Effects of medicines on cardiac remodeling

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ABBREVIATIONS

CR- CARDIAC REMODELING

MI –Myocardial Infarction

IHD – Ischemic heart disease

LV – Left ventricle

ECM – Extracellular matrix

RAAS – Renin angiotensin aldosterone system

ACEI – Angiotensin converting enzyme inhibitors

ARB – Angiotensin receptor bloclers

HF – Heart failure

SGLT2-I - sodium glucose linked co-transporter type 2 inhibitors

GLP – Glucagon like peptide

CMR – cardiac magnetic resonance

GLP - Glucagon like peptides

LVESV – left ventricular end systolic volume

ANP – Atrial natriuretic peptide

LVEF – Left ventricular ejection fraction

AT1 – Angiotensin 1

Beta adrenergic regulation – beta-AR

Camkii – calcium calmodulin dependant protein kinase 2

ROS – reactive oxygen species

EDV – end diastolic volume

ESV – end systolic volume

EF – ejection fraction

SHF – systolic heart failure

ARNI - Angiotensin receptor neprilysin inhibitor

DM – Diabetes mellitus

IGF1 – Insulin growth factor 1

Summary **Title: Effects of medicines on cardiac remodeling**

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Cardiac remodeling, currently 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. This results in poor prognosis because of its correlation with ventricular dysfunction and malignant arrhythmias. In spite of worldwide progression made in investigatory properties and treatment of cardiac remodeling, no advancement has been seen in clinical settings for different treatment strategies apart from targeting the RAAS. The importance of investigating further options for the pharmacological treatment against CR lies behind the fact that while angiotensin converting enzyme inhibitor, angiotensin receptor blockers and beta-blockers are the mainstay of pharmacologic therapy directed at limiting adverse remodeling, the benefits are most often seen in patients with large infarcts and individuals who are not candidates for reperfusion therapies, nor in patients with different pathological processes such as diabetic cardiomyopathy. Moreover, their use is associated with no more than a 20–25% reduction in major adverse cardiac events. Apart from LCZ696 there have been no new treatments introduced clinically for the past three decades that specifically target adverse LV remodeling. Active research has been done to investigate promising and potential drugs to induce a better result with less side effects and maximal positive outcomes. Apart from LCZ696, anti-diabetics such as anti-glucagon peptides or SGLT2 inhibitors, and even an extremely promising and potential natural herbal drug called Qiliqiangxin, currently used for the treatment of heart failure in several patients across China. Current investigations on new efficient therapy agents are hampered by the broad spectrum of changes in cardiac remodeling, given the fact that when speaking of said topic, hypertrophy, fibrosis and cardiomyocyte apoptosis are some of the cellular changes that occur. Furthermore, the heterogeneity between the patients as well as the many different pathological processes that give rise to cardiac remodeling limits the applicability of some promising and potential therapeutic drugs on improving cardiac function. Studies conducted on potential therapeutic drugs are currently focused on animal models with the aspiration of progressing into human clinical trials. Therefore,

the focus should be on aiming to advance into clinical trials while stratifying the current data available to us.

Keywords: Cardiac remodeling; Heart failure; Therapy; Effects of drugs

***Naslov*:** **Ućinci lijekova na srčano remodeliranje**

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Srčano remodeliranje je definirano kao skupina molekularnih, staničnih i intersticijskih promjena, koje se manifestiraju klinički kao promjene u veličini, težini, geometriji i funkciji srca nakon ozljede. Završava nepovoljnom prognozom zbog povezanosti s ventrikularnom disfunkcijom i malignom aritmijom. Unatoč napretku u istraživanju svojstava i načina liječenja srčanog remodeliranja u cijelom svijetu, nema napredovanja u kliničkom okruženju za različite strategije liječenja, osim ciljanja na RAAS. Važnost daljnjeg istraživanja opcija za farmakološko liječenje srčanog remodeliranja, leži u činjenici da, dok su ACEI, ARB i BB glavni oslonac farmakološke terapije usmjerene na ograničavanje nepovoljnog remodeliranja, najveća korist je viđena u pacijentima s velikim infarktima, pacijentima koji nisu kandidati za reperfuzijsku terapiju, a ne u pacijenata s različitim patološkim procesima, kao dijabetička kardiomiopatija. Štoviše, njihova upotreba je povezana s ne više od 20-25% smanjenja u većim nepoželjnim srčanim događajima. Osim LCZ696, nije bilo novih kliničkih načina liječenja unazad 30 godina koji bi specifično ciljali lijevo ventrikularno remodeliranje. Vrše se aktivna istraživanja nad obećavajućim potencijalnim lijekovima koji bi dali bolje rezultate, s manjim posljedicama i maksimalnim pozitivnim učinkom. Osim LCZ696, antidijabetički lijekovi kao anti glukagonski peptidi ili SGLT2 inhibitori, čak i vrlo obećavajući prirodni biljni lijek Qiliqiangxin, koji se trenutno koristi za liječenje srčanih zatajenja u Kini. Trenutna istraživanja na novim efikasnim terapijskim agentima su otežana širokim spektrom promjena u srčanom remodeliranju na staničnoj razini, kao što su hipertrofija, fibroza i kardiomiocitna apiptoza. Nadalje, heterogenost pacijenata i raznih patoloških procesa koji povećavaju srčano remodeliranje, ograničava primjenjivost nekih

obećavajućih potencijalnih lijekova koji bi poboljšali funkciju srca. Studije napravljene and tim lijekovima su trenutno u fazi ispitivanja and životinjama, s nadom prelaska na klinička ispitivanja na ljudima. Trenutni focus bi trebao biti na cilju prelaska na klinička ispitivanja i raslojavanju trenutnih podataka.

Ključne riječi: **srčano remodelikanje, terapija, Učinci lijekova**

Abstract:

Cardiovascular diseases have been for many years considered the most common cause of death in many different populations worldwide. Some of these pathologies include ischemic heart disease, which according to the WHO is responsible for 16% of the world's total deaths. In recent times, immense improvement has been made in the remedy of heart pathologies, although pathological ventricular remodeling oftentimes cause survivors to deteriorate from fatal heart failure. This review explores the distinct and peculiar options available or in research in order to either prevent or treat a potential CR before it achieves irreversibility and results in a poor prognosis.

