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EDITORIAL

Heart Failure – Pathophysiology and Current Therapeutic Implications

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The concept of translational medicine involves promoting the rapid transfer of observations made in the areas of research and pathophysiological understanding to the medical practice. This approach is a reality in major Brazilian research centers which link academia and clinical practice.

Heart failure (HF) is a complex syndrome that can manifest itself as heart failure with preserved ejection fraction (HFpEF), acute heart failure, or chronic heart failure with reduced ejection fraction (HFrEF). Here, we will cover the type of HF whose pathophysiology is understood the best and thus has disease-modifying treatments: HFrEF.

In 1785, in the United Kingdom, the physician and biologist William Withering outlined one of the first major moves towards treatment options for HF when he wrote the book "An Account of the Foxglove and some of its Medical Uses With Practical Remarks on Dropsy and Other Diseases.[1]" Known as a kidney disease that caused fluid to accumulate in the body, HF was primarily treated with an extract of Digitalis purpurea, a plant popularly known as foxglove. In his research, Withering described some cases where he administered this compound, now known as digitalis, to HF patients and noticed improvements in the disease symptoms. Although no scientific data has proven, to date, a change in hard outcomes with the use of digoxin (an active compound of digitalis) , this medication still has a prominent place in the treatment of HF. Since 1980, more rigorous studies have been performed to demonstrate the safety and efficacy of digoxin: 4 large studies – DIMT (1993),[2] RADIANCE (1993),[3] PROVED (1993),[4] and DIG (1997)[5] – substantiated its clinical use, demonstrating clinical improvement of the patients and a reduction in hospitalization, although not in mortality (Table 1).

During the 19th century and at the beginning of the 20th century, literature on the treatment of HF was mostly inexistent; for a long time, patients with this salt and liquid-retaining disease were administered only digitalis to improve cardiac contractility and diuretics to relieve edema. Until the late 1960s, HF was thought to follow a cardio-renal pathophysiological model summarized in edema and congestion. It was not until the 1970s that this conception was modified by the cardiocirculatory view of the system as, in a simplistic view, a system connecting vessels to a pump. From the moment HF was understood as the failure of a pump, which in turn was based on the Frank-Starling mechanism and the behavior of the vessels connected to it, generating preload and afterload, there was a commitment to discovering vasodilators. This endeavor owes greatly to professor Jay Cohn, who for 22 years recruited researchers who demonstrated how vasodilator medications could improve left ventricular function. He further pioneered the interest in hormones as contributors to vasoconstriction and promoted the concept that neurohormonal inhibition could inhibit the structural remodeling of the heart.[6]

In 1986, Cohn *et al.* published one of the first major studies that laid the foundation for HF specialists: "Effect of Vasodilator Therapy on Mortality in Chronic Congestive Heart Failure.[7]" The use of hydralazine in association with isosorbide dinitrate demonstrated that peripheral vasoconstriction not only contributed to the worsening of HF symptoms but also favored the deterioration of left ventricular function and sudden death. With a 38% reduction

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COMPARATIVE TRIALS: BETA-BLOCKERS				
TRIAL		US CARVEDILOL	MERIT HF	CIBIS - II
YEAR		1996	1999	1999
POPULATION		FC II, III, IV EF≤35%	FC II, III, IV EF≤40%	FC III, IV EF≤35%
N		1094	3991	2647
TREATMENT REGIMEN		(Carvedilol x Placebo) + ACEI/ARB + Digoxin + Diuretic	(Metoprolol x Placebo) + ACEI/ARB + Digoxin + Diuretic	(Bisoprolol x Placebo) + ACEI/ARB + Digoxin + Diuretic
FIRST ENDPOINT		Death or hospitalization due to cardiovascular causes	Reduction of mortality and symptoms in HF patients	Reduction of all causes of mortality in chronic HF
MORTALITY	DRUG	3.2%	7.2%	11.8%
	PLACEBO	7.8%	11.0%	17.3%
RRR		59.0	35.0	31.7%
ARR		4.6%	3.8%	5.5%
NNT		21	26	18

* FC - Functional class
* EF -Left ventricle ejection fraction
* ACEI/ARB -Angiotensin-Converting Enzyme Inhibitor /Angiotensin Receptor Blocker
* RRR - Relative Risk Reduction
* * ARR – Absolute Risk Reduction
* NNT - Number Needed to Treat

in mortality after 1 year, the hydralazine-nitrate combination proved that vasodilators were essential in the treatment of this disease.[7] In the struggle to change the natural history of HF, numerous trials were subsequently designed, validating the use of now well-established vasodilators. In the event of a drop in ejection fraction for a specific reason, vasodilation should facilitate the functioning of the cardiovascular system. However, it was observed that, in addition to improving functioning, it was necessary to stop the HF continuum, avoiding its perpetuation caused by the consequent dilation of the left ventricle.

