PREVENTION OF CVD

Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly

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Abstract | Dysregulation of the endogenous lipid mediators endocannabinoids and their G-protein-coupled cannabinoid receptors 1 and 2 (CB_1R and CB_2R) has been implicated in a variety of cardiovascular pathologies. Activation of CB_1R facilitates the development of cardiometabolic disease, whereas activation of CB_2R (expressed primarily in immune cells) exerts anti-inflammatory effects. The psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (THC), is an agonist of both CB_1R and CB_2R, and exerts its psychoactive and adverse cardiovascular effects through the activation of CB_1R in the central nervous and cardiovascular systems. The past decade has seen a nearly tenfold increase in the THC content of marijuana as well as the increased availability of highly potent synthetic cannabinoids for recreational use. These changes have been accompanied by the emergence of serious adverse cardiovascular events, including myocardial infarction, cardiomyopathy, arrhythmias, stroke, and cardiac arrest. In this Review, we summarize the role of the endocannabinoid system in cardiovascular disease, and critically discuss the cardiovascular consequences of marijuana and synthetic cannabinoid use. With the legalization of marijuana for medicinal purposes and/or recreational use in many countries, physicians should be alert to the possibility that the use of marijuana or its potent synthetic analogues might be the underlying cause of severe cardiovascular events and pathologies.

The 2016 report from the WHO on *The Health and Social Effects of Nonmedical Cannabis Use* states that marijuana or cannabis use is a risky behaviour with potentially harmful health consequences, including adverse cardiovascular effects[1]. The report also notes the dramatic increase in the potency of cannabis over the past decade, attributable to the increase in its Δ^9-tetrahydrocannabinol (THC) content from around 2–3% up to 20%, as a likely factor in the rise in cannabinoid receptor 1 (CB_1R)-mediated adverse cardiovascular effects. Since 1998, the use of cannabis for medical purposes has become legal in 29 states (according to state, but not federal law) in the USA, and numerous countries have also opted to legalize marijuana for medicinal use. The 2017 Cannabis Industry Annual Report (from New Frontier Data) estimated the legal cannabis market to be worth US$7.97 billion in the USA in 2017, with projected total market sales to exceed $24 billion by 2025, and possibly driving the creation of 300,000 new jobs by 2020, more than any other sector in the economy[2].

Another potentially dangerous development has been the increasing availability and recreational use of a growing number of psychoactive synthetic cannabinoids with potencies 10-times to 200-times greater than that of THC. These 'designer' drugs are commonly mixtures of several potent synthetic CB_1R agonists such as AB-CHMINACA, AB-FUBINACA, AB-PINACA, AKB4, AM-2201, cannabicyclohexanol, CP 55,940, HU210, JWH-018, JWH-073, JWH-200, UR-144, and XLR-11, to name just a few among several hundred largely unknown variants estimated by the United Nations Office on Drugs and Crime to be in circulation worldwide[3], with only 26 being considered as schedule I drugs by the Drug Enforcement Administration. These compounds and their mixtures, often sprayed on harmless herbs, or mixed with oily solutions or brownies, circulate most commonly as Black Mamba, Bombay Blue, fake weed, K2, and spice, but several hundred other names have been used. Strikingly, a new generation of these designer drugs are reported to be up to 170-times more potent than THC in activating CB_1R, with a dramatic increase in potency noted within the past 2 years[4]. These drugs were also responsible for recent clusters of poisoning outbreaks involving up to hundreds of individuals in Alabama, New York[5], and Mississippi[6], with numerous deaths reported. According to the Centers for Disease

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Key points

- Activation of cannabinoid receptor 1 (CB_1R) by endocannabinoids or synthetic ligands mediates acute haemodynamic effects and might contribute to pathology in cardiovascular disease; activation of cannabinoid receptor 2 (CB_2R) exerts anti-inflammatory effects
- The psychoactive constituent of marijuana, Δ^9-tetrahydrocannabinol (THC), exerts its cardiovascular effects via CB_1R activation; at low doses it might have beneficial properties via partial activation of CB_1R and CB_2R, and unrelated mechanisms
- The composition of marijuana (THC–cannabidiol ratio, terpenoids) can influence its therapeutic and cardiovascular adverse effects, with marijuana smoke being as harmful as tobacco smoke
- Most synthetic cannabinoids used for recreational use are full agonists of CB_1R (THC is a partial agonist) with up to several hundred-fold higher potency and efficacy than THC, causing more dangerous adverse effects
- In parallel with a tenfold increase in the THC content of marijuana and the widespread availability of synthetic cannabinoids for recreational use, the number of serious cardiovascular adverse effects reported has markedly increased
- Clinicians should be vigilant to recognizing potential cardiovascular effects of marijuana and synthetic cannabinoids; controlled clinical trials should determine the long-term consequences of the use of medical marijuana on cardiovascular morbidity and mortality

Control and Prevention (CDC), there were 3,572 calls to poison centres in the USA in the first half of 2015 owing to synthetic cannabinoids, a 229% increase from the same period in 2014 (REF. 7). The appearance of new and more potent spice variants also coincided with the increase in fatalities. The Mississippi outbreak alone was associated with nine synthetic cannabinoid-related deaths[6].

Numerous case reports and clinical studies during the past decade have linked acute or chronic marijuana and/or synthetic cannabinoid use with serious adverse cardiovascular events, including stroke, myocardial infarction, cardiomyopathy, arrhythmias, and cardiac arrest, which will be discussed in this Review, along with the role of the endocannabinoid system in cardiovascular disease, and its potential as a therapeutic target.

ECS in cardiovascular health

To facilitate the understanding of the acute and chronic consequences of marijuana and synthetic cannabinoid use, this section presents an overview on the role of the endocannabinoid system (ECS) in cardiovascular health and disease (reviewed in detail previously[8–12]). The ECS comprises endogenous lipid mediators or endocannabinoids (arachidonoyl ethanolamide [AEA or anandamide] and 2-arachidonoylglycerol [2-AG]), their biosynthetic and metabolic enzymes, and G-protein-coupled CB_1R and cannabinoid receptor 2 (CB_2R) (REFS 13–15), which also mediate the effects of the psychoactive component of marijuana, THC. At higher concentrations, endocannabinoids can also interact with additional receptors, such as the transient receptor potential cation channel subfamily V member 1 (TRPV1)[16].

CB_1R are the most abundant G-protein-coupled receptors in the mammalian brain, and are responsible for mediating the psychoactive effects of marijuana. Low, but functional, levels of CB_1R have also been detected in most peripheral tissues, including the heart and vasculature[17–19]. CB_2R are normally expressed in immune and immune-derived cells, but can be induced in other tissues under certain pathological conditions[20]. Cannabinoid receptors signal via $G_{i/o}$-protein-dependent pathways to inhibit adenylyl cyclase and modulate ion-channel function, but also activate mitogen-activated protein kinases (p44/42 MAPKs, p38, ERK, and JNK) or ceramide signalling[16,21], and can also engage G-protein-independent pathways via β-arrestins[22,23].