Introduction:

Ischemic heart disease as well as diabetic cardiomyopathy are some of the leading causes of heart failure related death worldwide, corresponding post-MI being a critical element of cardiovascular related diseases [1-3]. It is the single largest cause of death in countries for all income groups, meaning that it affects the population as a whole, moreover, the total global cost of cardiovascular diseases is thought to stand at approximately US$863 billion in 2010 [4]. Global epidemiological studies show that more than 70% of at-risk individuals have multiple risk factors for IHD, and only 2%-7% of the general population have no risk factors [2]. Even though medical and technological advances have been made to improve prognosis and quality of life in such patients, some may suffer from a CR, which can significantly impair the patient's cardiac muscle, hence cardiac function, which can ultimately result in death. Hockman and Buckey first introduced the term "remodeling" in 1982 in a myocardial infarction model. This term was intended to indicate the replacement of infarcted tissue with scar tissue [5]. CR is known to occur due to adaptive responses which initiate a group of molecular, cellular and interstitial changes that display clinically due to changes in morphology and function of the heart, which result in a bad prognosis because of its association with ventricular dysfunction and malignant arrhythmias. The significance of this is immense and in urgent need of further investigation in order to accurately treat and prevent the surging possibility of CR, and by that, possibly exponentially decreasing the mortality rate in the cardiovascular settings. According to the SAVE trial which was a prospective large cohort study observing patients post-MI with impaired LV function demonstrating that >50% sustain cardiovascular death and may develop LV dilatation during the initial 3.5-year follow-up period [6]. There are different pharmacological options available to this day or under investigation which is why the pharmacological treatment of CR can be divided into three strategies: stabilizers, promising and potential agents. Despite the relentlessness of heart diseases and their prognosis, there is promise, showing substantial progress in the investigation of CR, its cause and possible manageable options. The purpose of this review is to provide an observation into the different options of present and future medications effects on ventricular remodeling, and possibly display a lack of advancement into what can be considered a major culprit of death worldwide.

Pathophysiology:

In order to accurately investigate and manage CR, we need to fully understand its pathophysiological factors as well as the pathophysiological mechanism of cardiac dysfunction due to this remodeling. This is crucial so that one may understand, study and target those specific adaptive changes. CR has many different factors which directly influence to the pathological progression. Currently we can see from different studies that post myocardial infarction may be followed by pathological remodeling, which can be subdivided into: 1) Early remodeling (<72 hours) and 2) Late remodeling (up to 12 weeks) [7]. This is important considering the fact that at different times in the phases there are as well different pathological changes in CR. The early remodeling includes ischemia, cell death, and inflammation within hours to days after the acute myocardial insult. While late remodeling is characterized by ECM deposition which causes a reactive cardiac hypertrophy, cardiac fibrosis, and ventricular dilatation. All these changes together cause a transformation in the ventricular morphology, structure and function of the heart [8]. The pathophysiological cause of ventricular dysfunction in CR can be further investigated, showing a clear association between many elements, however the seemingly most important determinant of the following changes is the neuro-hormonal activation, provoking an increase in RAAS together with a shift of sympathetic activation. This neuro-hormonal activation induces the different factors that together lead to the ventricular dysfunction as previously mentioned. These factors include structural, genetic, biochemical, molecular and cellular changes, escalating to an increase in cell death, oxidative stress, inflammation, metalloproteinase and fibroblast proliferation and eccentric hypertrophy [1-2], [9]. The reason why the activation of RAAS is immensely important is due to the fact that it can be investigated and addressed to prevent all the previously mentioned factors, hence preventing the pathological remodeling associated with a poor prognosis.

Pharmacological approaches:

CR assists in the development and evolution of ventricular dysfunction, arrhythmias and overall poor prognosis, leading to increase mortality and morbidity in HF patients. Therefore, the basic pathophysiological processes can be therapeutically targeted in order to improve prognosis as well as possible complication arising from an acute insult to the myocardium. Pharmacological treatment can be subdivided either into tried and tested or under investigation and emerging. Another approach includes dividing the pharmacological treatment into three strategy stages: Disclosed, Promising and Potential. Within the Disclosed group we are able to place RAAS inhibitors (ACEI, ARB and direct renin inhibitors) as well as beta blockers, showing positive results from different studies, especially when used in combination therapy [10]. Within the promising strategy the main drug seen with promising results is known as LCZ696, comprising a combination therapy of an ARB with a Neprilysin inhibitor. In addition to this drug there are positive results observed with aldosterone antagonists such as Spironolactone and Eplerenone [11-22]. The last group includes the potential strategy to which most drugs are still under investigation and emerging, including anti diabetic drugs including Biguanides as well as SGLT2 inhibitors, GLPs, Quiliqiangxin and specific proteins seen to attenuate CR [23-25]. Both subdivisions can be united in order to look for specific advantages and disadvantages. Many distinctive drugs affecting particular aspects can be seen that may relieve, prevent and help against CR and the poor prognosis that follows. An important factor to look upon in the pharmacological treatment includes the evidence suggesting that dosages play a considerably importance which can be seen in some studies suggesting that in the treatment for HF, reversed cardiac remodeling is often not recognized due to low dosages [10], [26-27]. It is important and necessary to establish that due to largely irreversible histological changes in the myocardium that occur in remodeling, its “reversal” is not an inverse process; despite the improvement in cardiac chamber size and LV function that may occur in the context of reverse remodeling, most of the histological damage is sustained.

