Review Article

Heart Failure After Acute Myocardial Infarction: A New Phenotype of Acute Heart Failure?

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Coronary artery disease (CAD) and heart failure (HF) are among the most common causes of hospitalization and death worldwide.[1] Although the etiology of HF varies greatly around the world, in the main registries from Western and developed countries, CAD and systemic arterial hypertension are the predominant factors.[2] Acute myocardial infarction (AMI) complicated with HF (post-MI HF) is quite common in clinical practice its incidence among patients hospitalized for AMI varies between 14% and 36%.[3] In the GRACE registry (Global Registry of Acute Coronary Events), among 13,707 patients with Acute Coronary Syndrome hospitalized from 1999 to 2001, 13% had HF on admission, and another 5.6% developed HF during hospitalization.[4]

In addition to the great association between such pathologies, heart failure is also an important predictor of mortality among patients with AMI, with implications for treatment and prognosis. One of the factors that stands out most among the complications of ACS is cardiogenic shock; however, even less severe profiles in the HF spectrum are more common, also having a negative prognostic impact.[5]

Post-MI HF has peculiarities in its pathophysiological mechanisms that differentiate it from other HF etiologies, also leading to different clinical consequences and therapeutic possibilities, both in pharmacological treatment and in the indication of ventricular assistance devices and surgical approaches. These differences make HF after AMI a nosological entity that still requires better clarification regarding its approach. In this context, some questions from HF specialists have been raised, such as: What are the risk factors for the development of HF after an ACS? In the case of acute HF, which medications can be started first, which increases the patient's survival? Why have certain pharmacological treatments not had a good response in this situation, even though they have been shown to be useful in chronic HF? At what point does post-MI HF "turn" into chronic HF? When is the right time to recommend a ventricular assist device in this type of patient, and is there any difference with other etiologies? What is the role of myocardial revascularization? Would the indication and timing of a heart transplant be different?

This review article proposes to clarify some of these doubts, detailing the processes that are behind ventricular dysfunction resulting from acute myocardial infarction, as well as addressing the main studies that support the current treatment of this disease and future possibilities that could reduce the morbidity and mortality from such a serious disease.

Keywords

Heart Failure; Myocardial Infarction; Coronary Artery Disease

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Pathophysiology

Over the last few decades, much has been discovered about the pathophysiological processes of chronic HF, especially myocardial remodeling, signaling important pharmacological targets that have proven to impact clinical outcomes. In the scenario of post-infarction HF, some peculiarities in these processes have been better understood, helping to understand specific characteristics of this clinical phenotype of HF and enabling a more targeted approach in this scenario.

Initially, ischemia leads to loss of contractile function and consequently enlarges the ventricular cavity, which culminates in increased filling pressures and oxygen demand. Over time, cardiac work increases in an attempt to compensate for the increased pre- and post-load (due to all the hyperactivity of the sympathetic nervous system and the renin-angiotensin-aldosterone system),[6] in addition, pressure overloads and volume induce molecular pathways that determine ventricular hypertrophy, without an adequate proportion of myocardial thickness and volume, without concomitant adequate vascularization and with the emergence of fibrosis (resulting from the deposition of excess collagen in the extracellular matrix).[7,8]

Acute myocardial infarction triggers an inflammatory response characterized especially by cellular necrosis, releasing intracellular components that activate the immune system and recruit cells to initiate a corrective response that induces the formation of scar tissue (fibrotic). Even after this stage, a state of chronic activation of cytokines and myocardial infiltration of inflammatory cells remains.[9-11]

Concomitantly with this entire process, there is also metabolic remodeling that also participates in aggravating the development and progression of post-infarction ventricular remodeling[12]. This is a complex process that ranges from a cascade of gene regulation altering the main energy supply pathway of the myocardium to carbohydrates (fetal pattern) to an imbalance in mitochondrial calcium, leading to suboptimal energy production.[13,14]

