis, and LV dilatation. Along with neurohormonal activation, these changes lead to maladaptive LV remodeling and progressive deterioration of the remaining myocardium **(24)**

Prior studies, which have shown that increased ESV post-MI is associated with increased mortality **(25)**
Left ventricular (LV) end-systolic volume indexed to body surface area (ESVI) is a simple yet powerful echocardiographic marker of LV remodeling that can be measured easily. **(26)**
Echocardiography has become one of the most commonly used noninvasive modalities for assessment of ventricular volumes and function and can provide prognostic information for the prediction of future HF events. **(27)**
Although many sophisticated echocardiographic markers exist, ESV is a simple parameter that can be measured easily in clinical practice.1We sought to study ESV indexed to body surface area (ESVI) in patients with stable coronary disease to define its prognostic value. We hypothesized that ESVI, measured by echocardiography, is an important predictor of hospitalization for HF, even in patients with normal ejection fraction (EF). We also hypothesized that ESVI is a better predictor than other echocardiographic measures of LV systolic and diastolic enlargement, and that even subtle increases in ESVI would have prognostic importance.

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