Pharmacological Predictors:

Associations of cardiac remodeling and risk for poor prognosis extend beyond those patients with MI, as noted [1-3], [5], [28-29]. Undeniably, across numerous HF as well as CR drug trials, a close relationship between changes in LV parameters and mortality has been established, thus providing the importance of applying the imaging techniques and potential biomarkers as predictors of efficacy and efficiency of such pharmacological approaches in CR. Cardiac imaging is the gold standard for assessing CR, specifically serial echocardiograms which are most commonly used in clinical practice and have been evaluated more often in clinical studies. A reduction of LVESV is the most commonly used measurement of remodeling because it incorporates both geometric and functional data. Strain imaging is a method in echocardiography for measuring regional or global deformation of the myocardium, thus it is another imaging technique which can be used to evaluate systolic deformation of the LV and smaller abnormalities in systolic deformation, hence predicting greater predilection for remodeling [30]. The last imaging technique worth mentioning for evaluating the response of certain drugs on CR include a CMR, which compared to echocardiography it presents not only better contrast resolution but also a higher reproducibility, thus providing beneficial information regarding the presence and extent of myocardial fibrosis [18], [29-31]. Apart from imaging techniques, several biomarkers may play an important role for efficacious evaluation of certain drugs on CR. As it is known, concentrations of ANP are influenced by wall stress, which in turn is affected by LV chamber size, volumes, and LVEF. Thus, a correlation between serially measured natriuretic peptide concentrations and LV remodeling grants the option to be used in several clinical studies [32-36]. In addition to ANP, Troponin assay is a high sensitivity biomarker which grants the option to quantify the severity of cardiomyocyte cellular apoptosis. Soluble suppression of tumorigenesis-2 (SST2) is a promising biomarker of cardiac remodeling as seen that SST2 is released by cardiomyocytes as well as fibroblasts under stress and debilitate the anti-fibrotic effects of IL-33, thus its association to CR [37]. Other biomarkers for the pharmacological evaluation concerning to CR for further investigation include bone morphogenetic protein (BMP)-1 activity, carboxyterminal propeptide of type-I procollagen (PICP), tissue inhibitor of metalloproteinases (TIMP)-1, and matrix metallopeptidase (MMP)-9, micro-

RNA profiles and Galectin-3 (Gal-3) which have been demonstrated to participate in the development of cardiac fibrosis and remodeling post-MI as well as in patients with established HF [38-43].

Introduction to RAAS Inhibitors:

RAAS inhibitors are a group of drugs that act by inhibiting the renin-angiotensin-aldosterone system. This group include ACE-I (Ramipril, Captopril), ARB (Valsartan, Losartan) and direct renin inhibitors (Aliskiren, Eplerenone, and Spironolactone). Activation of RAAS is a progressive component in the process and development of left ventricular remodeling. Under pathological conditions, RAAS is activated by several factors – prominently, inflammation and endothelial dysfunction. This stimulation together with the overabundance of aldosterone, is responsible for extracellular matrix proliferation and contributes to the increased deposition of fibrous tissue within the ventricular myocardium. The presence of myocardial fibrosis and endothelial dysfunction may alter the coronary microcirculation. This may cause a decrease in myocardial capillary density which can assist in the progression of left ventricular remodeling towards heart failure [44-45]. RAAS inhibitors are beneficial against CR due to their ability to inhibit cardiac hypertrophy and reduce the proliferation of extracellular and interstitial fibrosis. Different antagonistic RAAS approaches act at different points within the system, with the direct renin inhibitor, Aliskiren, acting early in the RAAS pathway to block the hydrolysis of angiotensinogen to Angiotensin I by the enzyme renin [14-17]. Downward in the cascade ACE-Is prevent the hydrolysis of Angiotensin I to the key effector of the pathway, Angiotensin II. The effector actions of Angiotensin II are inhibited by ARBs, which block the binding of Angiotensin II to AT1 receptors.

- **ACE Inhibitors:**

ACE-I were the first drugs to be used in order to block the RAAS system. It has been shown by many different studies, such as Pfeiffer et al. The Survival and Ventricular Enlargement trial study, which exhibited an attenuation of ventricular enlargement in patients with an ejection fraction lower than 40% in those that were treated with Captopril [6], [45]. Pouleur et al. examined in the Studies Of Left Ventricular Dysfunction Treatment and Prevention (SOLVD) trial [46], patients with acute MI, ejection fraction <35%, with or without signs and symptoms of HF, who were allocated randomly to groups receiving either enalapril or placebo within the 24– 36 hours from their arrival to the hospital. The study showed an improved survival in patients receiving the ACEI. An echocardiographic sub-study of the SOLVD trial demonstrated a reinforcement to the latter results in left ventricular end-diastolic volume in the enalapril group with respect to those receiving placebo [47]. Doughty et al. demonstrated in the carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction Study (CAPRICON), that despite the continuous administration of ACEI therapy in patients with recurrent MI, the LVEDV continued to increase over a period of 6 months [48]. These results may suggest that the beneficial effects of ACEI may lessen during prolonged treatment (>6 months). Furthermore, there is evidence of a steady increase in plasma norepinephrine despite continued ACEI which directly supports the need for adjunctive dual therapy by an anti-adrenergic in order to prevent the long-term sequelae of progressive sympathetic system activation on the heart [49]. ACEI not only decrease formation of Angiotensin II, but also has been shown in different studies on animal models to cause a reduction in the degradation of the vasodilator effect of bradykinin, thereby assisting in an increase of bradykinin, with studies indicating that bradykinin directly inhibits the advancement of cardiac hypertrophy as well as cardiac fibrosis due to the direct increase in nitrous oxide release via the BK B2 receptor. The latter may be significant, indicating the importance of the Bradykinin – NO pathway playing an important role in the progression of cardiac remodeling [50-52]. ACE-I may show a double effect on the prevention of pathological cardiac remodeling by its direct effect on decreasing Angiotensin II while at the same time increasing the Bradykinin levels, therefore preventing the development of the late remodeling changes as mentioned

before, characterized by extracellular matrix deposition and its progression into cardiac fibrosis, reactive cardiac hypertrophy and ventricular dilatation [50-52]. Despite all positive data concerning ACEI in regards to CR, there have been no recent clinical trials to investigate present effects of newer drugs of this group. This can give us reason to believe there might be a different aspect and potential effect of newer ACEI to implement into the already existing regimen and possibly have the ability to avoid any dual therapy that is established to be required presently.