The biosynthesis of endocannabinoids occurs 'on demand' and can involve multiple pathways. Hydrolytic conversion of the precursor *N*-acyl-phosphatidylethanolamine (NAPE) via NAPE-selective phospholipase D (NAPE-PLD) leads to formation of anandamide, the first endocannabinoid discovered[24]. Additional parallel biosynthetic pathways of anandamide have also been identified[25,26]. The synthesis of 2-arachidonoylglycerol (2-AG), the second endocannabinoid identified, is largely driven by the sn1-specific diacylglycerol lipase: DGLα in the brain and DGLβ in the periphery[27–29]. Endocannabinoids have a short *in vivo* half-life[30] owing to their rapid degradation into arachidonic acid and other metabolites through the activity of fatty-acid amide hydrolase (FAAH)[31], monoglyceride lipase (MGL)[32], and other enzymes, including cyclooxygenase 2 (also known as prostaglandin G/H synthase 2) and lipoxygenases[33,34]. The ECS has been comprehensively reviewed previously[35–37].

In the cardiovascular system, cannabinoid receptors are located in the myocardium[38–43], vascular endothelial and smooth muscle cells[44–47], as well as circulating blood cells[48]. CB_1R are also present in the peripheral nervous system[49,50], including vagal afferent neurons[51], and can modulate cardiovascular function. Endocannabinoid synthesis has been detected in rat isolated kidney microvascular endothelial cells[45], human umbilical vein endothelial cells, aortic smooth muscle cells[44,52], human platelets[53], monocytes[54,55], THP-1-derived macrophage foam cells[56], lymphocytes[57], and dendritic cells[58]. These cells are also involved in endocannabinoid hydrolysis[45,52,57,59]. Other cells, including human neutrophils, can also hydrolyse endocannabinoids into metabolites including arachidonic acid, which is further metabolized into pro-inflammatory eicosanoids in these cells[60]. Endocannabinoids act locally in a paracrine or autocrine manner by activating cannabinoid receptors, as shown for example in isolated blood vessels[61]. In human or mouse primary vascular smooth muscle cells, pharmacological antagonism or genetic deficiency of cannabinoid receptors modulates tumour necrosis factor (TNF)-α or

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platelet-derived growth factor (PDGF)-mediated cellular responses, suggesting that inflammatory stimuli induce endocannabinoid-mediated cannabinoid-receptor signalling in an autocrine manner[46,62–64].

Endocannabinoids exert complex cardiac and vascular effects ranging from vasodilatation to vasoconstriction, and decreased myocardial contractility, depending on the vessel type and experimental condition (reviewed in detail previously[11,17,65–67]). In human cultured primary cardiomyocytes[42] and human coronary artery and umbilical endothelial cells[47,68], CB_1R activation triggers p38 and JNK MAPK signalling, which promotes cell death. In the intact organism, endocannabinoids have complex haemodynamic effects mediated by CB_1R in the vasculature, myocardium, and neurons in the central and autonomic nervous systems, leading to decreased myocardial contractility and blood pressure[65,69–71]. These effects are similar to the effects of synthetic CB_1R agonists[72], only of much shorter duration owing to the rapid degradation of endocannabinoids in peripheral tissues, including the heart and vasculature. In contrast to CB_1R agonists, which exert potent cardiovascular depressive effects in experimental animals[65], CB_2R agonists are devoid of cardiovascular effects[10,12]. The normal cardiovascular function in *Cnr1* (encoding CB_1R), *Cnr2* (encoding CB_2R), *Faah*, *Mgll*, or *Trpv1* knockout mice indicates that endocannabinoids under normal conditions are not tonically active[17].

ECS in cardiovascular disease

Preclinical studies

Cardiovascular collapse, cardiomyopathy, and heart failure. Interest in studying the role of the ECS in cardiovascular disease (FIG. 1) was rekindled by the discovery that endocannabinoids are overproduced by activated immune or endothelial cells and cardiomyocytes under pathological conditions, such as those associated

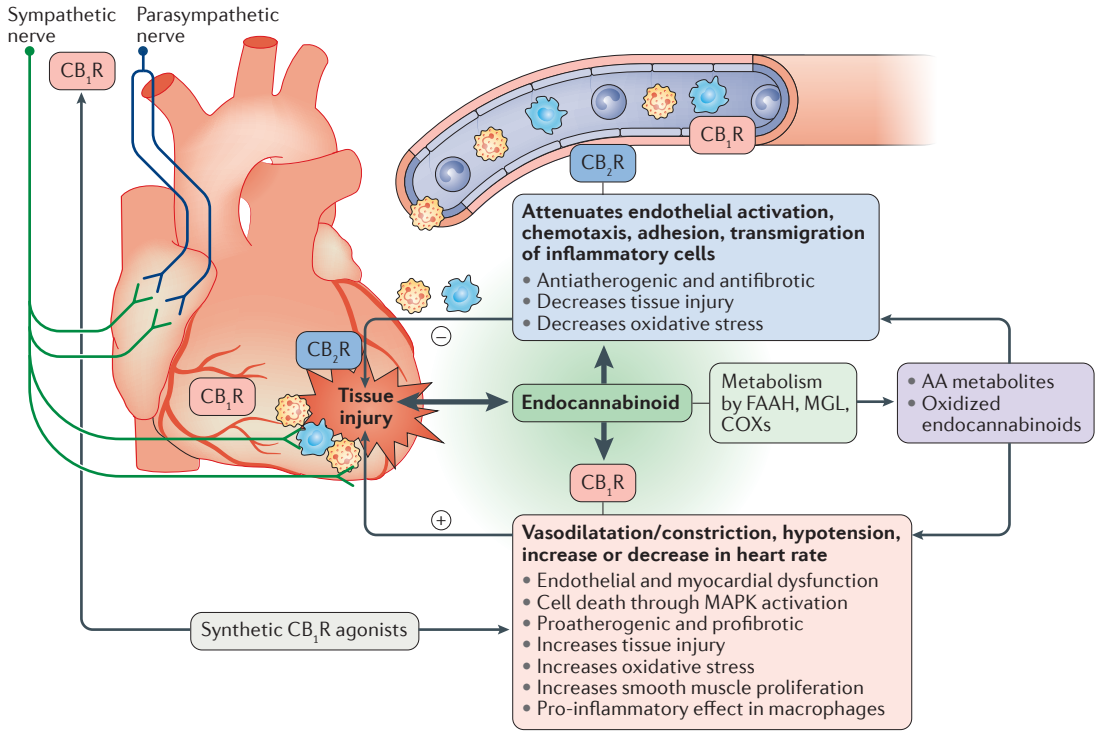

Figure 1 | **Pathophysiological effects of the endocannabinoid system in health and disease.** Endocannabinoids are overproduced during tissue injury and through cannabinoid receptor 1 (CB_1R) contribute to hypotension and decreased cardiac function associated with various pathologies (such as various forms of shock, cardiomyopathies, and heart failure). Endocannabinoid–CB_1R signalling via p38 and JNK mitogen-activated protein kinase (MAPK) activation and increased reactive oxygen species (ROS) generation also contributes to endothelial and cardiomyocyte cell death and cardiovascular dysfunction. In macrophages, CB_1R signalling promotes inflammatory and ROS signalling and also contributes to the development of vascular inflammation and atherosclerosis. In fibroblasts, CB_1R signalling is profibrotic. CB_1R signalling in central and peripheral nervous systems can also induce stimulation or inhibition of sympathetic and parasympathetic activity (largely dependent on dose, route of administration, and duration of the use of marijuana or synthetic cannabinoids, and on individual sensitivity). By contrast, CB_2R stimulation in immune and activated endothelial cells decreases the acute inflammatory response (chemotaxis, adhesion, and transmigration of inflammatory cells) and consequent oxidative stress, for example associated with acute myocardial infarction, and might exert beneficial effects on cardiomyocytes. Chronic treatment with CB_2R agonists also has antiatherosclerotic and antifibrotic effects in animal models. In contrast to CB_1R stimulation, CB_2R stimulation has no direct cardiovascular effects. Endocannabinoids are rapidly metabolized by fatty-acid amide hydrolase (FAAH), monoglyceride lipase (MGL), cyclooxygenases (COXs), and other enzymes to arachidonic acid (AA), and under particular conditions to various oxidized endocannabinoids. Consequently, under pathological conditions, endocannabinoids might be a substantial source of pro-inflammatory, anti-inflammatory, and vasoactive eicosanoids. The role of endocannabinoids in cardiovascular pathology is complex and might depend on the disease and stage of progression.