It is worth mentioning that advances in the concept of vasodilation as well as new explanations for the mechanisms involved in HF and its real impacts on mortality were brought by studies performed in the 1990s. The highlight of the renin-angiotensin-aldosterone system was revealed by the SOLVD trial (Effect of Enalapril on Survival in Patients with Reduced Left Ventricular Ejection Fraction and Congestive Heart Failure) in 1991. This study was the first to demonstrate the benefits of using angiotensin-converting enzyme inhibitors (ACEIs) in the treatment of HF.[8]

A few years earlier, in 1987, great evidence had already been provided by the CONSENSUS trial (Effects of Enalapril on Mortality in Severe Congestive Heart Failure) that this class of drugs, in addition to improving the functional classification of patients with chronic HF, could also reduce mortality.[9] In this trial, which randomized only patients with class IV HF (according to the New York Heart Association [NYHA]), mortality in the placebo group was 52% after 1 year. Comparing the causes of death in the 2 groups, it was noteworthy that sudden death was equally present in both. The absolute reduction in total mortality was 27%. The SOLVD study then proved this tendency of reduced mortality in patients with chronic HF treated with enalapril when compared to placebo, despite also observing no significant differences in sudden death rates.

These studies opened an era of discoveries regarding vasodilators and, in particular, ACEIs and angiotensin receptor blockers (ARBs). Various studies have proven the superiority of this class of drugs: V-Heft II (A Comparison of Enalapril with Hydralazine–Isosorbide Dinitrate in the Treatment of Chronic Congestive Heart Failure),[10] in particular, compared the nitrate-hydralazine combination to enalapril, revealing unprecedented data regarding a reduction of sudden death in the enalapril group. Therefore, in addition to the vasodilation effect, anti-proliferative, anti-apoptotic and inflammatory cytokine inhibitor effects were added to the disease.

Still in the 1990s, the decade in which the pathophysiology of HF was elucidated the most, what was long postulated was designed, tested and proven: the effect of catecholamines on the development of HF.[11] Beginning in 1897, Starling described tachycardia and peripheral vasoconstriction as components of this syndrome and responsible for an increase in cardiac contractility as a compensatory response.[12,] In 1964, Dr. Eugene Braunwald wrote an editorial titled "The heart as an endocrine organ,[13]" on the occasion of the discovery that it was able to synthesize norepinephrine.[14] These findings led to the hypothesis that sympathetic activation played an important role in the progression of HF. Norepinephrine can have direct and indirect adverse effects on the circulation, and interfering with its actions can slow the progression of HF in animal models.[15,16] In 1996, the large US-CARVEDILOL study evaluated the effect of the beta-blocker carvedilol on the survival of patients with HF.[17] The study had an early end because the observed benefit surpassed that envisaged by its design: patients treated with carvedilol had a 65% lower risk of death than those who received placebo. This remarkable effect was indicated by a decrease in risk of death both due to the progression of HF and to sudden death. Since then, other beta-blockers such as extended-release metoprolol succinate (MERIT-HF, 1999)[18] and bisoprolol (CIBIS II)[19] have been tested for HF and have shown a significant effect in reducing hard outcomes (Table 2).

By the end of the 20th century, the horizons of HF therapy had completely changed, and the disease that previously attracted little effort from the scientific community for being known as "terminal" now could be treated with interventions that significantly reduced mortality. The famous renin-angiotensin system, which was popular during the discovery of HF and its decompensations, remained the center of attention. In 1999, the RALES study evaluated spironolactone, an aldosterone antagonist, in the course of HF and observed a 30% reduction in mortality. The exact mechanism through which this was achieved is not yet well understood, but it is known that spironolactone improves hemodynamics, cardiac remodeling, and natriuresis in patients with HF.[20]