- **Angiotensin Receptor Blockers:**

ARBs are selective inhibitors of the AT1 receptors, to which they provide competitive antagonism of the angiotensin II receptors, for it has been speculated to reduce adverse effects and possibly improve clinical efficacy. ARBs displace angiotensin II from the angiotensin I receptor and produce their blood pressure lowering effects by antagonizing angiotensin II–induced vasoconstriction, aldosterone, catecholamine and arginine vasopressin release, water intake, and hypertrophic response [53-54].The selective blockade of angiotensin II receptor type 1 has been shown to be an alternative means by which to inhibit the RAAS and by that being beneficial in its association with favorable effects on left ventricular morphology and function. As previously mentioned, cardiac remodeling has many pathophysiological origins, in this case RAAS mediated effects on AT1 receptors include hypertrophy, fibrosis and vasoconstriction, and by that a direct link into the development of pathological CR. Considering that there are alternate pathways for the production of angiotensin II apart from its conversion by ACE that are unaffected by ACE inhibition, selective blockade of the AT1 receptor by ARB would naturally seem to add the most adequate means of opposing the deleterious effects of angiotensin II development of hypertrophy and fibrosis, thus potentially preventing pathological cardiac remodeling [55]. Several studies have shown the direct effects of ARBs in significantly improving cardiac morphology and function, although they have also shown that the leading effect can be accomplished by a combination therapy. Several studies have shown a direct correlation between the use of ARBs and a decreased mortality such as the CHARM and OPTIMAAL studies [56-58].The long-term effects of ARB on LV morphology were evaluated by Wong et al. in the Valsartan Heart Failure Trial echocardiographic study, which examined patients being treated by Valsartan. This study showed a statistically significant improvement in the LVEF when used in combination therapy with ACEI or Beta-blockers. This study however showed as well no improvement in the absence of dual therapy [59].

- **Direct Renin Inhibitors:**

As previously mentioned, in post-MI patients there is a reduced left ventricular systolic function which is correlated with an increased risk of LV remodeling, heart failure and mortality. Despite the efficiency of ACE-I as well as ARB, especially when used in dual combination therapy, direct renin inhibitors were tested in order to investigate whether the efficacy can be improved when adding Aliskiren to the standard medical regimen. This was a valid hypothesis, suggesting that since Aliskiren impedes the renin–angiotensin–aldosterone system proximally at the rate-limiting step, the compensatory mechanism which causes a rise in plasma renin activity and other downstream components of this system that occurs in the settings of ACE-I or ARB therapy, could be prevented. Additionally it has been suggested that plasma renin activity has a direct negative effect by itself [15-17]. This hypothesis however has been revoked by Solomon et al. in the Aliskiren Study in Post-MI Patients to Reduce Remodeling (ASPIRE) study in 2010, conducted in 154 centers from 23 countries involving a total of 672 stable patients at high risk of LV remodeling after AMI in addition to them matching all other inclusion/exclusion criteria. Out of the 672 patients, 329 patients were assigned to the placebo group and 343 patients in the Aliskiren group with evaluable echocardiograms available at a baseline and at end of the study in order to directly investigate the impact on cardiac morphology. This study lasted 36 weeks, with subjects beginning at a dose of 75 mg and titrated up to 300 mg once daily. It was concluded that there were no beneficial effects in improving cardiac remodeling in post-MI patients when combining Aliskiren to the standard medical regimen, including ACE-I, ARB, Beta-Blockers nor with Aldosterone antagonists [60]. The results of the studies are not fully understood since different studies showed the safety and efficacy of its combination [17], [61-62]. A possible explanation to this is believed to be that specifically in the post-MI setting, a single inhibitor of the renin–angiotensin system is sufficient to reduce late remodeling in otherwise well-treated patients [60]. The results of the ASPIRE study can be reinforced by Yang et al. with the Effects of Direct Renin Inhibitors on Left Ventricular Remodeling with AMI study (EDRI-LVR), conducted in 2014 involving a total of 42 patients post inclusion/exclusion, out of which the first group consisted of 21 patients being treated with ACE-I or ARBs, and the second group being treated with 150mg Aliskiren daily

combined to ACE-I or ARB therapy for a period of 10 months. The results showed no statistically significant improvement in left ventricular remodeling between both groups [63].

Beta–Blockers:

As previously discussed, it has been established that hemodynamic load and neuro-hormonal activation are major agents influencing the development of CR, showing a direct correlation between beta-AR and the RAAS regulation [6-7], [64-65]. Although CR is not fully understood, cardiomyocyte stretching is an established and important factor which induce an increase in norepinephrine activity leading to the activation of beta-AR. Beta blockers directly targets the beta-adrenergic receptor and has displayed favorable effects on CR by several mechanisms [66-67]. These mechanisms are worth specifying and will be discussed in detail with the specific drugs affecting them. Understanding these factors are paramount in order to fully understand the benefits of particular beta blockers, as well as to propose further investigation in order to evaluate and implement new drugs to target these mechanisms. Various clinical trials have demonstrated that specific beta-blockers accomplish positive effects on lowering the ESV/EDV or by improving the ejection fraction, which can be used as measurements to asses CR. Lechat et al. proposed in the Cardiac insufficiency Bisprolol study (CIBIS) conducted in 1997, that the preservation of left ventricular function was shown to be caused by improving fractional shortening as well as the reduction of end diastolic pressure and diameter, and by that having a direct improvement in cardiac morphology and function [68]. The latter however was shown to be true only in short term use of Bisprolol, nonetheless. A study conducted in 2000 in order to investigate the long term effect of Bisprolol concluded that it has no outcome on preventing left ventricular remodeling [69]. Multiple beta blockers, such as carvedilol, metoprolol, atenolol and propranolol, have been shown to prevent the development of CR by regulating Calcium handling proteins and channels. The importance of this lies in the fact that Calcium is a signaling molecule required for triggering hypertrophic responses, Furthermore, CaMKII is seen to induce apoptosis as mentioned in previous sections and directly contributes to

CR [70-71]. Carvedilol appears to be one of the most effective beta-blockers on reducing and even reversing CR. This is seen by many clinical trials showing an improvement in EDV, ESV and EF as well as in improvement in LV mass and geometry [72-74]. Metoprolol has been shown to selectively decrease myocardial expression of Bcl-xs, reducing the Bcl-xs/xl and Bcl-xs/Bcl-2 ratio, thus preventing apoptosis and favoring cell survival [75]. Another mechanism highly involved in the propagation of CR is oxidative stress which in turn causes the production of ROS, activating cardiac MAPK cascades and has been shown to be closely related to CR by causing hypertrophy. This can be potentially prevented by Nebivolol, as seen in animal models, with evidence demonstrating a reduction in the oxidative stress by reducing NADPH oxidase activity as well as promoting both NO bioavailability and synthesis [76]. Propranolol has been shown to prevent the propagation and up regulation of MMPs which are a major factor in the development of oxidative stress, thus CR [77].

