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A Systematic Review of Cannabidiol Effects in Coronary Syndromes: Challenges to Clinical Translation

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Abstract

Background: Myocardial ischemia in addition to other several cardiac syndromes represent a pathological proinflammatory state alongside a complex cellular microenvironment that can be modified by using cannabinoids. Cannabidiol (CBD), a non-psychoactive compound of cannabis has been recently proposed as an immudomodulatory and cardioprotective drug. **Objectives**: In this systematic review we sought to clarify and summarize the clinical and preclinical evidence of potential benefit of the use of CBD in coronary syndromes. **Methods**: We conducted a systematic search and review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Review of Animal Data from Experimental Studies (CAMARADES) guidelines, in the electronic database from PubMed, Web of Science and Scopus up to April 2022 using predefined search terms. Pre-specified exclusion and inclusion criteria were considered, finally 11 articles were chosen to be included for this peer review. **Results**: Currently there are no good-quality clinical trials with the use of CBD in acute or chronic coronary syndromes. A total of 11 preclinical studies where prescreened and 5 demonstrated reproducible positive cardiovascular outcomes on *in-vivo* models treated with CBD. Mechanisms of CBD cardioprotection observed: 1) reduction in oxidative stress and inflammation, 2) activation of adenosine receptors and 3) increased expression of angiotensin type 2-receptor. Experimental models included ischemia/reperfusion injury, myocardial infarction, arrhythmias, and metabolic syndrome-like conditions. **Conclusion**: No clinical recommendation can be

issued with the current evidence, on the use of CBD in acute and chronic coronary syndromes. Based on preclinical evidence, we considered there is enough evidence to propose the development of well-designed clinical trials that include CBD in the management of coronary syndromes.

Keywords

Cannabis, Cannabidiol, Acute Coronary Syndromes, Myocardial Infarction, Myocardial Ischemia and Oxidative Stress

1. Introduction

In the last decade of the 20th century, it was possible to partially elucidate the phytocannabinoids, which are the active substances of the *Cannabis* plant. Also the characterization of cannabinoid receptors (CBs) [1] in the central nervous system allowed the discovery of endogenous ligands, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), [2] [3] known as endocannabinoids (eCNBs), integrating the endocannabinoid system (ECS). [4] Nowadays, there are more clinical studies that describe alterations in the ECS associated with diabetes mellitus, [5] obesity, [6] systemic arterial hypertension [7] and heart failure, [8] as well as in coronary syndromes (CS), such as modifications in the serum levels of eCNBs during an acute myocardial infarction (AMI). [9]

Cannabinoid compounds have been shown to modulate different cardiovascular functions, such as heart rate, vascular tone and blood pressure when administered in healthy subjects under physiological and pathological conditions; mechanisms of production, degradation and signaling of endocannabinoids have also been described in myocardial and vascular tissue, platelets and immune cells using in-vitro and in-vivo models. [10]

CBD is a phytocannabinoid that does not cause neurological intoxication compared to Δ-9 Tetrahydrocannabinol (Δ-9 THC) [11] and currently represents a therapeutic strategy for medical conditions such as cancer [12], epilepsy [13] [14] and multiple sclerosis. [15] Recently it has been proposed to use CBD in chronic coronary syndromes (CCS) and acute coronary syndromes (ACS), due to its anti-inflammatory and antioxidant properties. [16]

However, there is currently no clinical evidence to suggest it as a treatment option in ACS or CCS. Thus, we performed a systematic review of the effects of CBD in the management of CS, in order to propose new treatment hypotheses for its validation in preclinical and clinical trials.

2. Background

The study of cannabinoids took an important turn in 1964 [17] with the characterization of a hashish sample, and the identification of Δ-9THC as the active substance of "*Cannabis Sativa*", this finding motivated the search for endogenous ligands in humans. Cannabinoid receptors type 1 and 2 (CB1, CB2), [4] are

coupled to protein G i/o, which respond to endogenous substances (eCNBs) [18] (**Figure 1**). The most studied eCNBs are AEA and 2-AG, among others.

The physiological and pathological functions of the ECS in the cardiovascular system are complex and have not yet been fully elucidated, nonetheless, since the evergrowing use of medical cannabis in the world, CBD has been pointed as a promising drug, hence it has been crucial understanding previous preclinical studies that showed the relationship between ECS and cardiovascular disease, in order to consider CBD as a possible cardioprotective strategy.