The aforementioned sustained hyperactivation of the renin-angiotensin system and the sympathetic system also participates in this process and, therefore, preventing its deleterious effects has been the basis of the current pharmacological treatment of HF.[15-17]

The big issue in this phenotype is that, unlike chronic HF, some of these pathophysiological changes occur extremely suddenly, mainly the decrease in contractile function and the increase in left heart filling pressures. These changes are not accompanied by vascular remodeling or changes in pre- and post-load as agile as they should be to minimize the clinical effects of this moment, leading to symptoms disproportionate to ventricular remodeling and, perhaps, to different therapeutic targets.[18]

Risk factors

The incidence of in-hospital HF is three times higher in patients aged 75 to 85 years when compared to those aged 25 to 54 years, as well as at discharge, where the incidence is six times higher in the older age group.[19] In some studies, female sex was independently associated with a higher risk of HF, ranging from 15% to 34%. This can be explained by several reasons, such as the presentation of AMI in women occurs in older patients, with more associated comorbidities, worse functional status, and admittedly less aggressive hospital care, including revascularization.[20]

The number of affected vessels and the location of the infarction also influence. The multivessel disease reflects a greater atherosclerotic burden, associated with greater endothelial dysfunction and more systemic inflammation, and is also commonly associated with other comorbidities. Anterior wall infarction is associated with a higher risk of adverse remodeling and IC.[21] Other factors that increase the risk of HF are high blood pressure, diabetes, atrial fibrillation, higher heart rate, chronic kidney disease, and the presence of previous angina.[20]

Biomarkers

Cardiac troponin is the marker of choice in AMI, and its values in the peak phase (48 to 72 h after the onset of symptoms) are associated with the extent of the infarction determined by cardiac resonance. Several studies have demonstrated the association of troponin with MACE, including IC;[22] however, its association with the troponin peak was not observed.[20]

Along with troponin, natriuretic peptides are associated with infarct size and cardiac dysfunction, not just its degree of elevation but also its standard of presentation. There is a monophasic pattern with a peak within 16 hours of admission and a biphasic pattern with a second peak at 5 days, and the latter pattern presented a greater risk of LV remodeling and IC20.[20,23] Furthermore, natriuretic peptides appear to have a protective effect in relation to the development of ventricular dysfunction, inhibiting angiotensin II and endothelin-1 signaling. Type A natriuretic peptide (ANP) inhibits collagen synthesis, a major source of myocardial fibrosis.[24] A study evaluating the infusion of recombinant human BNP before coronary angioplasty appeared to lead to some degree of myocardial protection, reinforcing this theory of BNP-mediated heart muscle protection.[25]

The prolongation of the post-infarction inflammatory response significantly contributes to LV remodeling and the development of HF.[26] Several methods for quantifying the inflammatory response show promise for predicting HF, such as levels of C-reactive protein, the neutrophil/lymphocyte ratio, interleukin 6, and interleukin 32, among others.[20]

The glomerular filtration rate (GFR) is also an independent factor associated with the risk of HF after AMI. Fox et al. demonstrated a risk of HF attributable to renal dysfunction ranging from 30% to 90%.[27] Similar results were observed in the VALIANT study, where the risk of HF increased by 10% for each 10 ml/min/1.72m^2 decrease in GFR.[28]

Some fibrosis biomarkers used as risk predictors in HF are recommended by the American College of Cardiology/American Heart Association, such as the soluble form of Tumorogenesis Suppressor (sST2) and Galectin-3. However, there is little evidence that evaluates them as predictive value after AMI.[29,30]

Other biomarkers, such as Matrix Metalloproteinases (MMPs), Clusterin, Lactic Dehydrogenase, and others, have shown an association with left ventricular remodeling, but there is still a lack of evidence in the post-MI context. Overall, studies have shown that combined biomarker analysis is superior to either of these individually. Much more important than choosing the best biomarker is the timing of measurement after AMI in predicting the risk of HF.[20]

Therapeutic options

Currently, the therapies we have available aim to improve mechanics and hemodynamics (cardiac output, pre- and post-load) and adjust the molecular mechanisms of remodeling. Even so, the primary and most important intervention to prevent or stop the development of ventricular dysfunction and myocardial remodeling in a patient suffering from an ischemic process is coronary reperfusion, when indicated.