LCZ696 (Angiotensin receptor – Neprilysing Inhibitor):

As mentioned previously in pharmacological approaches, this drug combination can be considered a promising agent in the treatment for CR. Sacubitril/valsartan (formerly known as LCZ696) is a first-in-class angiotensin receptor neprilysin inhibitor that synchronously represses RAAS activation through blockade of angiotensin II type 1 receptors and augments vasoactive peptides including natriuretic peptides through inhibition of neprilysin, the enzyme responsible for the degradation of vasoactive peptides, including natriuretic peptides and bradykinins [32-34]. LCZ696 intensifies the levels of these peptides, causing blood vessel dilation and reduction of extracellular fluid volume via sodium excretion. LCZ696 is considered to be one of the most important clinical break troughs in the field of cardiology over the past 10 years. Different studies have been made in order to investigate the efficacy and safety of ARNI in patients suffering from HF. One of these studies includes the PARADIGM-HF study by McMurray et al, a phase III clinical trial conducted in 2014. This was a randomized, double-blind study designated to test and compare the dominance of ARNI over enalapril (ACEI) in patients with chronic heart failure with reduced EF in order to potentially reduce mortality and morbidity among these patients that has been linked to be directly correlated to CR [32], [78-82]. PARADIGM-HF study included 985 sites across 47

countries. Patients had mean age of 64 years with the majority being males and had either NYHA class II or class III symptoms of HF. In total, 8442 patients after inclusion/exclusion criteria, administering doses ranging between 97/103 mg of ARNI in one group, and 10 mg of enalapril to the second group at different intervals [78-82]. LCZ696 demonstrated superior benefits over enalapril by reducing the risk of both CV death and hospitalization by 20% by distinctly improving LV size and hypertrophy compared with ACEI/ARB in HF with reduced EF patients. Patients appeared to benefit more in terms of CR treated with ARNI as early as possible and for at least 3 months [78-81]. These results are consistent and reinforced according to several different studies showing similar results [83-85]. LCZ696 can be considered a much better potential treatment due to the fact that not only it can treat MI induced HF patients. It can also direct the treatment for another major cause of increase mortality and morbidity correlating to HF, that being diabetic cardiomyopathy. This is one of the most important and persistant clinical features of diabetic cardiovascular complications which assists in the development of CR, hence contributing to the impairment of both the function and structure of the heart, therefore increasing morbidity and mortality risks in diabetic patients [3], [28], [86]. The studies for this however, have been done so far only on animal models, limiting out current information and data in order to fully investigate and be able to propagate into human clinical trial for the improvement of mortality and morbidity among diabetic patients. One of these studies includes the LCZ696 effect on diabetic cardiomyopathy (LCZ696-DCM) conducted in 2019. In this study a high glucose treatment and diabetes induction in mice generated oxidative stress and increased the expression levels of pro-inflammatory cytokines and pro-apoptotic factors, which as mentioned in previous sections are direct links to CR [1], [7-8] , [87-89]. These results were greatly ameliorated by the administration of LCZ696 both in vivo and in vitro. The results showed an improvement in both CR as well as cardiac function by several actions, including an inhibition of overproduction of ROS, thus decreasing the inflammatory processes as well as the oxidative stress. An inhibition of Bax/Bcl-2 was observed, thus suppressing phosphorylation of pro-apoptotic factors and an overall improvement in cardiac morphology [86-94]. The LCZ696-DCM study investigated these changes by using transthoracic echocardiography to investigate morphological changes which

displayed that the LV contraction and diastolic functions of diabetic mice were severely impaired, but this impairment was relieved in diabetic mice treated by LCZ696 for 16 weeks in compared to untreated mice [86], [94]. In order to ascertain an appropriate result in regards to the heart structure, the LCZ696-DCM study stained the mice heart tissue sections with Sirius red staining, which demonstrated increased levels of collagen fibers in diabetic mice cardiomyocytes. The latter however was also improved by the administration of LCZ696 despite being a partial improvement [86]. This study concluded that the administration of LCZ696 can and should be further investigated and implemented in human clinical trials for the amelioration of CR in diabetic cardiomyopathy-HF patients.

Aldosterone antagonists:

Aldosterone is a well know factor which causes detrimental effects through multiple mechanisms in HF patients, some of these mechanisms include sodium retention, potassium loss, endothelial dysfunction, vascular inflammation, hypertrophy and cardiac fibrosis [19], [21], [95-97]. Due to its contribution to the progression towards CR it is important to investigate the implementation of an aldosterone antagonist such as Spironolactone to the pharmacological regimen in patients suffering from any disease inducing CR. Several studies show the beneficial effects of Spironolactone when introducing it into a regimen of ACE-I or ARBs. Findings by Chan et al. reported a statistically significant beneficial effect of dual therapy blockade of Angiotensin II with ARB and Aldosterone antagonists on reverse remodeling in patients with chronic mild-to-moderate systolic HF with significant reduction of LV volume and index in those treated by dual therapy, which is thought to be due to a reduction in cardiac fibrosis [18], [98]. Despite the positive results, it is important to mention that this study was conducted in 2007 with a total of 51 patients post inclusion/exclusion criteria, and with 48 patients concluding the 1 year follow up. This is worth mentioning due to the relatively small sample size we cannot draw accurate conclusions. The results from this study can be reinforced by the Aldo-DHF trial conducted in 2015 which was a multicenter, randomized, placebo-controlled, double-blind study to investigate the effect of Spironolactone on patients suffering from HF with preserved EF, demonstrating a significant improvement in LV diastolic function as well as reverse remodeling[19], [21],

[97]. Interestingly, Spironolactone efficacy was also investigated for its implementation in different cardiomyopathies, including dilated and hypertrophic subtypes, which showed no significantly statistical improvement in any pathophysiological processes of CR induced cardiomyopathies [20-22].