Once the progression of the disease has been alleviated with established pharmacological therapies, the main cause of mortality in patients with HF is now recognized as sudden death from malignant arrhythmias. Two proposals have been made to reduce the risk of these arrhythmias: the use of antiarrhythmics such as amiodarone and the implantable cardioverter-defibrillator (ICD). In 2002, the MADIT-II study (Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction) compared patients with ischemic cardiomyopathy and a left ventricular ejection fraction (LVEF) < 35% who received an ICD as primary prophylaxis or were submitted to conventional therapy. This study showed a 31% reduction in the risk of dying from a malignant arrhythmia after ICD implantation.[21] In 2005, the SCD-HeFT trial (Amiodarone or an Implantable Cardioverter–Defibrillator for Congestive Heart Failure) demonstrated that ICD implantation in patients with NYHA class II HF reduced mortality by 12% in 5 years when compared to amiodarone, thus establishing its indication for ischemic and symptomatic patients[22] (Table 3).

Regarding cardiac stimulation devices, it is worth mentioning cardiac resynchronization therapy (CRT). Still quite debatable, despite being proven effective, CRT has brought benefits in improving survival, symptoms, and reducing hospital readmissions. However, some patients have been observed to not respond to this therapy in the clinical practice. One of the first trials to assess CRT was published in 2003 and was named MIRACLE (Cardiac Resynchronization in Chronic Heart Failure).[23] It aimed to assess whether patients with delayed intraventricular conduction would have clinical benefits with the implantation of this device. The study recruited 453 patients with ejection fractions (EFs) ≤ 35%, NYHA class III or IV, QRS ≥ 130 ms, and left ventricular end-diastolic diameter ≥ 55 mm. After 6 months, it was concluded that the device was capable of providing important clinical improvements to the HF syndrome: patients in the intervention group showed changes in quality of life, NYHA functional class, and the 6-minute walk test.

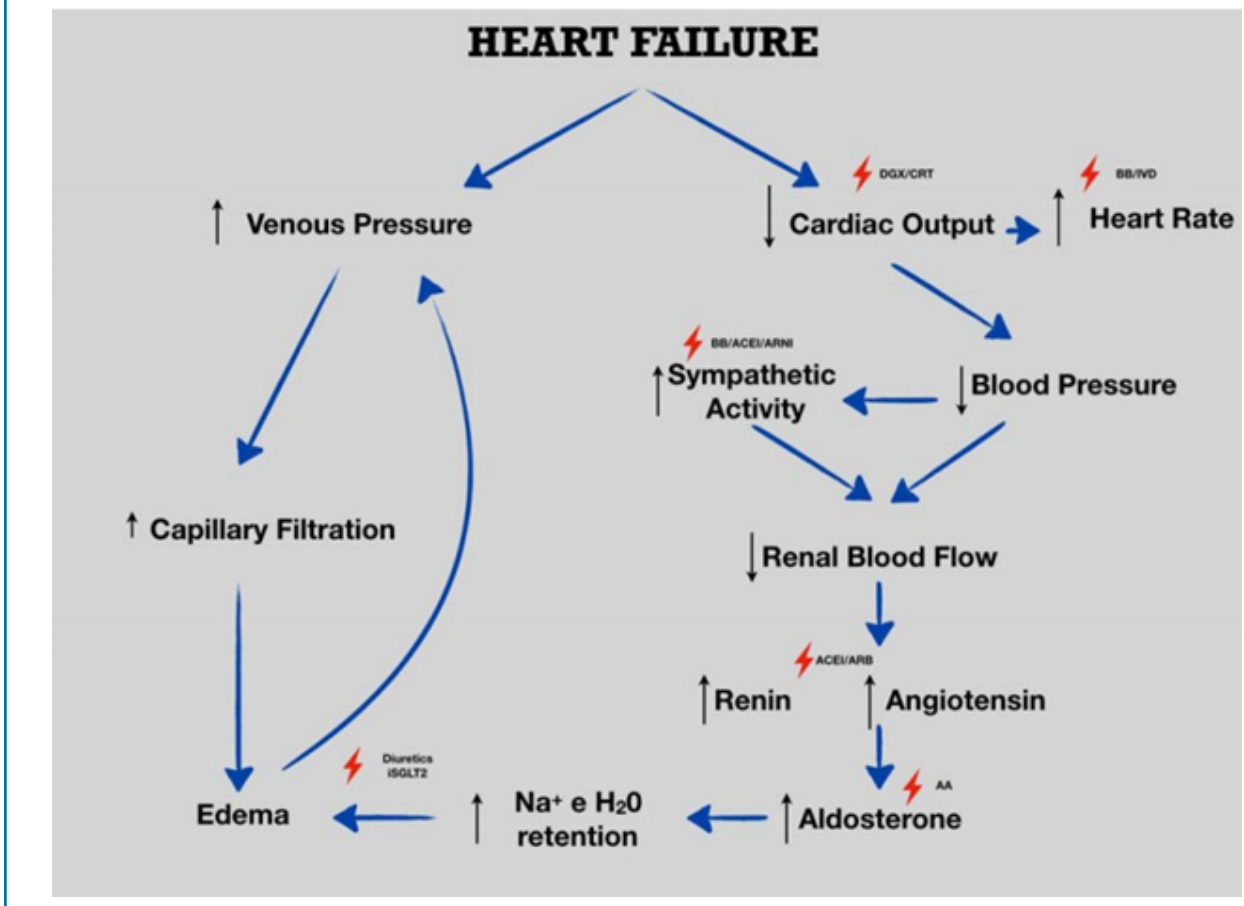
In order for this new therapy to be added to the HF treatment arsenal, other studies were conducted to verify if the device could modify hard outcomes. Since 2002, various studies have proven a reduction in the mortality of patients with QRS > 120 ms, who are sinus rhythm, belong to NYHA classes ≥ III, or are under optimized drug therapy (ODT): COMPANION (Cardiac-Resynchronization