Polymorphonuclear cells are rich in CB1 and other non-CB1/CB2 receptors (orphan receptors) [19], and their activation by different ECS components has been suggested to have a deleterious role in the progression of atherosclerosis. Jiang L *et al.* demonstrated the activation of the ECS (CB1 overexpression) by ox-LDL, promoting cholesterol accumulation in macrophages, by increasing the expression of CD36 and decreasing the expression of the ATP-1-dependent transporter protein. [20] Sugamura *et al.* noted increased expression of RCB1 in anatomical specimens from human coronary atherectomy samples with lipid-rich atheroma, compared with samples with predominately fibrotic plaques. [21] Montecucco *et al.* reported a decrease in CB2 in human carotid atherectomy specimens, which was related to plaque instability. [22]

Therefore, there is a dichotomy between CB1 and CB2 and their functions in macrophages, endothelium, and arterial smooth muscle cells, where apparently CB1 agonism promotes atherogenesis and CB2 agonism protection. Steffens *et al.* demonstrated in macrophages that CB2 activation with Δ-9THC, inhibited the progression of atherosclerosis by reducing monocyte adhesion and their infiltration into the subendothelial space. [23] Yuan *et al.* carried out in-vitro studies to elucidate the anti-inflammatory properties of 9-ΔTHC, verifying that in the presence of monocyte chemotactic protein-1, this compound inhibited macrophage chemotaxis as well as decreased gamma interferon, an atherogenic cytokine produced by TH1 lymphocytes, also suggesting a pathophysiological relationship of the ECS with atherogenesis. [24] Rajesh *et al.* reviewed the negative effects of CB1 activation on atheromatous plaque; its activation is accompanied by a cascade of intracellular second messengers that activates mitogen-activated protein kinase (MAPK) stimulating the release of inflammatory substances, promoting plaque instability. [25]

In this context, attempts to prove the benefits of manipulating the ECS were carried out by the "RIO-Lipids" (Rimonabant in Obesity) study, an international work group that assessed the effect of Rimonabant on reducing body weight and other cardiometabolic risk factors [26] [27] [28] [29] [30] in patients at high cardiovascular risk. Antagonism of CB1 significantly reduced body weight and improved the metabolic profile of these patients (decreased triglycerides, increased high-density cholesterol). [28] [29] [30] However, the CRESCENDO [31] study whose primary objective was a reduction in cardiovascular events over three years in a randomized sample of more than 15,000 patients with high

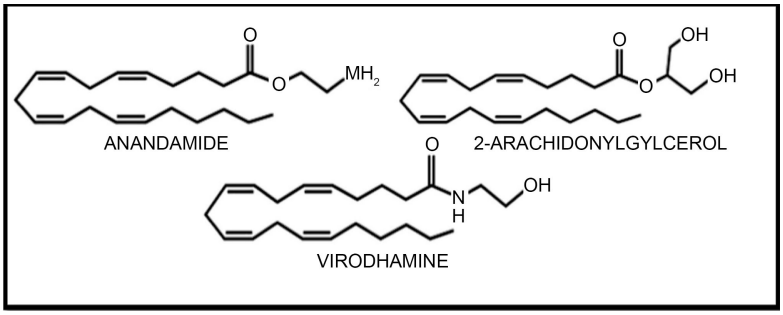

Figure 1. "Most Studied Endocannabonids". Endocannabinoids are highly versatile lipid messengers whose functions extend beyond pure cannabinoid receptor agonism; Recognized as new homeostatics in health, these substances impact the physiology and pathology of the systems and organs of the human body.

cardiovascular risk had to be terminated early by the health authorities since there were four suicides in the Rimonabant arm and one in the control arm.

Lastly, a recent case report [32], highlighted the utility of a medicinal cannabis extract (1:1 CBD: Δ-9THC) in a patient with a history of type 4 coronary syndrome refractory to optimal medical treatment, the cannabis extract improved symptom frequency and characteristics, as well as the suspension of other morphine-type analgesics together with an increase in his functional class and quality of life.

CBD comes naturally from different strains of the Cannabis plant, representing up to 40% of the phytocannabinoids found in it. [33] Its pharmacokinetics depend on the route of administration; the bioavailability of the drug through the oral route is low (20%) and its maximum concentration is reached from 1 to 6 hours after its administration. It travels bound to proteins in the blood and up to 10% adheres to erythrocytes. Given its lipophilic property, it tends to accumulate in adipose tissue with chronic use. It is metabolized via the liver through cytochrome P450 isoenzymes, this is important when it comes to avoiding unwanted drug interactions. [34]