with various forms of circulatory (haemorrhagic[73], septic[74], or cardiogenic[55,75]) shock, cardiomyopathies (doxorubicin-induced[43], diabetic[41], or associated with advanced liver cirrhosis[54,76]), and chronic ischaemia-induced heart failure[77], and contribute to acute cardiovascular collapse (hypotension or cardiodepression) via CB_1R signalling (BOX 1). These studies demonstrated that CB_1R antagonists (such as rimonabant) not only markedly improved the pathological haemodynamic alterations when administered acutely[8], but also attenuated cell death, inflammation, and adverse tissue remodelling, and improved metabolic parameters in chronic treatment regimens[41,43,77–80]. Genetic deletion of the AEA-metabolizing enzyme FAAH was associated with increased CB_1R-dependent cardiac dysfunction, inflammation, cell death, and mortality in a doxorubicin-induced cardiomyopathy model[78].

In contrast to the deleterious effects of CB_1R activation, selective CB_2R agonists are cardioprotective in models of myocardial infarction[40,81–83], stroke[84,85], and restenosis[63], which is largely owing to the attenuation of inflammatory responses and of the interaction between activated endothelium and inflammatory cells (chemotaxis, rolling, adhesion, and transmigration) — a subject reviewed extensively previously[10,20,67,86,87].

Box 1 | **Pathological consequences of cannabinoid receptor 1 signalling**

Cardiomyocytes
- p38 and JNK mitogen-activated protein kinases (MAPKs) activation, apoptosis
- ERK1/2 activation and cardiac hypertrophy?
- Increased generation of reactive oxygen species
- Decreased contractility
- Decreased mitochondrial biogenesis?

Endothelium
- p38 and JNK MAPKs activation, apoptosis
- Pro-inflammatory response (nuclear factor-κB activation and increased expression of adhesion molecules)
- Chronic endothelial dysfunction
- Acute endothelial-dependent relaxation in particular vessels (uncertain whether this effect is irreversible, causing initial release and subsequent depletion of nitric oxide)

Vascular smooth muscle
- Vascular smooth muscle proliferation and migration, and neointima proliferation (Rac, ERK1/2-dependent?)
- Type 1 angiotensin II receptor–NADPH oxidase-dependent generation of reactive oxygen species and vascular dysfunction

Fibroblasts and myofibroblasts
- Profibrotic effect (enhanced transforming growth factor-β signalling? Secondary consequence of oxidative stress and pro-inflammatory response?)

Macrophages
- Generation of reactive oxygen species, p38 MAPK-dependent pro-inflammatory response (tumour necrosis factor-α, IL-1β, and C-C motif chemokine 2 secretion)
- NLRP3 inflammasome activation
- Accumulation of oxidized LDL
- Macrophage chemotaxis

Adipocytes
- Decreased adiponectin secretion
- Enhanced lipogenesis and decreased lipolysis
- Decreased mitochondrial biogenesis
- Promotion of differentiation (increased cell size)
- Decreased insulin sensitivity

Atherosclerosis and stroke. A number of reports have demonstrated that cannabinoids and their endogenous counterparts can modulate plaque development in experimental models of atherosclerosis. THC at low doses was found to have antiatherosclerotic effects by reducing pro-inflammatory cytokine production and macrophage migration, thereby leading to reduced plaque development[88]. Similar effects were observed with the synthetic cannabinoid WIN55212-2 (REFS 89,90). In these studies, the antiatherogenic effect was inhibited by CB_2R antagonism, suggesting an atheroprotective role for CB_2R signalling[88–90]. Accordingly, the deletion of *Cnr2* in mice with an atherosclerosis-prone background ($Apoe^{-/-}$) or LDL-receptor deficiency ($Ldlr^{-/-}$) resulted in higher plaque content of macrophages[91–93], lipids[93], smooth muscle cells, and collagen[91]. *In vitro*, reduced susceptibility of macrophages from $Cnr2^{-/-}$ mice to undergo oxidized LDL-induced apoptosis was reported[94]. This finding is in accordance with a reduced number of apoptotic cells in plaques of $Cnr2^{-/-}Ldlr^{-/-}$ mice[91]. However, plaque size was not different in CB_2R-deficient $Apoe^{-/-}$ or $Ldlr^{-/-}$ mice compared with controls[91–93], whereas chronic treatment with the CB_2R agonist JWH133 reduced atherosclerotic plaque development in $Apoe^{-/-}$ mice[92]. Other investigators found no anti-inflammatory effects of JWH133 in $Ldlr^{-/-}$ mice[93]. Overall, these findings support the notion that pharmacological or endogenous stimulation of CB_2R inhibits atherosclerotic plaque development and inflammation.

This notion is in contrast to the suggested proatherogenic role of CB_1R[95]. CB_1R blockade substantially reduced plaque development in $Ldlr^{-/-}$ mice, accompanied by reductions in food intake, weight gain, and cholesterol levels[96]. Further experiments suggest that CB_1R blockade has antiatherogenic effects independent of reduced weight gain and, at least at lower doses, independent of changes in plasma cholesterol levels[96]. Reduced pro-inflammatory cytokine expression in macrophages might explain, at least in part, the inhibitory effect of CB_1R antagonism on plaque development in experimental atherosclerosis[96,97]. Furthermore, endogenous CB_1R activation decreases cholesterol transporter ATP-binding cassette subfamily A member 1 (ABCA1) expression in macrophages, which is not only crucial for cellular cholesterol clearance[98], but is also involved in suppressing haematopoietic stem cell proliferation[99]. Decreased expression of ABCA1 enhances leukocytosis in hypercholesterolaemic mice, which triggers atherogenesis[100]. In another study, chronic rimonabant treatment did not affect plaque size and composition in $Apoe^{-/-}$ mice, but improved endothelium-dependent vasodilatation in isolated aortas, together with decreased expression of type 1 angiotensin II receptor, activity of NADPH oxidase, and production of reactive oxygen species[101]. In accordance with a pro-inflammatory role of CB_1R in atherosclerosis, CB_1R expression is higher in coronary artery plaques from patients with unstable versus stable angina[97].