As already mentioned, the change in contractility is the first change that leads to a progressive increase in volume and intracavitary pressure, intensifying parietal stress and workload to compensate for pre- and post-load, culminating in greater oxygen consumption and stimulation of the sympathetic nervous system and RAAS. This neurohormonal stimulus maintains cardiovascular balance in the initial phase, but over time, it becomes harmful, promoting cell death, fibrosis, and adverse remodeling. The degree of activation of these systems correlates with the severity of the dysfunction and is a predictor of poor prognosis. Preventing the harmful effects of SNS and RAAS is the basis of current pharmacological treatment.[31]

Tests on murine models carried out in the 1980s had already demonstrated the benefit of using captopril post-MI, with reduced filling and remodeling pressures.[32] The SAVE clinical trial reinforced its benefit in post-AMI, showing a reduction in mortality and incidence of cardiovascular events in patients with asymptomatic ventricular dysfunction (EF $<$ 40%).[33] Subsequently, the AIRE and TRACE studies confirmed the benefit of angiotensin-converting enzyme inhibitors (ACEIs) in this context. The AIRE showed a reduction

of approximately 27% in all-cause mortality and a 19% reduction in cardiovascular events with the use of Ramipril in patients with symptomatic ventricular dysfunction in the first 30 days after AMI, and the TRACE study showed a 25% reduction in mortality, as well as a reduction in sudden death and progression to severe HF with the use of Trandolapril starting 3 to 7 days after AMI. In the latest Brazilian HF guideline (2018), it is recommendation I, with a level of evidence A, the use of ACE inhibitors for patients with symptomatic LV dysfunction.[34-36]

Angiotensin II receptor blockers (ARBs) in post-MI HF were initially analyzed in 2002 in the study OPTIMAAL that compared losartan 50mg/day with captopril 50mg three times a day in more than 5000 patients with ventricular dysfunction (EF <40%) after AMI. This clinical trial showed no statistically significant difference in morbidity and mortality between the two medications over 2.7 years of follow-up.[37] Likewise, the VALIANT clinical trial demonstrated that the use of the ARB, Valsartan, in the first 10 days after AMI in patients who developed HF with reduced ejection fraction was as effective as captopril in reducing mortality. However, the combination of these two medications increased the prevalence of adverse effects without improving outcomes.[38] ARBs have, therefore, become an effective alternative when there is intolerance to ACE inhibitors.

Following the neurohormonal rationale of RAAS inhibition, one of the first studies that demonstrated clinical benefit from the use of mineralocorticoid antagonists in HF was RALES, showing a reduction in mortality, hospitalization, and symptoms related to HF with the use of spironolactone in patients with HFrEF. NYHA functional class III-IV, whose etiology was mostly ischemic (more than 50% of patients) but not necessarily post-AMI,[39] with EMPHASIS increasing the indication for functional class II HF.[40] However, it was the EPHESUS study that evaluated patients with HF after AMI and also found a benefit from the use of eplerenone in reducing total mortality, sudden death, and the combined outcome of cardiovascular mortality or hospitalization for HF. A post hoc analysis of this study showed that early initiation of eplerenone (between the third and seventh day of AMI) reduced the risk of death from all causes by 31%, the risk of cardiovascular death and hospitalization by 24%, and of sudden death by 34% when compared to placebo. On the other hand, starting this drug 7 days after AMI did not show a statistically significant difference between the groups, demonstrating the benefit of starting this medication early.[41]