CBD has multiple mechanisms of action, [16] it has a low affinity for CBs, so it does not present the classic neurological effects of Δ-9 THC consumption, it has been reported as an inverse agonist of CB2, an agonist of TRPV1, peroxisome proliferator-activated receptor gamma agonist and CB1 allosteric modulator, in turn, it alters the metabolism of eCNBs, promoting an increase in serum levels of AEA and/or other metabolites such as adenosine. In summary, it is recognized that CBD has indirect (endogenous modulation of metabolites) and direct (receptor agonist and/or antagonist) molecular mechanisms by which it might modify the ECS and cardiovascular disease (**Figure 2**). [35]

Thus, CBD could potentially be considered as an effective cardioprotective drug aimed at reducing the injury from ischemia and reperfusion (I/R). Reperfusion of coronary flow is mandatory if the aim is to rescue ischemic myocardium in the context of an AMI. [36] The preservation of cardiomyocytes and the decrease in cardiovascular mortality, are inversely proportional to the time invested in

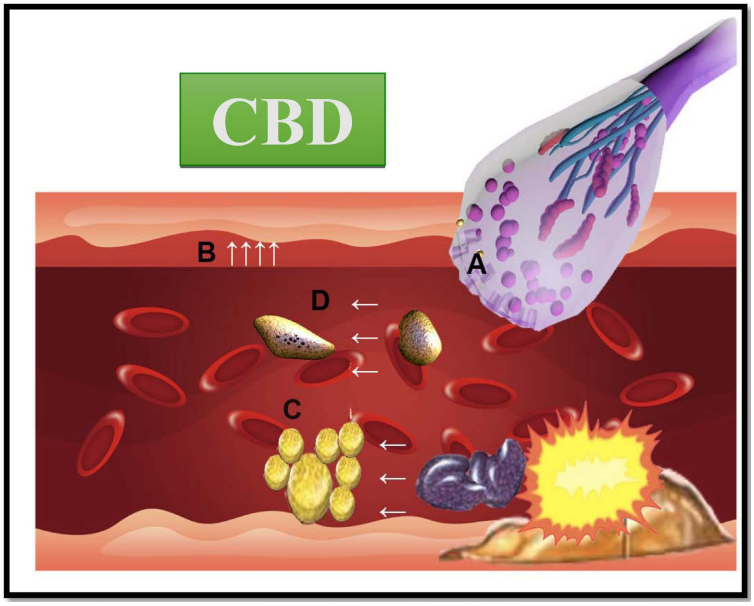

Figure 2. "ECS interaction with multiple pathophysiological components of cardiovascular disease". (A) The autonomic nervous system regulates arterial tone by releasing local messengers together with the ECS, stimulating RCB1 and TRVP1. (B) RCB1 agonism in endothelial cells generates relaxation. (C) LDL-ox cholesterol stimulates RCB1 in macrophages, promoting foam cell formation. (D) Cannabinoids modify platelet function due to their secondary metabolites. [ECS: Endocannabinoid System, RCB1: Cannabinoid Receptor type 1, TRPV1: Transient receptor potential cation channel subfamily V member 1 V1, LDL-ox: Oxitated low-density lipoprotein].

establishing reperfusion. Paradoxically, this reperfusion can lead cardiomyocytes to significant dysfunction, known as reperfusion injury or (I/R) injury. [37] Myocardial stunning, microvascular dysfunction and cell necrosis are complications that limit the survival of patients with AMI after mechanical or medical reperfusion. Investigating new treatments to reduce I/R injury is imperative in order to preserve myocardial tissue and functionality.

In this systematic review, we provide summarized evidence that allows us to take into account the potential cardioprotective benefits of CBD for the management of CS. The current translational strategy implemented for this analysis led to multiple working hypotheses on how to replicate these findings in a well-designed clinical trial. To our knowledge, this is the first systematic review of CBD effects in CS.

3. Methods

3.1. Search Strategy

We conducted a systematic search and review following the international guidelines of PRISMA and CAMARADES. The protocol itself was previously uploaded at PROSPERO as recommended per guidelines. Preclinical and clinical research studies were sought in English and/or Spanish through the PUBMED, Web of Science, and Scopus database search engine from its inception to April

2022, using the following keywords and boolean operators: CBD OR Endocannabinoids OR Cannabinoids OR Cardiovascular Disease OR Myocardial Ischemia OR Coronary Disease OR Myocardial Infarction OR I/R OR Oxidative Stress OR Heart Disease, in the title or abstract, finally, results were manually conditioned as follows [(CBD AND Cardiovascular Disease), (CBD AND Myocardial Ischemia), (CBD AND Coronary Disease), (CBD AND Myocardial Infarction), (CBD AND I/R), (CBD AND Oxidative Stress), (CBD AND Heart Disease)].