Other studies focused on endocannabinoid metabolic pathways to clarify the contribution of endocannabinoids to atherosclerosis. *Faah*$^{-/-}$ mice have elevated levels of anandamide and related *N*-acylethanolamines sharing the same metabolic pathway. Genetic FAAH deficiency on the *Apoe*$^{-/-}$ background inhibited plaque growth, but despite smaller size, these plaques had a higher neutrophil content and increased expression of the plaque-destabilizing enzyme matrix metalloptroteinase (MMP) 9, but fewer smooth muscle cells[102]. This change might be related to enhanced recruitment of neutrophils into the plaque, as shown by live imaging of carotid arteries under hypercholesterolaemic conditions[102]. In support of these findings, treatment of *Apoe*$^{-/-}$ mice with an FAAH inhibitor resulted in increased plaque neutrophil content and MMP9 expression, but reduced collagen content[103]. These findings suggest that targeting FAAH might modulate plaque composition towards a more unstable phenotype. Montecucco and colleagues reported elevated 2-AG levels in advanced atherosclerotic plaques of the aortas of *Apoe*$^{-/-}$ mice fed a high cholesterol diet, suggesting a potential role of 2-AG in promoting atherosclerosis[104]. In another study, myeloid-specific deletion of sn1-specific diacylglycerol lipase, a key biosynthetic enzyme of 2-AG, inhibited atherogenesis in *Apoe*$^{-/-}$ mice, suggesting that 2-AG generated in myeloid cells might promote vascular inflammation and atherogenesis[105].

Several earlier studies found beneficial effects of non-selective CB_1R agonists in rodent models of stroke, but these protective effects were subsequently attributed to CB_1R-mediated hypothermia, which does not occur in humans, and protective effects of CB_1R antagonists were also described in the same models[12,67]. Several studies investigating the role of CB_2R in stroke found that CB_2R agonists decreased endothelial cell activation, attachment of inflammatory cells to the activated endothelium, rolling, transmigration, and consequent tissue inflammation and injury[10,67].

Clinical studies

CB_1R antagonists in obesity. The ECS has an important role in the peripheral and central regulation of energy homeostasis as well as lipid and glucose metabolism, and patients with metabolic abnormalities have an overactivity of this system[106–108]. Patients with metabolic disorders such as obesity, dyslipidaemia, and diabetes mellitus have an increased risk of developing cardiovascular disease[109]. In this context, clinical studies that have been conducted with the CB_1R antagonist/inverse agonist rimonabant are of particular interest not only because of its beneficial effects on visceral obesity, but also because of improvements in related cardiometabolic risk factors[95]. In large-scale, multicentre, phase III trials conducted in the early 2000s, rimonabant was beneficial in causing weight loss; improving HDL-cholesterol, triglyceride, fasting glucose, and insulin levels; decreasing insulin resistance, and reducing the prevalence of metabolic syndrome[110–116]. On the basis of these promising findings, the ADAGIO-Lipids trial[111] was designed to study the effect of rimonabant on HDL-cholesterol and triglyceride levels as primary end points in obese patients with atherogenic dyslipidaemia. Secondary end points included changes in visceral and liver fat, which were measured using CT. Rimonabant significantly improved the primary end points and other circulating lipid markers, as well as C-reactive protein and adiponectin levels. In addition, a significant loss of visceral fat and mobilization of liver fat in individuals treated with rimonabant was reported, suggesting a beneficial effect on atherosclerosis in patients with dyslipidaemia and excess visceral adiposity and liver fat.

Subsequent clinical studies with rimonabant in patients with obesity specifically focused on primary cardiovascular end points[117–119]. The aim of the STRADIVARIUS trial[117] was to investigate whether rimonabant reduces coronary atherosclerosis in patients with abdominal obesity. The primary end point was the change in percent atheroma volume after 18 months of 20 mg rimonabant daily, monitored using intravascular ultrasonography. Disappointingly, the study showed no improvement in the primary end point, although the secondary end point (normalized total atheroma volume) was significantly decreased[117]. Concerns were raised about high rates of adverse neuropsychiatric events in the rimonabant treatment group[120]. Similarly, the AUDITOR trial[119] found no significant effect of rimonabant on the primary end point of quantitative progression of atherosclerosis, as assessed by noninvasive ultrasonography measurement of carotid artery intima–media thickness. Despite significant reduction in body weight and waist circumference, and increased HDL-cholesterol levels in patients receiving rimonabant in both the STRADIVARIUS and AUDITOR trials, these changes were apparently insufficient to affect progression of atherosclerosis. The CRESCENDO trial[118] was designed to investigate whether rimonabant reduces the risk of myocardial infarction, stroke, or death as a result of acute cardiovascular events in patients with obesity at increased cardiovascular risk. Owing to safety concerns related to increased incidence of psychiatric disorders (depression, anxiety, and suicide) in patients receiving rimonabant, the drug was suspended in November 2008 and finally withdrawn from the market in Europe in January 2009; rimonabant was never approved in the USA for similar reasons[121]. Despite the premature discontinuation of the CRESCENDO trial[118], data from >9,000 individuals in both the rimonabant and placebo groups were collected with a mean follow-up of 13.8 months, and revealed no difference in the primary end points of myocardial infarction, stroke, and survival. Although the numbers of successful suicide attempts in the placebo and treatment groups (one versus four) were probably clinically irrelevant, the study was prematurely terminated.

Endocannabinoid–CB_1R signalling and cardiovascular risk. Plasma levels of AEA and 2-AG in individuals with obesity were positively correlated with coronary circulatory dysfunction[122] and coronary endothelial dysfunction[123], raising the possibility of using plasma endocannabinoid levels as biomarkers of cardiovascular risk in obesity. Humans and mice with severe obesity also had increased myocardial CB_1R levels determined by PET imaging and/or absolute quantification using

digital droplet polymerase chain reaction[124]. CB_1R was upregulated in epicardial fat from human ischaemic hearts[125] and in atherosclerotic plaques of patients with unstable angina[97].

Genetic studies. Association studies of genetic polymorphisms with complex diseases help to clarify whether pathogenic factors identified in animal disease models might be relevant for human pathophysiology, but do not prove a causal relationship. Several polymorphisms in genes encoding proteins involved in the ECS have been associated with abnormal lipid homeostasis and other cardiometabolic risk factors[126–130], suggesting that genetic variations affecting endocannabinoid signalling might predispose to cardiovascular disease.

In particular, genetic variations in the gene encoding the CB_1R, *CNR1*, and its promoter have been linked to abnormal HDL-cholesterol levels[126,128–130]. The association between dyslipidaemia and *CNR1* gene variations was in part independent of BMI, as shown in a family cohort study (the TOPS study[126]) using six representative nucleotide polymorphisms (tagSNPs) and haplotype-based association analysis. The identified haplotype H4 associated with higher BMI, insulin resistance, and dyslipidaemia contains a unique SNP within the *CNR1* promoter which is directly associated with HDL-cholesterol levels. A second promoter SNP identified in the same family cohort study is associated with triglyceride and total cholesterol levels, but not HDL-cholesterol levels. A subsequent study further characterized the relationship between 22 tagSNPs in the *CNR1* gene and dyslipidaemia in individuals with very severe obesity (BMI >40 kg/m^2)[128]. In this study, a genetic variation (the H3 haplotype) was described that protects against obesity-related dyslipidaemia, namely a decrease in HDL-cholesterol level, which usually accompanies weight gain. However, the causal variants in this region responsible for the association were unidentified. Of note, there are sex-specific differences in the relationship between *CNR1* variations and HDL-cholesterol response to changes in dietary fat intake[130]. In 2013, rs806371 was identified as a causal variant in the *CNR1* promoter that links CB_1R expression to HDL-cholesterol level[129]. Functional *in vitro* experiments confirmed that rs806371 enhances DNA-protein binding and reduces *CNR1* promoter activity.