COMPARATIVE TRIALS: DIGOXIN				
TRIAL	DIMT	RADIANCE	PROVED	DIG
YEAR	1993	1993	1993	1997
POPULATION	FC II, III	FC II, III EF≤35%	FC II, III EF≤35% + Sinus Rhythm	FC I - IV EF≤45%
FOLLOW-UP	6 Months	3 Months	3 Months	37 Months
N	161	178	88	6800
TREATMENT REGIMEN	Ibopamine x (Digoxin + Placebo)	Digoxin x Placebo	Digoxin Withdrawal (Placebo) x Digoxin	[Digoxin x Placebo] + Diuretics + ACEI
FIRST ENDPOINT	Efficacy and safety of this ibopamine in mild and moderate chronic HF	Effect of digoxin suspension in patients with chronic HF receiving [captopril or enalapril] + diuretic + digoxin	Efficacy in HF patients	Mortality
RESULTS	Digoxin increased exercise time / Mortality was not affected	Worsening of HF = functional capacity + worsening of the Ejection Fraction + increased cardiac frequency + weight increase.	Worsening of HF = functional capacity + greater treatment failure + worsening of the Ejection Fraction + increased cardiac frequency + weight increase	34.8% (digoxin) x 35.1% (placebo). Significant P for secondary outcome of HF hospitalization reduction

* FC - Functional Class
* EF - Left Ventricle Ejection Fraction
*ACEI - Angiotensin Converting Enzyme Inhibitor

Therapy with or without an Implantable Defibrillator in Advanced Chronic Heart Failure),[24] CARE-HF (The Effect of Cardiac Resynchronization on Morbidity and Mortality in Heart Failure),[25] MADIT-CRT (Cardiac-Resynchronization Therapy for the Prevention of Heart-Failure Events),[26] and RAFT (Cardiac-Resynchronization Therapy for Mild-to-Moderate Heart Failure).[27] The indication for CRT was established by the Brazilian Guidelines for Chronic and Acute Heart Failure with level of evidence IA for patients presenting the following: EF ≤ 35%, left bundle branch block, sinus rhythm, QRS ≥ 150 ms, and symptoms despite ODT.

In 2010, after observational studies,[28] heart rate (HR) was considered one of the factors with the worst prognosis in HF. A continuously high resting HR is responsible for the progressive worsening of not only the ventricular function but also coronary atherosclerosis and ventricular arrhythmias. Thus, considering the effect already provided by beta-blockers, a new drug acting only on the sinus node was proposed for selective inhibition of the If current. It has been validated for patients that are symptomatic despite therapeutic optimization, in sinus rhythm, and with a HR > 70 bpm. In the SHIFT study (Ivabradine and Outcomes in Chronic Heart Failure), 6558 randomized patients were randomly assigned to receive ivabradine or placebo, in a 1:1 ratio. After a 22.9-month follow-up period, patients who received the drug had a relative risk for the primary endpoint of 18%, with a number needed to treat (NNT) of 20 and $p < 0.001$.[29] In 2018, ivabradine



was incorporated by the Brazilian Guidelines for Chronic and Acute Heart Failure with a class IIA recommendation and level of evidence B.