During this phase, we found there are no randomized clinical trials that utilize CBD as an experimental intervention in the context of CS, thus we continued looking for preclinical evidence.

3.2. Study Selection

Two certified physicians from the cardiology department of our medical center, independently analyzed the titles and abstracts of preclinical studies that contained the pre-specified terms and criteria for inclusion and exclusion. Inclusion criteria were: studies with in-vivo experimental animal models of myocardial infarction, myocardial I/R, coronary disease, myocardial ischemia and/or oxidative stress, that use CBD as a pharmacological intervention in control groups against experimental groups and that report primary and secondary objectives related to CS. Subsequently, the two physicians again independently, reviewed the full text of the studies choosen in the previous phase and select those that met the inclusion criteria. The differences in the review and choice made for each study were agreed upon by V.G as the third reviewer. The electronic platform developed by CAMARADES was used for the compilation and review of studies.

3.3. Data Extraction Process

Pre-established data was included on a verification sheet by 3 researchers independently during the review of the selected works, these were: the study design and its methodology, the number of animals, the intervention, the outcomes, the results and finally miscellaneous data (funding source, key conclusions of the study authors). Numerical data from tables, graphs, text and/or figures were used to generate a table that describes the data obtained and synthesize the information. CAMARADES format was used to handle these data. Summaries of the interventions for each study were made by calculating RR (dichotomous variables) and/or SD (continuous variables), using dedicated statistical data management software. During data management, it was prematurely concluded that meta-analysis would not be possible due to the limited number of included studies and the very heterogeneity of the experimental models.

3.4. Synthesis Methods

The qualitative information was treated and reported through a narrative textual synthesis, structured around the type of intervention (CBD), the characteristics of the animals, the types of outcomes and the clinical value of the intervention.

3.5. Bias Assessment

Included studies were evaluated for publication bias utilizing the tools suggested by Cochrane and SYRCLE group [38], strict adherence to international regulations on the management of animal models and previously ethical approval on all studies was mandatory.

4. Results

The initial search documented 942 articles. After removing duplicates, 825 articles were reviewed for titles and abstracts, including those that met our inclusion criteria. 11 papers were included for full-text analysis, excluding the rest for the most part, because they were completely unrelated to the topic. The workflow diagram is shown in Figure 3. During the review, 6 experiments simulating clinical scenarios other than myocardial ischemia were documented; 3 researchers decided to exclude them from data extraction. Table 1 summarizes the data obtained.