In the same period, studies with beta-blockers in HF were developed, showing an important reduction in morbidity and mortality in patients with HFrEF regardless of the etiology. A meta-analysis published in 1999 with 31 randomized trials that included approximately 25,000 patients with a history of AMI showed that long-term use of beta-blockers reduced the risk of reinfarction and death during an average of 2 years of follow-up but highlighted that this drug class was still very underused at the time.[42] As the neurohormonal pathophysiological concept of HF gained strength, other studies began to be designed. At the end of the 90s, several studies with beta-blockers were published, such as US carvedilol, MERIT-HF, CIBIS II, and COPERNICUS, showing a reduction in mortality from all causes and a reduction in sudden death.[43-46] These randomized trials were truncated due to the significant benefits compared to placebo. The long-term efficacy of carvedilol in patients with ventricular dysfunction (EF ≤40%) after AMI was evaluated in the CAPRICORN study (2001), which showed a reduction in all-cause mortality as well as cardiovascular mortality, non-fatal AMI and cardiovascular mortality or non-fatal AMI compared to placebo, but without statistical difference in relation to the primary outcome of all-cause mortality or hospitalizations for cardiovascular causes.[47] The COMMIT-CCS2 study (2005), which randomized more than 45,000 patients with AMI in multiple centers in China to the use of Metoprolol (up to 15 mg, IV followed by 200 mg/day, PO) or placebo, showed no beneficial effect on the established primary outcomes of death, reinfarction or cardiac arrest and death from any cause, but reducing reinfarction and ventricular arrhythmias in isolation, a benefit that was counterbalanced by the increase in cardiogenic shocks in the metoprolol group, especially when used on the first day of admission. Around 20% of patients were in Killip II at the time of randomization, and 5% in Killip III. The latter were more likely to progress to cardiogenic shock, showing that the early use of high intravenous doses of Metoprolol appears to be harmful for patients who present with HF in the presence of acute coronary syndrome.[48]

Due to the considerable evidence of reduced morbidity and mortality and cardiac remodeling in post-MI with drugs that block the RAAS and after proving the efficacy of sacubitril-valsartan in comparison with enalapril in patients with HFrEF in the PARADIGM-HF study, subsequent studies sought to evaluate the potential of this new drug in patients with HFrEF after AMI.[49] The benefit of sacubitril/valsartan on cardiac remodeling was tested in patients with asymptomatic ventricular dysfunction (EF ≤ 40%) in the late phase after AMI (≥ 3 months), comparing it with valsartan alone, showing no statistically significant difference between the two groups in the primary outcome of reduction in LV stroke volume measured by MRI at the 52nd week.[50] The PARADISE-MI study, published in the same year, compared sacubitril/valsartan with Ramipril in patients with ventricular dysfunction and at risk of developing HF in the first 7 days after AMI and also showed no statistically significant difference between the two groups in relation to the primary outcome of cardiovascular death and worsening HF.[51]

After the success of ISGLT2 in reducing the cardiovascular outcomes of death and hospitalization due to HF, regardless of the presence of diabetes,[52,53] other studies were designed to investigate the potential of these medications in cardiac remodeling. A study with non-diabetic pigs after induced AMI demonstrated an improvement in cardiac remodeling after 2 months of using empagliflozin compared to placebo. This study also found that empagliflozin changed the energy consumption of the myocyte, replacing glucose with free fatty acids, ketone bodies, and branched-chain amino acids, thus improving the metabolic profile of the myocardium after AMI.[54] Two large studies aim to evaluate

this class of drugs post-MI. EMPACT-MI, not yet published, compares empagliflozin with placebo in patients with LVEF < 45% or congestive signs and symptoms in the first 14 days after AMI and will evaluate the composite outcome of all-cause mortality or time to first hospitalization for HF.[55] The recently published DAPA–MI compared dapagliflozin versus placebo in patients hospitalized for AMI and with some evidence of global or segmental left ventricular dysfunction, or if assessment of left ventricular function was not available, with the presence of pathological Q in the electrocardiogram. The study did not demonstrate the benefit of this drug in relation to the primary outcome of death, hospitalization for HF, non-fatal AMI, atrial fibrillation or flutter event, new diagnosis of type 2 diabetes, improvement in NYHA functional class and weight loss, despite was a safe strategy with good cardiometabolic effects.[56]