Anti-Diabetic drugs:

Diabetes is a recognized comorbidity that is known to aggravate cardiac function as well as cardiac morphology through multiple mechanisms including at cellular and molecular levels [99-100]. Population based studies with HF trials show a prevalence of type 2 DM among patients suffering from HF to be estimated around 12%-49% and a median survival of 4 years [36], [101-103], so it is crucially important to investigate any anti-diabetic drug that may have beneficial effects on both diabetes as well as CR pathophysiology.

- **SGLT-2 Inhibitors**: A very promising and potential new drug with positive results includes the sodium glucose linked co-transporter type 2 (SGLT2) inhibitors. Several different studies suggest that this group is the only class of glucose lowering agent to decrease the risk of cardiovascular events that result from CR. One of these studies includes the research into the effect of SGLT2 inhibition on left ventricular remodeling in patients with heart failure and diabetes mellitus (REFORM) study being conducted since 2015. The REFORM trial is a randomized, double blinded, placebo controlled single-center study conducted in order to compare the SGLT2 inhibitor effects to other anti-diabetic drugs such as Metformin [104]. The beneficial effects are thought to be through its mechanism of action, employing a novel mechanism to lower blood glucose by preventing the reabsorption of glucose in the renal tubules and by competitively blocking the SGLT2 receptors in the proximal convoluted tubules and inhibition of sodium-hydrogen exchange in the kidneys leading to natriuresis, hemo-concentration, and decreases in both body weight and blood pressure, all of which act in synergistically to reduce cardiac wall stress and by that decreasing cardiac injury [105]. Cardiac dysfunction is additionally prevented by inhibition of sodium-hydrogen exchange in the heart failure, thus reducing intracellular

calcium and cardiomyocyte injury and preventing the reabsorption of filtered sodium and glucose, resulting in glycosuria and natriuresis [105-108]. An important evidence of the benefits of SGLT2 inhibitors is the fact that they function independently of insulin levels, pancreatic function and insulin resistance which is a key feature that differentiates SGLT2 inhibitors from any other anti-diabetic drug. The importance of this drug in this review paper however does not specifically lie on its glycemic effects, but on its cardiac functions effects, which is seen in the additional natriuretic effect and resultant osmotic diuresis of SGLT2 inhibitors which could potentially be beneficial in patients with cardiovascular disease, especially those with HF, thereby distinguishing SGLT2-inhibitors from all the other oral anti-diabetic agents [104], [106-108]. In experimental animal models it is evident that inhibition of SGLT2 slows the development and propagation of cardiac hypertrophy as well as cardiomyopathy [109-111]. It has been suggested that inhibition of the sodium-hydrogen exchanger minimize cardiomyocyte injury and slows the evolution of cardiac hypertrophy, fibrosis, remodeling, systolic dysfunction, and heart failure; these advantages have been shown by a wide range of experimental animal models [112-118]. It is important to mention that the beneficial effects of empagliflozin on hospitalization for heart failure seem to appear rapidly in EMPA-REG-OUTCOME (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial conducted in 2015 which was a randomized, double-blind, placebo-controlled trial to examine the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg) against placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event, being a composite of death from cardiovascular causes that occurred, in at least 691 patients [119].The key secondary outcome was a composite of the primary outcome including hospitalization. Both the primary and secondary outcomes occurred in a significantly lower percentage of patients in the empagliflozin group than in the placebo group. It is important to mention that although the beneficial effects of

empagliflozin on hospitalization for heart failure seem to appear rapidly in EMPA-REG-OUTCOME, the effect of empagliflozin has never been investigated in subjects with acute MI with or without Type 2 DM, Therefore a separate study is being done, known as the Impact of Empagliflozin on cardiac function and biomarkers of heart failure in patients with acute Myocardial infarction (EMMY) trial in process since 2019, with the sole purpose of investigating the impact of empagliflozin on biomarkers (NT-proBNP) of HF patients with MI with and without DM type 2 within 6 months post occurrence [120].

- **Biguanide**: As previously mentioned, Metformin, a biguanide, is the second anti-diabetic drug that will be reviewed in this paper, solely due to the fact that it is the first line therapy in DM type 2. To this date, no clinical study has been carried out to investigate the effect of metformin on LV remodeling. The results of the ongoing MET-REMODEL trial [121], a phase IV, randomized, placebo-controlled trial, aimed at investigating the efficacy of metformin in reverting of LV hypertrophy in patients with coronary artery disease and insulin resistance are actively anticipated. In spite of the fact that studies in humans are currently lacking, in animal models metformin shows potent anti-remodeling properties, evidently through reduced interstitial fibrosis, reduced inflammation-related myocardial damage, and seemingly restricting myocardial hypertrophy. Metformin demonstrated a reduction in cardiac hypertrophy within animal models, specifically in mice subjected to chronic pressure overload, partially through AMPK-independent molecular pathways [122]. Metformin was also shown to decrease cardiac fibrosis and suppress collagen synthesis in both a mouse model of pressure overload-induced HF and a mouse model of oxidative stress-induced ventricular hypertrophy, in which it can significantly impede the overexpression of TGF-1 and FGF [123-124]. . Interestingly, also in a canine model of tachycardia-induced HF, metformin reduced myocardial fibrosis through reduced TGF-1 mRNA, and could prevent progression of HF as well [125]. Nevertheless, in mice induced hypertrophy, metformin significantly improved LV fractional shortening, reduced LV dilation, and was associated with

a smaller increase in serum ANP [126]. This effect was observed in both wild-type and AMPK-knockout animals, indicating that metformin can exert cardiac protective effects through an AMPK-independent molecular pathway. Similar beneficial effects have been proved also for long-term metformin administration in rodent models of ischemic HF, wherein both short (4 weeks) [127] and long-term (12 weeks) [128] metformin treatment after MI significantly attenuated cardiac remodeling and delayed the progression of ischemic cardiomyopathy and HF. Moreover, in a model of spontaneously hypertensive insulin resistant rats, it was demonstrated that 12 months-long metformin treatment was associated with reduced echographically-assessed LV volumes and wall stress, as well as histologically-proven perivascular fibrosis and cardiac lipid accumulation in an AMPK-dependent mechanism. In the same study, metformin induced a marked activation of endothelial NOS and vascular endothelial growth factor with reduced TNF- expression, resulting in a significantly decreased myocyte apoptosis.