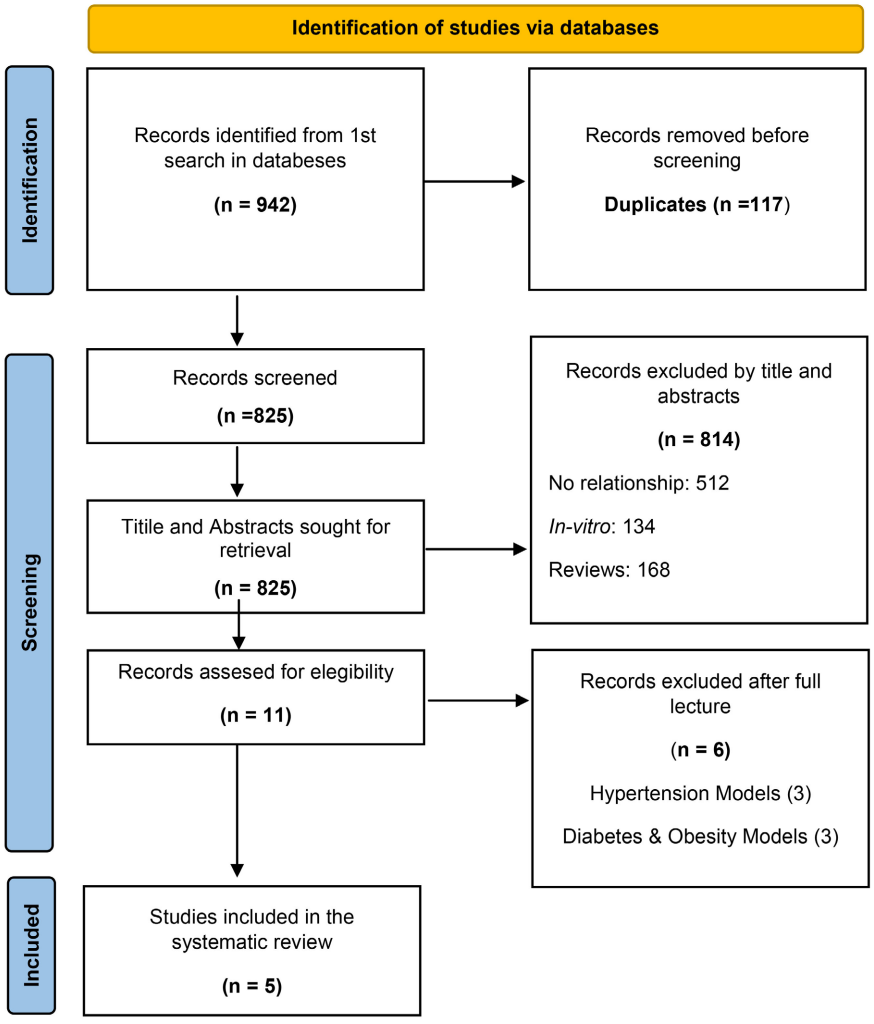

Figure 3. "Workflow diagram for the systematic review".

Table 1. Details of included studies for data extraction.

Authors	Model	Experimental Model	CBD dose & Route of administration	Cardiac & Chemical Outcomes	Other Findings (Proposed mechanism of action)
1) Durst *et al.* 2007	Induction of myocardial infarction and reperfusion in rats	Male Sprague Dawley rats were operated with LAD occlusion for 30 min and then released	*In vivo*: intraperitoneal CBD 5 mg/kg one hour prior to surgery and once a day for the next 7 days	Infarct size significantly reduced in the CBD group (66% reduction) Lower inflammatory response in the CBD group.	Immunomodulatory effect (IL6-lowering effects) Activation of adenosine receptors
2) Feng *et al.* 2015	Induction of myocardial infarction and reperfusion in rabbits	Ischemia Reperfusion Model. Through surgery, the the circumflex artery is occluded for 90 minutes.	CBD 100 μm/kg intravenously 10 minutes before occlusion and 10 minutes before reperfusion.	Significantly less Trop I in rabbits treated with CBD Significant improvement in lateral wall thickness Significant increase in coronary flow to the region of the infarct Minor zones of microvascular occlusion The smaller size of the infarct area Fewer areas of hemorrhage, fewer leukocytes, and less apoptosis	Increased adenosine, increased NO levels CBD binds to PPARɣ which decreases the expression of inducible ON synthase It has also been seen to decrease monocyte adhesion and transmigration (atherosclerosis)
3) Castillo *et al.* 2021	Induction of ischemia/ reperfusion in rats	Male Wistar rats were divided into 3 groups. Surgery to ligate the LAD and cause ischemia for 45 minutes.	Control (SHAM for I/R surgery) Group with I/R I/R group treated with CBD 5 mg/kg intraperitoneal for 10 days prior to surgery	Better hemodynamic parameters in the hearts of rats treated with CBD Significant reduction of the infarct zone Increased expression of AT2, without elevation of AT1 in rats treated with CBD Increased expression of Akt and ERK	Activation of AT2 could explain RISK activation, the latter has been found to be decreased in heart failure and I/R injury
4) Walsh *et al.* 2010	Induction of arrhythmias during reperfusion injury in rats	Surgery to occlude the LDA for 30 minutes and then reperfusion for 2 hours in male Sprague Dawley rats	Intravenous, 2 doses 10 and 50 μg/kg 10 minutes before occlusion and 10 minutes before reperfusion	Treatment with 50 μg/kg CBD prior to occlusion significantly reduced VT and ventricular ectopic beats. The administration of 50 μg/kg CBD prior to ischemia and prior to reperfusion decreased the size of the infarct 50 μg/kg CBD reduced platelet aggregation ex vivo	CBD decreased VT when given before ischemia, but not before reperfusion. CBD can have a PPAR gamma effect and through this effect be anti-inflammatory. GPR55 receptor antagonist. CBD improves Ca homeostasis through NCX.
5) Gonca *et al.* 2015	Induction of arrhythmias during reperfusion injury in male rats	Albino Wistar rats. Surgery to tie the LAD for 6 minutes and then untie for another 6 minutes.	4 experimental groups Control CBD 50 μg/kg IV 10 minutes before occlusion DPCPX selective A1 receptor antagonist 15 minutes before occlusion CBD followed by DPCPX 10 and 15 minutes before IV occlusion	CBD alone decreased arrhythmias, VT duration time. Co-administration of both did not reduce arrhythmias. None of the drugs affected the QT.	Effect of CBD by inhibiting rectifying current K channels, which prolongs the action potential and QT interval and suppresses arrhythmias in ischemia animals. Activation of the A1 receptor through inhibition of adenosine uptake by ENT.