Since ischemia is the predominant etiology in the genesis of HF, multiple other therapies have been evaluated. Trimetazidine, for example, alters the energy metabolism of myocytes, providing a cytoprotective action, but it is still unclear whether this provides benefit against cardiac remodeling after AMI.[57] Statins showed improvements in cardiac remodeling when compared to placebo in a study with rats with extensive induced AMI. This benefit was associated with a reduction in the expression of fetal genes in the myocardium as well as collagen and an increase in endothelial NO.[58] The CORONA and GISSI-HF studies were carried out to evaluate the efficacy and safety of rosuvastatin in patients with HFrEF over 60 and 18 years of age, respectively. In both studies, rosuvastatin did not show a reduction in primary outcomes but was shown to be safe in this group of patients.[59,60] Since Ivabradine reduces HR by inhibiting the *If* currents of the sinoatrial node, reducing cellular energy expenditure, it was tested in comparison with a placebo in patients with chronic CAD and ventricular dysfunction (EF <40%) in the study BEAUTIFUL, published in 2008. In this study, Ivabradine did not show superiority over placebo in the combined primary outcome of cardiovascular death or hospitalization for AMI or HF but reduced secondary outcomes of hospitalization for fatal and non-fatal AMI and coronary revascularization in patients with FC above 70.[61]

Invasive treatment

Several surgical procedures, such as implantable cardioverter defibrillator (ICD) implantation, cardiac resynchronization therapy, and revascularization, have demonstrated significant benefits in reducing mortality and hospitalizations in patients optimized in relation to drug therapy for HF of ischemic etiology.[62]

Old studies, such as CASS in the 1980s and more recent studies, such as STICH and STICHES, have shown positive results when revascularizing patients with ischemic heart failure and left ventricular ejection fraction (LVEF) less than 35%. These studies demonstrated a 28% reduction in all-cause mortality or hospitalization due to HF over a 10-year follow-up period. Currently, the main guidelines around the world recommend myocardial revascularization in patients with multiple arterial lesions, significant obstruction of the left anterior descending artery, and LVEF below 35%.[63,64]

It is important to highlight that the use of devices such as the ICD for secondary prevention of sudden death is already well founded, with a class I recommendation for patients who have had aborted sudden death, ventricular tachycardia with hemodynamic instability, or ventricular fibrillation documented in electrophysiological studies. The SCD-HEFT and MADIT II studies demonstrated significant benefits when implanting ICDs in patients with HF of ischemic etiology after myocardial infarction, with the latter showing a reduction in the absolute risk of death by 6%.[62,64,65]

The recommendation for cardiac resynchronization therapy in patients with post-infarction HF follows the same guidelines as for patients with HF of non-ischemic etiology. Although large studies, such as MADIT-CRT, were not specifically designed for post-infarction patients, ischemic etiology was one of the most common causes, and these studies also showed benefits in reducing mortality and hospitalizations due to HF.[65]

In the context of acute post-AMI HF, mechanical complications also occur, such as rupture of the free wall, rupture of the interventricular septum, and acute mitral insufficiency. The incidence of these complications has decreased with the advent of myocardial reperfusion and easier access to early revascularization, but they remain serious complications with very high mortality.[66]

The rupture of the left ventricular free wall may occur in less than 1% of patients during the first week after a transmural infarction, manifesting with sudden pain and/or cardiogenic shock. Factors such as advanced age, lack of reperfusion, or delayed fibrinolysis appear to be associated with an increased incidence of cardiac rupture. Progression to hemopericardium and cardiac tamponade, leading to a shock, is usually fatal. Mortality rates range from 20% to 75%, depending on the patient's condition and the size and morphology of the rupture. Indeterminedpatients, cardiac magnetic resonance (CMR) can complement the diagnosis, identifying the contained cardiac rupture and its anatomical characteristics to guide surgical intervention.[66,67]