Moreover, SNPs in the *FAAH* gene have been associated with obesity[131] and obesity-related dyslipidaemia[127]. Again using the TOPS obesity family study cohort and five haplotype tagSNPS for the *FAAH* gene, only rs324420, a previously identified coding SNP (C385A) linked with obesity[131], was associated with BMI, and triglyceride and HDL-cholesterol levels, but not insulin sensitivity[127]. The same SNP was associated with worse cardiometabolic profile (weight, adipocytokines levels, TNF-α level, and insulin resistance) in patients with diabetes mellitus[132].

Little is known about associations between *CNR2* gene variants and cardiovascular risk. Only one large-scale study, the German MI family study[133], is available in the literature, in which associations between common *CNR2* polymorphisms and myocardial infarction or cardiovascular risk were analysed. In this study, 13 SNPs essentially within the *CNR2* coding region (that is, the second exon) as well as 5′ and 3′ untranslated regions were analysed, and no significant association between the 13 SNPs and myocardial infarction or traditional cardiovascular risk factors (obesity, hypertension, hypercholesterolaemia, and diabetes mellitus) was found.

Taken together, human genetic studies suggest that the endocannabinoid–CB_1R axis is involved in maintaining lipid homeostasis, and that unbalanced signalling under pathophysiological conditions might trigger dyslipidaemia, thereby promoting atherosclerosis.

Cardiovascular effects of marijuana

The *Cannabis sativa* plant contains >700 different chemical compounds, including 104 unique cannabinoids[134,135]. The principal psychoactive cannabinoid in the plant is THC (a partial agonist of both CB_1R and CB_2R), which underlies most of the CB_1R-mediated adverse effects on the cardiovascular and central nervous systems, whereas cannabidiol is a nonpsychoactive compound, which has also been shown to exert antioxidant and anti-inflammatory properties in various models of tissue injury[134,136]. Similarly to cannabidiol, some other minor constituents of marijuana (discussed below) might also exert beneficial actions.

The cardiovascular effects of marijuana largely depend on several factors, including composition of the plant (the higher the THC content in the plant, the higher the likelihood of CB_1R-mediated cardiovascular effects) and the route of administration (inhalation route can lead to rapid increases in plasma levels with more rapid decline, whereas oromucosal administration of marijuana extracts, such as nabiximols, or pure THC can result in lower, but more stable levels; fat in the food can enhance oral absorption if ingested orally, such as in brownies). Depending on smoking methods and inhalator used, the inhaled amount of toxic burn products as well as THC can vary considerably. Another factor is the quality of the soil — the marijuana plant can accumulate large amounts of heavy metals, pesticides, fungi, and various toxins from the soil.

Beneficial effects

Cannabidiol is the most or second most abundant cannabinoid in the marijuana plant, depending on the variety. Cannabidiol does not stimulate CB_1R and has no psychoactive properties. Initially, it was considered to be devoid of biological activity, until a study by Nobel Laureate Julius Axelrod and his group discovered that both cannabidiol and THC were neuroprotective antioxidants with a potency exceeding that of many known reference antioxidants[137]. Subsequently, a large number of preclinical studies demonstrated potent anti-inflammatory effects of cannabidiol in neuroinflammation, neurodegenetion, colitis, liver and kidney injury, primary diabetes[138–140], and diabetic complications[134,141,142]. On the basis of *in vitro* assays, numerous mechanisms have been proposed to account for the anti-inflammatory and tissue-protective effects of cannabidiol, but these mechanisms have not been validated *in vivo*[134].

Beneficial effects of cannabidiol were demonstrated in animal models of myocardial infarction[143,144], stroke[145–151], doxorubicin-induced and diabetic cardiomyopathies[152–154], and autoimmune myocarditis[155]. In a type 1 diabetic cardiomyopathy model, chronic cannabidiol treatment attenuated diabetes-induced myocardial dysfunction, cardiac fibrosis, oxidative and nitrative stress, inflammation, cell death, and interrelated signalling pathways[154]. Moreover, cannabidiol in human primary cardiomyocytes attenuated the high glucose-induced nuclear factor-κB activation, generation of reactive oxygen species, and cell death[154]. In doxorubicin-induced cardiomyopathy, cannabidiol markedly improved cardiac dysfunction, oxidative and nitrative stress, and cell death, and reversed the impaired cardiac mitochondrial function and biogenesis[152]. Chronic cannabidiol treatment in a mouse model of autoimmune myocarditis improved cardiac dysfunction, decreased the $CD3^+$ and $CD4^+$ cell-mediated inflammatory response and injury, and myocardial fibrosis[155]. These results, coupled with the known safety of cannabidiol in humans[156] and its efficacy for treatment of rare forms of treatment-resistant childhood epilepsy (Dravet syndrome and Lennox–Gastaut syndrome)[157–159], might open a new avenue to test cannabidiol in multiple cardiovascular disorders[159]. Preliminary results of clinical trials with cannabidiol in graft-versus-host disease are also encouraging[160].

Tetrahydrocannabivarin is another constituent of marijuana with potential medical benefits. Tetrahydrocannabivarin was reported to be a CB_1R antagonist at a low dose, but a CB_1R agonist at a high dose, as well as a CB_2R partial agonist, and produced relevant beneficial metabolic effects in preclinical disease models of obesity and steatohepatitis[161,162]. Tetrahydrocannabivarin was safe in a phase II clinical study[163,164]. Various other minor cannabinoids and terpenoids contained in cannabis (such as β-caryophyllene) can also exert important biological effects, which could be exploited for therapeutic benefit[165].

Of note, THC is not only a fairly weak partial CB_1R agonist, but also a CB_2R agonist, and might have additional anti-inflammatory and antioxidant effects, independent of CB_2R. Therefore, at very low doses THC might not elicit substantial CB_1R activation, which underlies the majority of its cardiovascular adverse effects, and might even exert some anti-inflammatory effects. For example, as previously mentioned, low doses of THC attenuated atherosclerosis and vascular inflammation in mice in a CB_2R-dependent manner[88]. By contrast, at higher doses, THC was ineffective, possibly because of pro-inflammatory effects caused by CB_1R activation.

Interestingly, Waldman and colleagues described that a single, ultralow dose (three to four orders of magnitude lower than the conventional doses) of THC given before myocardial infarction in mice exerted cardioprotective effects[166]. The involvement of cannabinoid receptors in the cardioprotection observed was not evaluated[166]. Chronic THC administration was previously reported to downregulate CB_1R dose-dependently in particular neurons of the brain[167]. A subsequent study surprisingly found that chronic administration of THC at a low dose improved cognitive function in ageing, but not young, mice via CB_1R-dependent mechanisms[168]. In young to middle-aged humans, cannabis use dose-dependently impairs learning and memory, and can also trigger psychosis in susceptible individuals[17]. With the markedly increased use of cannabis among the older US population[169], further research is warranted to investigate the cognitive and cardiovascular effects of marijuana in the ageing population.