Given the limited number of studies included, and the heterogeneity of the experimental models, the association of the results for meta-analysis was not carried out, this also to avoid publication bias. We then implemented a textual narrative synthesis strategy structured around the type of intervention (CBD), the characteristics of the animals, the types of outcomes and the clinical value of the intervention.

4.1. Cannabidiol in Ischemia/Reperfusion Models, Myocardial Infarction

In 2007, Durst *et al.* [39] carried out the first study with CBD in experimental models of myocardial infarction. CBD 10mg/kg intraperitoneal was administered 1 hour prior to the obstruction (30 minutes) of the left anterior descending artery (LAD) and subsequently the same dose of CBD for 7 days in Sprague Dawley rats. Finally, the ex vivo hearts were analyzed; the infarct size (IS) was smaller in the CBD group vs control (9.6% ± 3.9% vs 28% ± 7%, $p < 0.001$) the cellular inflammatory infiltrate was also smaller in the CBD group, finally, interleukin-6 was also found to be significantly lower (CBD 264 ± 254 pg/ml vs control 2812 ± 500 pg/ml).

Feng *et al.* in 2015 [40] reproduced myocardial infarction and reperfusion models in medium-sized animals using rabbits, with the aim of standardizing the use of in-vivo magnetic resonance imaging (IVMRI) to assess the effect of intervention with CBD in experimental models. 100 um/kg of CBD was intravenously administered 10 minutes prior to the obstruction of the circumflex artery (90 minutes) and 10 minutes before reperfusion. The rabbits had 24 hours to recover, to later undergo IVMRI and finally blood extraction and ex vivo analysis. Serum troponin I levels were significantly lower in the CBD group vs the control group (3.99 ng/ml ± 1.955 vs 6.39 ng/ml ± 2.93, $p = 0.02$). The IS was also lower in the CBD group vs control (60.51% ± 12.94% vs 72.66%, p. 0.05). Other reported outcomes in IVMRI such as parietal thickening of the lateral wall was better in the CBD group vs control (34.84% ± 8.515% vs 23.35% ± 9.89%, $p < 0.05$), microvascular obstruction as well (7.25% ± 2.3% vs. 14.91% ± 4.17%).

The most recent work on CBD in models of myocardial infarction/reperfusion is that of Vadillo *et al.* [41], who in 2021 reproduced the experimental model of Durst [39], but by modifying the intervention with CBD, giving 5mg/kg intraperitoneal for 10 days in rats, prior to LAD obstruction (45 minutes) and 3 control groups. In turn, they documented new mechanisms of action not previously proposed, by directly studying the molecular expression of angiotensin 1 and 2 receptors (AT-1 and AT-2) and the function of the "RISK" (Reperfusion Injury Salvage Kinase) celullar pathway studying the expression of AKT/PKB and ERK proteins. No means were reported for the IS, but rather a 20.55% reduction in the CBD group vs. the control group. AT-2 elevation was found in the models with CBD vs control (p 0.0002). All forms of AKT and ERK were found to be increased in the CBD group vs controls (p 0.0001).

4.2. Cannabidiol in Models of Ischemia/Reperfusion Arrhythmias

In 2010, Walsh *et al.* [42] carried out the first experiment on arrhythmias by I/R in rats; different doses of CBD (10 and 50 um/kg intravenous) and placebo were administered in 4 experimental groups, 10 minutes before the obstruction of the LAD and 10 minutes before reperfusion. At the same time, they sought to determine its effect on IS and mechanisms related to platelet aggregation and degranulation of mast cells. CBD treatment was able to decrease IS in the group receiving 50 μm /kg when administered before ischemia and before reperfusion vs control ($p < 0.001$). Treatment before ischemia also significantly reduced the incidence of ventricular tachycardia and ventricular ectopic beats. On the other hand, the same dose of 50 um/kg was able to decrease ex vivo collagen-induced platelet aggregation in a sham-operated experimental group ($p < 0.05$). There were no significant differences when studying mast cell degranulation in any group.