Twenty-five years after the establishment of enalapril, biomarkers have taken center stage in the HF scenario. In 1988, professor Hisayuki Matsuo discovered a natriuretic peptide synthesized in the brain of pigs, which he named cerebral natriuretic peptide.[30] Later, confirming Dr. Braunwald's predictions from 1964, it was discovered in humans that the main source of this peptide was the heart, and it became known as B-type natriuretic peptide (BNP). In 2002, a prospective study evaluated BNP levels in 1586 patients who arrived at an emergency room with acute dyspnea, showing that these levels alone were more accurate than any historical or physical findings in identifying congestive HF as a cause of dyspnea. After the publication of this "BNP Multinational Study" trial in the New England Journal of Medicine, there was great impetus for the practical application of findings related to endogenous vasoactive peptides.[31]

In September 2014, McMurray *et al.* published PARADIGM-HF,[32] a fundamental study for HF specialists. Based on the inhibition of neprilysin (an enzyme responsible for the degradation of vasoactive peptides such as natriuretic peptides), as well as bradykinin, adrenomedullin, and angiotensin II, the new sacubitril-valsartan drug was proposed as another form of neurohormonal inhibition in HF. Similarly to US-CARVEDILOL, PARADIGM-HF was interrupted early (after an average follow-up period of 27 months) due to a significant reduction in mortality with a NNT of 21 for the primary event and 32 for mortality.

Every paradigm-modifying trial should be read and interpreted by each expert with a critical eye. PARADIGM-HF is no different. The entry of sacubitril-valsartan in the market occurred with great support from the pharmaceutical industry and, although the use of this medication is currently commendable in many cases, the traditional ACEI still holds its importance in the treatment of HF. The standard treatment of this syndrome comprising ACEI + beta-blocker + mineralocorticoid receptor antagonist has been put to the

COMPARATIVE TRIALS: ICD						
TRIAL	MADIT - II	SCD - HeFT				
YEAR	2002	2004				
POPULATION	FC I - IV + Primary AMI EF≤30%	FC II, III EF≤35%				
N	1.232	2.521				
DURATION	20 Months	45.5 Months				
TREATMENT REGIMEN	ICD X Drug Treatment (3:2)	Amiodarone x (Placebo + ICD)				
FIRST ENDPOINT	Mortality from any cause	Mortality from any cause				
P	0.016	0,07				
RRR	28.00%	ICD	24.00%	Amiodarone	3.50%	
ARR	5.60%	x	4.00%	x	1.00%	
NNT	17.8	p	14.0	p	100.0	

* FC - Functional Class
* EF:left ventricle ejection fraction
* ICD – implantable cardioverter-defibrillator.
* RRR - Relative risk reduction
* ARR - Absolute risk reduction
* NNT - Number needed to treat
*AMI - Acute Myocardial Infarction
*P - Placebo

test and, in well-defined cases, has already given way to the sacubitril-valsartan + beta-blocker + mineralocorticoid receptor antagonist triad.

Finally, the most recent major advance in HF drug therapies, the SGLT2 inhibitors, cannot go unmentioned. This drug class was developed primarily for the treatment of type 2 diabetes mellitus (T2DM), but a significant trend was observed in the improvement of patients with HF. As further explained below, it is currently being tested for the treatment of patients with HF regardless of the presence of T2DM.

The healthy human kidney does not excrete glucose because the proximal tubule contains co-transporters (SGLT1/2) responsible for its reabsorption, carrying it to the epithelial cell against a concentration gradient using ATP through the Na^+/K^+ pump. SGLT2 reabsorbs approximately 90% of the filtered glucose but is unable to do so when the glucose concentration in the ultrafiltrate is too low. In light of this knowledge, in 1987, Rossetti *et al.* used a murine model of diabetes to demonstrate that phlorizin, a competitive inhibitor of SGLT, could correct hyperglycemia, improve insulin secretion, and reverse insulin resistance.[33] This medication was not clinically tolerated in humans because it caused an intense diarrhea; however, it attracted attention to a possible target for the treatment of diabetes. As SGLT2 transports sodium and glucose in a 1:1 ratio, the higher the glycosuria, the greater the natriuretic effect. This knowledge has important implications for the treatment of patients with HF.