Interestingly, an epidemiological study using a quantile regression approach based on National Health and Nutrition Examination Surveys (NHANES 2005–2010, encompassing participants aged 20–59 years; $n = 1{,}115$ recently active cannabis smokers and 8,041 nonsmokers, identified via confidential audio computer-assisted self-interviews) concluded that cannabis smoking might be associated with reduced serum levels of C-reactive protein[170]. Analysis of NHANES 1988–1994 data also indicated that marijuana use was independently associated with a lower prevalence of diabetes mellitus[171]. Another study found no changes in insulin sensitivity and glucose tolerance in chronic marijuana smokers[172]. These findings are in contrast to the THC-induced acute insulin resistance[173] and glucose intolerance in drug-naive individuals, and the documented efficacy of chronic CB_1R antagonism in improving visceral obesity and its complications, including insulin resistance and type 2 diabetes in both humans and experimental animals[174]. This apparent contradiction might be reconciled by the known capacity of THC to cause profound and long-lasting downregulation of CB_1R at doses producing plasma levels similar to those in heavy users[106,108,110–113,115,117,167,175].

Further clinical studies are clearly needed to determine the effects of acute and chronic marijuana use on inflammation and glycaemic control. One major limitation of epidemiological studies on marijuana is the uncertainty about the composition of the marijuana used by the surveyed individuals (THC content, THC–cannabidiol ratio) that might result in diverse, even opposing, cardiovascular consequences.

Adverse effects

Heart rate and blood pressure. Depending on the dose, frequency, route of administration, and duration of use, marijuana or its active constituent THC can have diverse effects on heart rate and blood pressure, both in experimental animals and in humans[8,17]. The most common acute effect in healthy volunteers is increase in heart rate and decrease in blood pressure, depending on dose, route of administration, and the individual. The synthetic THC (dronabinol or Marinol; AbbVie, USA) and its analogue nabilone (Cesamet; Meda Pharmaceuticals, USA), approved by the FDA for chemotherapy-induced nausea and vomiting and stimulation of appetite in AIDS-induced cachexia, and also approved in Canada for management of chronic pain, similarly elicited dose-dependent increases in heart rate and decreases in blood pressure[176].

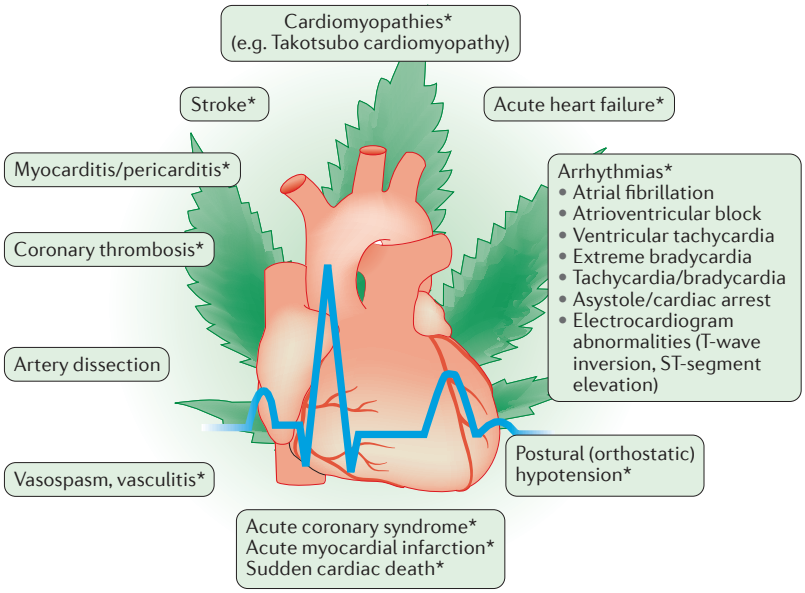

Figure 2 | **Reported cardiovascular adverse consequences of recreational marijuana and synthetic cannabinoid use.** *Adverse effects that were reported for synthetic cannabinoids; note almost complete overlap with the adverse effects of marijuana.

Several studies investigated the development of tolerance to the psychoactive and cardiovascular effects of THC or marijuana and their dependence on CB_1R. Gorelick and colleagues reported the development of tolerance to the subjective intoxication, but not to the tachycardia and hypotension induced by a high oral dose of synthetic THC taken daily for 6–13 days by healthy marijuana users[177]. All these effects or the similar effects of smoked marijuana were antagonized by single or multiple doses of rimonabant[178–180]. Similarly, the central nervous system and cardiac effects of inhaled THC were inhibited by surinabant, another selective CB_1R antagonist[181].

The demonstration of an important role for peripheral CB_1R in pain[182] was the rationale for the development of peripherally-restricted CB_1R agonists as analgesics devoid of psychoactive effects, such as the peripherally restricted, orally active mixed CB_1R/CB_2R agonists AZD1940 and AZD1704, introduced by AstraZeneca for the treatment of pain[183,184]. However, in clinical trials in healthy volunteers, peripheral CB_1R agonism was associated with adverse cardiovascular and metabolic effects, including weight gain, hypotension, heart rate abnormalities, and mild hepatotoxicity, which ultimately led to the termination of the study and dismissal of peripheral CB_1R as a potential therapeutic target for pain[183,184].

Vascular disease and myocardial infarction. The studies described above, using fairly low doses of THC or marijuana with low THC content in healthy volunteers, provided proof that, similar to their effects in rodents, the acute cardiovascular effects of marijuana and THC are indeed mediated by CB_1R in the cardiovascular system. In parallel with the dramatic increase in the THC content of marijuana, a growing number of case reports and clinical studies associate recreational marijuana use with adverse cardiovascular consequences ranging from acute coronary syndrome[185–188]; coronary thrombosis[189]; myocardial infarction[185,190–196]; cardiomyopathies[197–199]; heart failure[200]; stroke[185,200]; vasospasm, vascular inflammation, or artery dissection[185,201]; arrhythmias (atrial fibrillation[202–204], atrioventricular block[205,206], ventricular tachycardia or fibrillation[207,208], asystole[209]), and sudden death[210] (FIG. 2). Mittleman and colleagues assessed the risk of acute myocardial infarction in 124 marijuana smokers (37 were smoking marijuana within 24 h of myocardial infarction) in a cohort of 3,882 patients in the MI Onset Study[191]. Marijuana smokers had a 4.8-fold higher risk of developing acute myocardial infarction during the first hour of exposure, with a rapidly declining risk thereafter[191]. A longitudinal, prospective follow-up study involving 1,913 adults (52 reported marijuana use during the previous year) hospitalized with myocardial infarction at 45 US hospitals between 1989 and 1994 with a median follow-up of 3.8 years, evaluated the effect of marijuana on mortality after acute myocardial infarction[196]. Cannabis use less than once per week was associated with 2.5-fold increased risk of dying[196]. This risk was further exacerbated by more frequent marijuana use, yielding up to fourfold elevated risk[196]. The investigators concluded that marijuana use might particularly increase the risk of infarction in susceptible individuals with coronary heart disease[196]. The study was also followed up 5 years later to evaluate the consequences of marijuana use on long-term mortality among survivors of acute myocardial infarction[192]. During follow-up (up to 18 years), 519 patients died, including 22 of the 109 reported marijuana users[192]. Habitual marijuana use was associated with a nonsignificant 29% increase in mortality over the ensuing 18 years[192].