- **Glucagon-like-peptide 1**: GLP-1 agonists are anti-diabetic drugs for the use against type 2-DM. GLP-1 is an intestinal hormone that exerts profound effects in the regulation of glycemia, stimulating glucose-dependent insulin secretion, pro-insulin gene expression, and β-cell proliferative with anti-apoptotic properties. There is clear clinical evidence that may suggest GLP agonists are effective in decreasing the incidence of major cardiovascular events [129-131]. While the molecular mechanisms underlying the cardio-protective effects of this class of drugs have yet to be identified, there are preclinical studies that suggest GLP1R agonists may also be beneficial when administered shortly after MI and that the underlying mechanism might be due to the activation of mitophagy, which is a type of selective autophagy [119]. DeNicola et al. conducted a study in 2014 showing that mice subjected to permanent coronary artery ligation and administered daily injections of the anti-diabetic drug exendin-4 showed less myocardial hypertrophy, reduced interstitial fibrosis, and increased survival due to the normalization of cardiac steatosis and oxidative stress [133-136]. Qiao et al. investigated in 2018 the possibility that the anti-diabetic drug Liraglutide

would protect against cardiomyocyte death in the infarcted heart and found that rats treated with Liraglutide for 4 weeks after an infarct showed a reduction in cardiac fibrosis and apoptosis [137]. These results, however, contradict the earlier finding by Kyhl et al. in 2017 where a similar liraglutide treatment in rats showed no effect on adverse remodeling or cardiac function [138]. The most recent study includes the Intermittent Use of a Short-Course Glucagon-like Peptide-1 Receptor Agonist Therapy study conducted in 2020, with the main purpose of highlighting its attenuating effects on limitation of CR in the molecular level as well as cellular levels [139]. This study used a short-course glucagon-like peptide-1 receptor agonist therapy 2 known as quinoxalinamine, 6,7-dichloro-N-(1,1-dimethylethyl)-3-(methylsulfonyl)-,6,7-dichloro-2-methylsulfonyl-3-N-tert-butylaminoquinoxaline (DMB) on animal models, specifically mice. In order to get acceptable and established reports, echocardiography and histology were used in order to assess morphologically the LV remodeling and cardiac function. In order to asses remodeling in the cellular level western blot was used for autophagy and mitophagy markers. The findings in this study showed positive and negative effects, on one hand a short-term intermittent administration of the quinoxaline GLP-1 receptor agonist (DMB) after infarction attenuates adverse remodeling and improves cardiac function; on the other hand DMB intensifies autophagy, mitophagy, and mitochondrial biogenesis. In summary it was found that DMB given post-infarction significantly reduced adverse LV remodeling and hinder the decline of cardiac function with a paralleled increase in autophagy, mitophagy and mitochondrial biogenesis [139].

Qiliqiangxin (QLQX):

QLQX consists of 11 herbs, including ginseng, astragalus, aconite, semen lepidii, salvia, safflower, alisma orientale, cassia twig, polygonatum, cortex periplocae, and tangerine peel, which represents a traditional Chinese formula widely used to treat HF in China. Despite its use, QLQX mechanism of action remains a mystery. Few studies have been conducted to explore the direct role of QLQX on CR, despite the fact that many studies

have been done which investigate the many different factors that induce the eventual CR. QLQX has been reported to perform protective effects in heart failure patients in a multicenter randomized double blind study [140]. Moreover, QLQX treatment was shown to reduce myocardial apoptosis and cardiac fibrosis, therefore ameliorating cardiac remodeling and improving cardiac function in a murine model of AMI [141]. A study by Lin et al. conducted in 2015 investigated the metabolic effects of qiliqiangxin on cardiomyocytes, specifically its effect on cardiac mitochondria for the sole purpose of exploring new therapeutic strategies in order to improve and stabilize mitochondrial function [142]. This is of great clinical importance since mitochondrial dysfunction was shown to contribute to cardiomyopathy with various clinical manifestations, and impaired mitochondrial homeostasis was also reported to lead to heart failure over time [143]. The results of this study demonstrates that QLQX improves cardiomyocyte metabolism and increases mitochondrial biogenesis which might contribute to its clinical therapeutic effects on adverse CR and HF, hence directly influencing the progression of CR. This study can be reinforced by multiple similar studies, such as Zhao et al. which conducted a study in 2019 in animal models for the purpose of demonstrating QLQX ability and efficiency to diminish oxidative stress dependent apoptosis in cardiomyocyte, which is a known molecular factor as previously mention to produce CR. This study highlighted very positive results, demonstrating not only an increase in cardiac function, but also a marked lowering of oxidative stress with anti-apoptotic properties , all being major elements in the development of CR [144]. Shen et al. study also indicated that QLQX attenuates adverse CR after MI in mice via activation of PPAR-γ [145]. All data in regards to QLQX appears to be extremely promising and calls for further advancement into human clinical trials. This is demonstrated by Zhou et al. study conducted in 2020, which investigated QLQX effect to reduce cardiomyocytes apoptosis and improved heart function in infarcted animal models heart [146]. Mice were intragastrically treated with QLQX (0.25 g/kg/d, QLQX group) or saline (saline group) for 4 weeks, with post-surgical evaluation by echocardiography for morphological changes, immunohistochemistry and western blot to investigate the results of efficiency and efficacy of QLQX. Results were very promising, demonstrating that although survival rates of saline group and QLQX-treated group were similar within the first 24 h,

nevertheless, the mortality rate of saline group mortality was higher than QLQX group over 28 days (37.5% for saline vs 22.5% for QLQX) a statistically significant difference. Moreover, the cardiac function in the saline group was significantly worse than that in QLQX group, specifically the LVEF. As previously mentioned myocardial apoptosis is a major characteristic of ventricular remodeling post-MI, which was found to be significantly decreased in the QLQX group as assessed when compared to saline group. In order to examine the anti-apoptotic results, the ratio of Bax/Bcl-2 was measured, which in normal setting shows a significant increase after MI. This was shown to be reversed by QLQX. QLQX is a potential potent natural made medicine that could alleviate and improve cardiac function and relieve mortality worldwide by reducing the overall factors the progress to CR. This certainly can be proven if human trials are implemented.