Post-MI interventricular communication typically presents as rapid clinical deterioration with acute heart failure or cardiogenic shock. It can occur within 24 hours to several days after AMI, with equal frequency in anterior and posterolateral wall AMIs. The diagnosis is confirmed by echocardiography and Doppler, which differentiate this condition from acute mitral regurgitation, define the rupture and its size, and quantify the shunt. The use of a Swan-Ganz catheter can more accurately confirm the shunt. In some selected cases, the intra-aortic balloon pump (IABP) can stabilize patients in preparation for angiography and surgery. Early surgery is associated with a high mortality rate, reported at 20-40%, and a high risk of recurrence of ventricular rupture, while late surgery allows for easier repair of the septum into scar tissue but increases the risk of extension of rupture and death while awaiting surgery. For this reason, early surgery should be performed in all patients with severe heart failure who do not respond quickly to

therapy, but late elective surgical repair may be considered in patients who respond well to heart failure treatment.[65]

Acute mitral regurgitation typically occurs 2 to 7 days after AMI due to rupture of the papillary muscle or chordae tendineae. Rupture may be complete or involve one or more of the heads of the papillary muscle, being up to 6 to 12 times more common in the posteromedial papillary muscle due to its unique blood supply from the right coronary artery. Papillary muscle rupture usually manifests as rapid hemodynamic deterioration with acute dyspnea, acute pulmonary edema, and/or cardiogenic shock. In this context, immediate treatment is based on reducing afterload to reduce the volume of regurgitation and pulmonary congestion. The use of intravenous diuretics, vasodilators/inotropes, and IABP can stabilize patients in preparation for angiography and surgery. Emergency surgery is the treatment of choice, although it carries a high operative mortality (20-25%). Mitral valve replacement is often necessary, but cases of successful papillary muscle suture repair have been increasingly reported and appear to be a better option in experienced hands (Figure 1).[68]

Prognosis

The correct identification and treatment of HF in post-AMI patients is crucial to guarantee survival and quality of life for patients, given the size of the impact that heart failure can have on individuals. In the SOLVD treatment study, patients with LVEF ≤ 35% and a previous infarction had two times more hospitalizations for decompensated HF and four times more mortality compared to those without previous AMI.[69] The SAVE trial found in patients with ventricular dysfunction a 70% increase in the risk of cardiovascular death and increased LV as a result of a previous heart attack compared to patients without a previous heart attack.[70,71] Data from the Canadian registry[72] and the GRACE4 registry showed that the presence of HF on admission increased the chances of hospital mortality between 1.87 and 2.2 times, while a French registry showed that these patients, in relation to those who do not develop HF in this scenario has a significantly increased risk of death during hospitalization (12.2% x 3%) and at one-year follow-up (26.6% 5.2%).[73] For patients affected by an acute ischemic event, one way to achieve prognosis is by applying the Killip classification. In the GRACE risk score, this classification was the most important predictor of mortality when compared to the absence of HF during the presentation of AMI.[74]

A large population-based cohort in Minnesota analyzed 2,596 patients over a mean follow-up of 7.6 years after a first episode of AMI and found that in this setting, HF strongly increases the risk of death from all causes, cardiovascular death and non-cardiovascular death. as well as showing that patients with HFrEF and HFpEF share a similar prognosis, while HF that develops > 3 days after AMI confers a worse prognosis than HF occurring concomitantly with the ischemic event or in the first 72 hours. One explanation for this last finding is that early post-MI HF reflects extensive myocardial damage and is thus related to the characteristics of the infarction (location, size, and reperfusion time), whereas "late-onset" HF has been associated with other mechanisms, such as progressive remodeling, recurrent myocardial infarction, and even subclinical ischemia. Despite this, the definition of whether the event is early or late (>3 days) was absolutely arbitrary.[75]