Jouanjus and colleagues analysed all cardiovascular complications related to cannabis use based on reports from 2006 to 2010 in the French Addictovigilance Network[185]. They found that in 35 out of 1,979 cannabis-related reports, 30 men with an average age of 34 years had cardiovascular complications, including 20 cases of acute coronary syndrome, 10 cases of peripheral vascular complications (lower limb or juvenile arteriopathies and Buerger-like diseases), and three cases of cerebral complications (acute cerebral angiopathy, transient cortical blindness, and cerebral artery vasospasm). The results of this study were striking not only because they involved fairly young individuals with no prior cardiovascular disease, but also because 25.6% of the affected patients (nine individuals) died from the cardiovascular complications of cannabis use[185]. An increasing number of case reports describing severe cardiovascular complications of marijuana use in young individuals (including previously unreported fatalities)[185–187,189,190,198,201,203,204,209,210] support the conclusions of the French study, thus raising serious concerns about the cardiovascular safety of marijuana use. Reis and colleagues investigated the effects of marijuana on the development of incident cardiovascular and cerebrovascular outcomes based on data from the CARDIA study[211] in 4,286 adults aged 18–30 years in 1985–1986 and who reported a history of marijuana use. The researchers found that neither

recent use of marijuana nor cumulative lifetime use was associated with increased incidence of cardiovascular disease[211]. By contrast, Draz and colleagues conducted a cross-sectional study performed on 138 male patients (23 positive for cannabis) aged <40 years with acute myocardial infarction, and concluded that cannabis smoking was a potential risk factor for the development of cardiac ischaemia[187]. A retrospective study presented at the AHA Scientific Sessions in 2016 suggested that active marijuana use doubles the risk of Takotsubo cardiomyopathy, especially in young men[199]. Kalla and colleagues performed the most comprehensive analysis of health records to date, based on the Nationwide Inpatient Sample 2009–2010 database of individuals aged 18–55 years with a history of cannabis use (presented at the ACC Scientific Sessions in 2017). Demographics, risk factors, and cardiovascular event rates were collected on these patients and compared with general population data. They identified 316,397 (1.5%) cannabis users and 20,499,215 (98.5%) nonusers in the database, and found that the incident of cerebrovascular accidents, heart failure, coronary artery disease, sudden cardiac death, and hypertension were significantly higher in patients with cannabis use. After multivariate regression analysis adjusting for age, sex, diabetes, hypertension, coronary artery disease, and tobacco and alcohol use, cannabis use remained an independent predictor of both heart failure and cerebrovascular accidents[200].

Stroke. Several studies have investigated the association between stroke and marijuana use. Falkstedt and colleagues used a population-based cohort of 49,321 Swedish men, born between 1949 and 1951, who were in military service between the ages of 18 and 20 years, to investigate the association between cannabis use and early-onset stroke, when accounting for the use of tobacco and alcohol[212]. Although they found an almost doubled risk of ischaemic stroke in those with cannabis use >50 times, this risk was no longer significant when adjusted for tobacco usage, which by itself showed dose-dependent association with stroke[212]. Di Napoli and colleagues analysed an international, multicentre, observational database of 725 patients with spontaneous ischaemic stroke, 8.6% of whom were positive for cannabinoids, and found no relationship between cannabis use and specific ischaemic stroke characteristics[213]. Surprisingly, cannabinoid use was associated with milder ischaemic stroke presentation and less disability at discharge from hospital[213].

Rumalia and colleagues investigated the relationship between marijuana use and hospitalization for acute ischaemic stroke[214] and for aneurysmal subarachnoid haemorrhage[215] using the Nationwide Inpatient Sample from 2004 to 2011. They found that among younger adults (aged 25–34 years), recreational marijuana use was independently associated with a 17% increased likelihood of hospitalization for acute ischaemic stroke and with an 18% increased likelihood of hospitalization for aneurysmal subarachnoid haemorrhage. Behrouz and colleagues evaluated the relationship between cannabis use and outcomes in patients with aneurysmal subarachnoid haemorrhage, analysing the records of 108 patients, 25.9% of whom were positive for urine cannabinoids. Their preliminary data implied an independent association between cannabis use (positive urine) and delayed cerebral ischaemia and possibly poor outcome in patients with subarachnoid haemorrhage[216]. Hemachandra and colleagues examined the risk of nonfatal stroke or transient ischaemic attack among cannabis users in the general Australian community[217]. In a cohort of 153 patients with stroke or transient ischaemic attack, individuals who had used cannabis in the past year had a 3.3-fold higher event rate than nonusers after adjusting for age, or a 2.3-fold higher rate than nonusers after further adjustment for covariates related to stroke, including tobacco smoking. This increased risk was specific to participants who used cannabis weekly or more often[217], suggesting that heavy cannabis users in the general community have a higher rate of nonfatal stroke or transient ischaemic attack than low-frequency users or nonusers of cannabis[217]. An analysis of 29 studies suggesting an association between exposure to cannabis-based products and cardiovascular disease concluded that the evidence is stronger for an association with ischaemic strokes than for any other cardiovascular diseases, although evidence indicates that cannabis use can have negative cardiovascular consequences, particularly at high doses[218].

Wolff and Jouanjus analysed 98 cases of cannabinoid-related strokes (85 of which followed marijuana use and 13 of which followed synthetic cannabinoid use) in young adults (mean age 32.3 years; 73% men)[219]. Overall, 81% of patients with cannabinoid-related strokes were chronic cannabis users and in two-thirds of the patients, cannabis was smoked with tobacco. The researchers found that 87% of the reported strokes were ischaemic and/or a transient ischaemic attack, and 8.1% were haemorrhagic[219]. Despite a favourable outcome in almost half of the patients, five (5.1%) died[219]. The investigators noted a strong temporal correlation in the majority of the reports between cannabinoid use (natural or synthetic) and the occurrence of stroke[219]. They also speculated that enhanced generation of reactive oxygen species induced by cannabinoids, and consequent oxidative stress (a known mechanism of stroke in humans) might be an underlying pathological mechanism[219]. This hypothesis is in agreement with the previously described increased, CB_1R-dependent generation of reactive oxygen species in human and mouse cardiomyocytes, coronary artery endothelial and vascular smooth muscle cells, macrophages, and podocytes[41,42,47,101,220,221] (BOX 1). Increased superoxide in the vasculature immediately reacts with nitric oxide to form a reactive oxidant and nitrating species peroxynitrite via diffusion-limited reaction, which also uncouples nitric oxide synthases[222]. The resulting rapidly decreased nitric oxide bioavailability can lead to endothelial dysfunction, functional hypoxia, and/or vasospasm[222]. In susceptible individuals, the cannabinoid-induced marked CB_1R-mediated vasodilatation and drop in total peripheral resistance with consequent profound and prolonged hypotension might also precipitate ischaemic stroke.