Nanoparticles:

Nanoparticle-based drug delivery systems are widely applied in biomedicine, owing to its excellent physical, chemical and biological properties. Nanoparticles can be used as delivery vehicles of small molecules, polypeptides to improve ventricular remodeling. Nanoparticles refer to particles smaller than 100 nm, which given the inherent nanometer size of cell's biological components, can be considered as delivery vehicles of proteins, nucleic acid and small molecules which may potentially provide sustained treatment in damaged tissues. Several research demonstrate that nanoparticles packed with Nox2-NADPHoxidase siRNA, IGF-1 or pitavastatin enhanced cardiac function post-MI [147-149], suggesting the unlimited possibilities of nanoparticles in the treatment of ventricular remodeling specifically, post-MI. Currently, the drugs used for the treatment of heart failure only aim at its pathophysiological process, but do not target the cause. Furthermore, the current available means of delivering cardio-protective drugs often miss the deadline of reversible repair of cardiomyocytes and inevitably undergo a series of remodeling processes. An important aspect of nanoparticles is its ability to achieve controlled drug release by assembling a release system in response to internal stimuli such as pH, which is seen in infarcted hearts under ischemic conditions. More importantly, is the fact that nanotechnology-based drug delivery system can also be applied to improve not only the biocompatibility, but also increase the precision of drug

targeting and the level of drug accumulation in the desired area. Katsuki et al. utilized Poly-lactic-co-glycolic acid (PLGA) as the carrier of Pitavastatin and tested its efficacy in a MI model. They found intravenous treatment with PLGA-Pitavastatin nanoparticles lowering post infarct ventricular remodeling by interfering with monocyte recruitment and reducing monocyte: macrophage ratio accumulation in the heart [149]. Despite the positive results behind nanotechnology and nanoparticles, not all drugs can be used in these setting due to their size and structure. However, there are several proteins which will be discussed in the following section that can be sustained by such system in order to increasingly impair adverse remodeling and improve prognosis. Despite the beneficial results, current research in this area is still limited to animal models and cell experiments with no reliable clinical trials to support the hypothesis. More work is urgently needed to achieve clinical transition of nanoparticles.

Proteins for ventricular remodeling:

Several proteins have been found to contribute in cardiac repair and attenuate adverse remodeling with several studies demonstrating different proteins involved with cardio-protective effects. Xiao et al found that VEGF promotes cardiac stem cell differentiation into vascular endothelial cells [23]. IGF-1 is an additional protein that was shown by Jackson et al to promote stem cell growth and differentiation [24]. Cerrada et al showed a multifactorial effect of HIF-1α, specifically shown to promote cardiac function, angiogenesis, cardiomyocyte proliferation and reduction of fibrotic tissue with no induction of cardiac hypertrophy [25]. Despite the many positive results shown by different studies, their effect is quite limited due to their short half-lives in vivo in their free form. This however, may be resolved by using nanotechnology-based drug delivery system as previously discussed. In fact, some of them have been nano-particulated for use in the treatment of post infarct ventricular remodeling in animal experiments. For example, injecting PLGA-IGF-1 nanoparticles into the myocardium of MI mice was effective to narrow infarct size, prevent cardiomyocyte apoptosis and improve left ventricle ejection fraction 3 weeks after the left coronary ligation surgery [148].

Discussion:

The World Health Organization estimates that about 23 million people accounting for 12.8% of total deaths will die of cardiovascular disease each year by 2030 [4]. The damage of heart function post CR and the consequent quality in many aspects of life has become dramatically serious in public health care worldwide. It is because of this reason that investigating, understanding and implementing newer medications for the treatment and reversal of CR is utterly important. Despite the knowledge we have today of some specific medications and their usefulness against CR, there is still much to be accomplished in this topic, for it remains as one of the higher mortality pathologies worldwide and a paramount public health problem as previously discussed. When discussing CR it is important to mention that not only it is harmful health wise but it is also an economic burden worldwide. The data suggests that cardiovascular diseases alone and all that it encompasses, make up almost 50% of non-communicable diseases deaths. It is estimated that by the year 2030 the total global cost of cardiovascular diseases is set to increase from approximately US$863 billion in 2010 to a staggering US$1.04 trillion as WHO data demonstrate [4]. Many different aspects of CR should be looked upon for further examination, for the fact that different mechanisms are involved in the rise of CR which involve molecular, cellular and interstitial changes that eventually lead to adverse changes in LV size, shape and function after injury or stress [1]. As shown in this review paper, CR and its reversal has different stages and different points of treatment to improve the resultant symptoms and potentially relieve both the health aspect and economic burden as well. Further research is needed to establish evidence in the pharmacological field to identify correlations, patterns and relationship among different data available to us by contextualizing different findings with previous theories and researches, specifically for the causative agents as well as for the pathophysiological features of CR, since there is quite a shortage of such clinical studies and human trial.

Conclusion:

The goal of this paper was to review the most important treatment being currently in use for cardiac pathologies and their effects in the settings of CR. Despite the progress in

recent years in regards to the therapy of cardiac diseases, CR remains associated with the development and progression of ventricular dysfunction, arrhythmias and poor prognosis, with mortality rates related to cardiac remodeling/dysfunction remaining high. Therefore, the burden of CR persist high within the priorities of public health worldwide, hence, understanding the pathophysiological mechanisms as well as the medicines direct/indirect effect on such system involved in remodeling process is crucial and in desperate need of additional human clinical trials and research is primordial.

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