Gonca *et al.* in 2015 [43] analyzed the work of Walsh [42], deciding to reproduce the same but with a shorter ischemia time. Walsh produced 30 minutes of ischemia and observed a greater number of ventricular arrhythmias. Gonca performed small periods of I/R every 6 minutes in 4 experimental groups. Walsh had previously proposed that adenosine and its receptors might be involved in the antiarrhythmic effects of CBD, so he included a group treated with the selective adenosine type 1 receptor antagonist (DPCPX). CBD 50 μg/kg intravenously was administered 10 minutes before obstruction, and CBD + DPCPX 10 and 15 minutes before obstruction, respectively. Treatment with CBD decreased the incidence of ventricular tachycardia (CBD 2.2 ± 0.4 vs Control 4 ± 0.4) and its duration vs control (CBD 21 sec ± 5 vs 80 sec ± 22). Concomitant administration of DPCPX abrogated these effects.

Some studies that were included in the initial full-text analysis were excluded after their complete reading due to their experimental model. Also, during the review of these models, there were differences that could not be agreed upon by the researchers, so it was ultimately decided to exclude studies that simulated states similar to metabolic syndrome for their mention in this section.

5. Discussion

Reperfusion strategies during an AMI have managed to improve long-term cardiovascular outcomes without any doubt, however, there is still an unmet need in relation to the injury generated by the I/R. In this sense, new cardioprotection alternatives are necessary to improve the deleterious impact of l/R. [44] There is previous evidence that demonstrates the usefulness of this type of therapy, such as therapeutic hypothermia, vagal stimulation and ischemic preconditioning, however, its results in clinical trials have been controversial [44].

In this context, 5 studies included in the systematic review were grouped by their experimental model, the intervention with CBD and the report of outcomes [39] [40] [41] [42] [43] associated with the I/R injury, myocardial infarction and arrhythmia.

5.1. Cannabidiol Administration during ACS and CCS

The studies reported a significant reduction in IS in the groups receiving CBD compared to controls, using 2,3,5-triphenyltetrazolium chloride (TTC) stained histopathology. Within the pathophysiology of the I/R, key moments are recognized to establish proper treatment, under this concept, we could not determine the ideal moment to administer the CBD, since the 5 models provided CBD at different moments, however, Feng *et al.* used IVMRI results and compared them ex vivo with TTC staining, presenting an adequate correlation with a decrease in IS. IS is an important factor in the prognosis of patients with an AMI, the cardioprotective mechanisms suggested in these models are probably related to multiple forms of attenuation of cardiomyocyte death.

Durst *et al.* demonstrated a reduction in IL-6, perhaps regulating cell necroptosis and pyroptosis, since this form of cell death promotes different proinflammatory pathways. Feng *et al.*, documented a decrease in serum troponin values in the CBD models, also proving a lower IS.

There is also scientific information regarding the CBD anti-inflammatory propierties, the studies presented here suggests that administration previous to myocardial reperfusion and during reperfusion can lead to reduce IS; thus, we beleive that CBD might provide cardioprotection in multiple scenarios of myocardial ischemia, not only during ongoing ischemia like ACS, but also in chronic scenarios where inflamattion is perennial.

The physiological aspects of ischemic conditioning have been proposed as effective cardioprotective strategies, but with difficult technical reproducibility in clinical settings, particularly due to their inconclusive results. The intracellular signaling cascades involved in ischemic conditioning have 3 well-documented components: an activation pathway through G protein-coupled receptors and type A, C, and G protein kinases; the RISK signaling pathway, which involves inhibitory G-protein receptors, RACa serine/threonine protein kinase (AKT), and extracellular regulatory kinase (ERK); and the last one, known as *survival activation factor enhancement* (SAFE), mobilized by activation of JAK and STAT-3 and 5 cytokine receptors. Valdillo demonstrated for the first time the activation of the RISK signaling pathway in their animal models, as well as increased expression of AT-2 receptors. Their results suggest that one of the cardioprotective mechanisms of CBD could be the modification of this signaling pathway.

5.2. Cannabidiol for the Prevention of Arrhythmias during ACS

Arrhythmias caused by myocardial I/R are related to a worse clinical prognosis. Two studies were grouped in this scenario due to the similarity of the intervention with CBD and the reporting of outcomes.

The 2 models that used CBD in I/R-induced arrhythmias, differed in the time at which the coronary artery was ligated. One study ligated the artery for 30 minutes and evaluated a dose of 50 μg/kg of CBD prior to obstruction and reperfusion respectively, demonstrating a notable decrease in ventricular arrhythmias, particularly ventricular ectopic beats. The second study, with a coronary ob-

struction time of 6 minutes, demonstrated a decrease in post-reperfusion arrhythmias and correlated these effects to the levels of adenosine and its receptors. The beneficial effects of adenosine have not been reproducible in clinical trials with patients suffering from ST-elevation ACS. However, CBD has been shown to alter adenosine metabolism, so we also suggest that CBD has cardioprotective effects upon activation of adenosine receptors.