Another American cohort that simultaneously analyzed patients hospitalized with AMI without concomitant or previous HF showed that almost 1 in 5 patients hospitalized with acute myocardial infarction and without a history of HF develop a subsequent diagnosis of HF within 5 years (18.8%) and Appropriate medical therapy with aspirin, P2Y12 inhibitor and statin at hospital discharge from infarction was associated with reduced incidence of future HF.[76]

Conclusion

Post-MI HF has significant nuances within the spectrum of acute HF presentations, appearing to be an intermediate phenotype between acute HF and chronic HF. In this scenario, there are well-established risk factors that should draw the clinician's attention regarding the chance of its development, which should motivate an active search for its diagnosis in order to initiate appropriate treatment at the correct time. The pathophysiological understanding of this entire process, but mainly the acute installation of the entire cascade of mechanisms that attack the myocardium, explains the peculiarities of this presentation of HF. Drugs such as ACE inhibitors, beta-blockers, and mineralocorticoid antagonists have a well-established role in the therapy of these patients and should be started at the right time and never neglected. Post-AMI mechanical complications also need to be observed due to their high short-term lethality. More studies need to be carried out targeting this entity in order to minimize its negative prognostic impact.

Author Contributions

Conception and design of the research: Campos CCM, Montenegro CEL; Acquisition of data, Analysis and interpretation of the data and Writing of the manuscript: Campos CCM, Rezende CCG, Silva BMS, Fraga FJO, Suassuna DC, Montenegro CEL; Critical revision of the manuscript for important intellectual content: Campos CCM.

Potential conflict of interest

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This article does not contain any studies with human participants or animals performed by any of the authors.

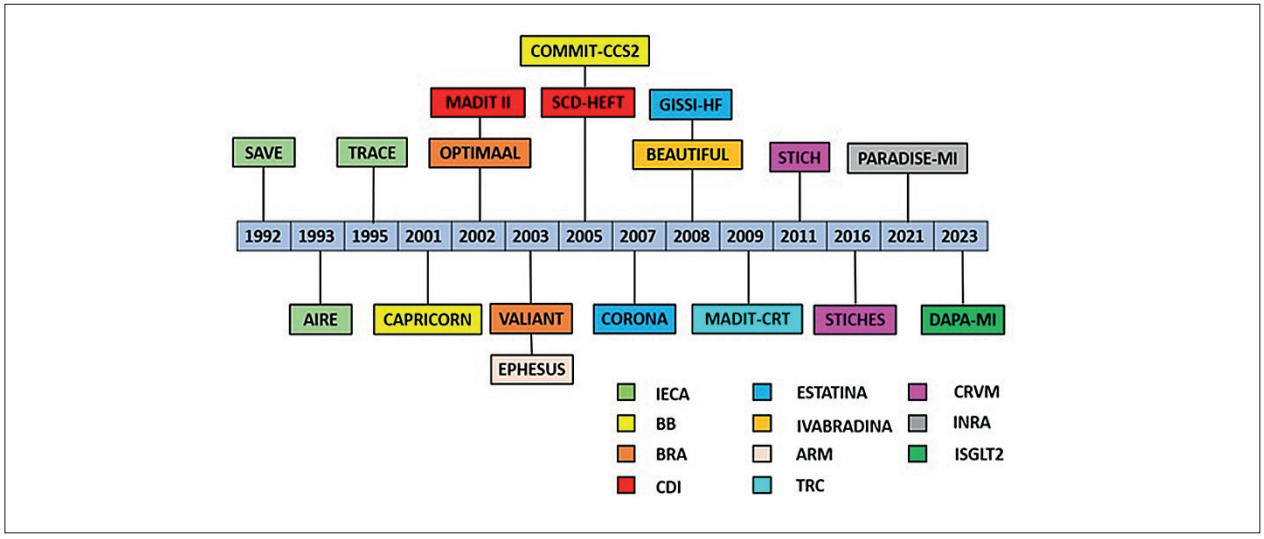

Figure 1 – *Timeline of post-MI HF trials.*

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