The EMPA-REG (Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes) study, published in 2015, was the first to demonstrate a significant cardioprotective effect of the use of SGLT2 inhibitors (SGLT2is). This drew the attention of the scientific community to a possible new drug for completing the quadruple arsenal for the treatment of HF.[34] Empagliflozin showed a 38% relative risk reduction in mortality from cardiovascular causes, 35% in hospitalizations due to HF, and 32% in mortality from any cause when compared to placebo. Subsequently, studies evaluated other gliflozins (canagliflozin and dapagliflozin) and pointed to a sustainable benefit in improving HF.

Recently, in 2019, DAPA-HF (Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction) was the first study to provide evidence of the benefit of gliflozins in non-diabetics, which should expand their indication (currently limited by glycated hemoglobin). In this study, McMurray *et al*. demonstrated that, after an average follow-up period of 18 months, this medication reduced the risk of cardiovascular death by 26% and avoided worsening HF (defined as emergency care that required intravenous

therapy or hospitalization for HF) compared to placebo. A very interesting finding was the size of this benefit, which was almost identical between patients with or without T2DM (25% and 27% reduction, respectively). When analyzed separately, cardiovascular death and worsening HF were significantly reduced in patients treated with dapagliflozin (18% and 30%, respectively). In addition, the treatment reduced the risk of death from all causes by 17%.[35]

The mechanism through which SGLT2is provide such impressive cardiovascular benefits is still unclear. It appears to be secondary to the hemodynamic effects provided by natriuresis and osmotic diuresis, which result in a reduction in intravascular volume and blood pressure. The consequent decrease in preload and afterload reduces pulse pressure and oxygen consumption in the myocardium. Although this mechanism is not yet fully elucidated, the fact is that all studies considering different SGLT2is demonstrated cardiovascular protection and a reduction in the development of HF (Table 4).

Finally, the big question remains: will we have a quadruple therapy dedicated to HF? Does the benefit of these new drugs have any bearing on the fact that all patients in the study are correctly using the standard therapy? The possibility of obtaining these answers is highly unlikely because taking a step back and comparing ACEIs or beta-blockers alone in each arm with new drugs is not ethically feasible. Moreover, the rapidly increasing body of knowledge on the pathophysiology of the HF syndrome also leads us to confront new dilemmas that we may not be able to solve (Table 5).

COMPARATIVE TRIALS: SGLT2is				
TRIAL	EMPA-REG	CANVAS Program	DECLARE - TIMI 58	DAPA -HF
YEAR	2015	2017	2018	2019
TREATMENT REGIMEN	Empagliflozin x Standard treatment	Canagliflozin x Standard treatment	Dapagliflozin x Standard treatment	Dapagliflozin x Standard treatment
FOLLOW-UP TIME	37.2 Months	28.8 Months	74.4 Months	18.2 Months
N	7024	10142	17160	4744
CARDIOVASCULAR DISEASE	100.00%	65.60%	40.60%	100.00%
HEART FAILURE	10.10%	14.40%	10.00%	100.00%
FIRST ENDPOINT	MACE, all-cause mortality, cardiovascular mortality, myocardium infarction, stroke, cardiovascular hospitalization, disease progression, or renal mortality.	MACE, all-cause mortality, cardiovascular mortality, myocardium infarction, stroke, cardiovascular hospitalization, disease progression, or renal mortality.	MACE, all-cause mortality, cardiovascular mortality, myocardium infarction, stroke, cardiovascular hospitalization, disease progression, or renal mortality.	Hospitalization or visit to the emergency room due to HF, hospitalization for HF, visit to the emergency due to HF or cardiovascular death
P (SUPERIORITY)	Not significant	Not significant	Not significant	<0.001
RRR	13.00%	15.00%	0.06%	23.00%
ARR	1.60%	0.46%	0.60%	4.90%
NNT	62.50	217.00	166.00	20.00
SECONDARY ENDPOINT (hospitalization due to HF)				
P	0.002	<0.001	**0.005	
RRR	35.00%	37.00%	18.00%	
ARR	5.10%	3.20%	2.50%	
NNT	19.00	31.00	40.00	

* MACE - Cardiovascular death, myocardium infarction or stroke
* RRR - Relative Risk Reduction
* ARR – Absolute Risk Reduction
* NNT - Number Needed to Treat
** cardiovascular death or hospitalization due to HF

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