5.3. Cannabidiol in Metabolic Syndrome Like Conditions

Two studies with CBD in models of provoked diabetes excluded for data extraction demonstrated positive effects by reducing oxidative stress, inflammation, cell death and fibrosis. Both models described cellular signaling pathways that allow the mechanism of action of CBD to be correlated within the inflammatory substrate of coronary syndromes.

Rajesh *et al.* [45] used treatment with CBD for 11 weeks, managing to reduce the levels of proinflammatory cytokines by modifying the NF-κB signaling pathway, CBD also modified the overactivation of activated mitotic kinases (MAPK) documented in diabetic versus CBD models. They were also able to demonstrate increases in AKT activation, which, as we had commented in the Castillo *et al.* models, is related to cardioprotection through RISK. For their part, Rahman *et al.* [46] used a synthetic analogue of CBD, called abnormal cannabidiol, which has previously show cardioprotective effects by GPR18 receptor activation and been pointed out as responsible for the positive effects observed on ventricular function of the heart in a previous experimental model and its relationship with adiponectin, a protein involved in the metabolism of fatty acids and glucose. The abnormal CBD compared to the placebo-managed to improve the expression of the GPR18 receptor as well as the levels of adiponectin, in turn, by means of molecular analysis of the AKT proteins, an ERK 1/2 increase in their expression was observed in comparison with the rats not treated with CBD. The effects studied in this model were abolished after the administration of the antagonist (O-1918) of the GPR18 receptor.

5.4. Limitations and Future Perspectives

One of the limitations of this review is the few publications found and the heterogeneity presented in the studies included. However, this is the first systematic review of preclinical evidence to objectively synthesize the effect of CBD intervention in the context of I/R models. The decrease in IS is a very important prognostic variable for the justification of experimental drugs that seek to offer cardioprotection; one study was even able to quantify this result by means of IVMRI, giving high translational value to the findings.

6. Conclusions

The treatment of CS still requires new treatments that modify their inflammatory substrate. In this systematic review, we have demonstrated the benefits of CBD in experimental models of acute myocardial infarction, ischemia/reperfusion, arr-

hythmias due to I/R and in conditions similar to metabolic syndrome. CBD is a safe and well tolerated cannabinoid thay might just be a promising cardioprotective strategy for the magnagment of ACS and CCS patients.

CBD and its utility on terms of CS management is a scientific and therapeutic paradigm yet to be resolved, however, we are convinced in the need for clinical investigation to design and perform new randomized clinical trials with this compound to validate its usefulness in CS.

7. Clinical Perspectives

- Competency in Medical Knowledge: The work has the responsibility of generating scientific background for the dissemination and education about cannabinoids in cardiovascular disease. CBD has been proposed as a cardioprotective treatment for ischemic heart disease.
- Competency in Patient Care: Cannabis use and its many products have become very popular in the last decade, to provide medical advice for patients using these products it's crucial; CBD can cause harm when patientes are taking other drugs, is vital to provide education in this matter to reduce treatment interactions.
- Translational Outolook 1: New cardioprotective treatments aim to reduce the inflammatory background of myocardial ischemia, CBD has proven in preclinical studies that it modifies this inflammatory activity.
- Translational Outlook 2: Randomized clinical trials with CBD are needed to prove and evaluate its efficacy in reducing infarct size and realted AMI complications.

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Disclosures

M.D Zuñiga Mario previously presented this work at ACC Latin America 22 as a poster. No relationship with the industry nor other conflicts of interest were present for this work.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abreviations

-CBD (Cannabidiol)
-CS (Coronary Syndromes)
-ECS (Endocannabinoid System)
-CBs (Cannabinoid Receptors)
-CB1 (Cannabinoid Receptor type 1)
-CB2 (Cannabinoid Receptor type 2)
-eCNBs (Endocannabinoids)
-ACS (Acute Coronary Syndromes)
-CCS (Chronic Coronary Syndromes)
-AMIs (Acute Myocardial Infarction)
-AEA (Anandamide)
-2-AG (2-Araquidonilglycerol)
-FAAH (Fatty Acid Amide Hydrolase)
-A.A (Arachidonic Acid)
-CNS (Cental Nervous System)
-Δ-9 THC (Δ-9 Tetrahydrocannabinol)
-TRPV1 (Transient Receptor Potential Cation Channel Subfamily V Member 1)
-I/R (Ischemia/Reperfusion)
-IP (Intraperitoneal)
-LAD (Left Anterior Descending Artery)
-IS (Infarct Size)