A retrospective follow-up study of 1,213 NHANES participants (21% of whom used marijuana only, 20% marijuana and cigarettes, and 16% marijuana and were past smokers) investigated the associations between marijuana use (average duration 11.5 years) and death from hypertension, heart disease, or cerebrovascular disease, controlling for cigarette use and demographic variables including sex, age, and ethnicity[223]. Surprisingly, the investigators found that marijuana users had a 3.42-fold increased risk of death from hypertension, with a 1.04-fold greater risk for each year of use. However, no association between marijuana use and death from heart disease or cerebrovascular disease was established.

Effects of marijuana smoke. Marijuana smoke (like tobacco smoke) is harmful and can exert adverse cardiovascular effects independent from cannabinoid receptors. For example, one study demonstrated that 1 min of exposure to marijuana second-hand smoke impaired femoral artery flow-mediated dilatation to a similar extent as caused by equal concentrations of tobacco second-hand smoke, but recovery was considerably slower for marijuana[224]. The investigators found that exposure to marijuana second-hand smoke directly caused cannabinoid-independent vasodilatation that subsided within 25 min, whereas flow-mediated dilatation remained impaired for ≥90 min in rats. Impairment occurred even when marijuana lacked cannabinoids, suggesting that impairment of flow-mediated vasodilatation does not require cannabinoids or nicotine[224]. As with tobacco smoke, marijuana can also increase carboxyhaemoglobin levels, independent from cannabinoid receptors, resulting in decreased oxygen-carrying capacity[191]. The increased heart rate after acute marijuana smoking peaked 10–30 min after the beginning of smoke exposure, and probably resulted from compensatory sympathetic activation, in response to the THC-induced, CB_1R-mediated decrease in total peripheral resistance and blood pressure. Of note, these acute cardiovascular effects of marijuana or THC in humans were almost completely prevented or reversed by two different CB_1R antagonists (as discussed earlier). Nevertheless, in susceptible individuals, acute marijuana smoking might be associated with a transient increase in myocardial oxygen demand paralleled by a decrease in oxygen supply[191], promoting a situation favouring the development of myocardial ischaemia and infarction, particularly if the cardiac reserve capacity is decreased.

Mortality. In the absence of large-scale, long-term, controlled studies (known marijuana composition, route, dose, and frequency of administration) with repeated measures of marijuana use, one cannot draw a firm conclusion on the long-term effect of cannabis use on cardiovascular mortality. However, marijuana (presumably with increased THC content) can induce dangerous, often life-threatening cardiovascular effects, probably mediated by the activation of CB_1R. The use of synthetic 'designer' CB_1R agonist mixtures (spice variants) with greatly increased potency at CB_1R compared with THC, is likely to increase the levels of cardiovascular morbidity.

Synthetic cannabinoids

These 'seemingly innocent, herbal products', many of which are not controlled and are easily available online or in grocery stores, could be far more dangerous than THC in marijuana used for recreational purpose[225–239]. As with marijuana, the route of administration of synthetic cannabinoids can importantly influence their biological, including cardiovascular, effects.

Mir and colleagues described three cases of acute myocardial infarction in boys aged 16 years after smoking K2 or spice, who presented in the emergency department 1 day after K2 use complaining about chest pain. Myocardial infarction was diagnosed by electrocardiogram and myocardial enzymes[225]. At that time, K2 or spice contained mainly JWH-018, JWH-073, and similar derivatives[225]. Subsequent cases of cardiac arrest, myocardial infarction, and fatal toxicities were also described after K2 use in young teenagers or young adults[226–230]. Orsini and colleagues described a case of acute hypoxaemic/hypercapnic respiratory failure as a consequence of acute congestive heart failure developed from myocardial stunning, which was the result of myocardial infarction without ST-segment elevation[231]. Two cases of synthetic cannabinoid 'bonsai'-induced cardiovascular adverse effects were described in individuals aged 16 and 18 years, consistent with AMI[232].

Obafemi and colleagues reported on 11 symptomatic patients aged 20–57 years, who unknowingly ingested brownies laced with analytically confirmed synthetic CB_1R agonists, including AM-2201 (REF. 233). Neuropsychiatric and cardiovascular symptoms were predominant (memory impairment, blurring of vision, facial numbness, increased heart rate, and/or increased blood pressure). All patients were discharged within 10 h in a stable condition[233]. A retrospective analysis of 22 patients aged 12–25 years, presenting to emergency departments with analytically confirmed intake of JWH-210 from a poison centre database from March 2011 to June 2014, evaluated the most common cardiovascular and central nervous system adverse consequences, which ranged from restlessness, agitation, tachycardia, nausea, somnolence, and hypertension, to syncope, T-wave inversion on the electrocardiogram, and bradycardia[234]. Of note, in 80% of the patients, the adverse changes in heart rate and blood pressure were accompanied by electrocardiogram abnormalities[234]. Hill and colleagues described seven patients who were hospitalized because of synthetic cannabinoid MDMB–CHMICA-related toxicity in England, featuring respiratory, metabolic, or mixed acidosis; reduced level of consciousness; tachycardia or bradycardia; convulsions; and agitation[235].

Monte and colleagues aimed to determine the clinical characteristics of patients abusing synthetic cannabinoids in a multicentre analysis of a prospective cohort of patients between 2010 and 2015 who presented for medical care after inhalation of synthetic cannabinoids. The researchers identified 353 cases out of 39,925 hospital visits that involved synthetic cannabinoid-related toxicity. The most common symptoms were agitation, delirium or psychosis, and increased or decreased heart rate often reaching <50 bpm (REF. 236). In some patients,

seizures also developed[236]. The investigators concluded that synthetic cannabinoids were associated with severe central nervous system and cardiovascular effects[236].

The Emergency Department at Lincoln Medical Center, New York, USA, noted changes in symptoms in K2 abusers during an outbreak in the summer of 2015. These changes included marked bradycardia and hypotension while maintaining global neurological function[237]. Alarmingly, synthetic cannabinoid-related mortality is also rising with the introduction of extremely potent variants of spice in 2014–2015, which also caused cluster toxicities[6,230].

FIGURE 3 shows the dramatic cardiovascular effects after intravenous administration to rats of the potent synthetic cannabinoid CB_1R agonist HU210, which is also used in spice variants. HU210 caused a rapid decrease in cardiac performance (left ventricular pressure, left ventricular contractility, and shift of pressure–volume loops to the right) and blood pressure, which could be almost completely reversed by an acute dose of CB_1R antagonist SR141716 (rimonabant). This finding, coupled with the previously discussed evidence on the rapid reversibility of all cardiovascular effects of THC or marijuana in healthy volunteers, strongly suggests that rimonabant could be repurposed and used as an antidote in cases of acute toxicity caused by marijuana or synthetic cannabinoids.

Synthetic cannabinoids have also been reported to cause severe acute and chronic kidney injury in children and young adults, and the CDC has issued a warning[238,239]. These nephrotoxic effects of synthetic cannabinoids are not surprising given the important role of CB_1R in promoting both glomerular and tubular injury in preclinical models of acute and chronic kidney disorders, in which CB_1R inhibition or deletion has beneficial effects[221,240–243].

Conclusions

Both preclinical and clinical evidence supports the involvement of the endocannabinoid–CB_1R system in obesity, metabolic syndrome, and diabetes, and the associated cardiovascular risk (such as abdominal obesity, plasma lipid alterations, hepatic steatosis, and leptin and insulin resistance). This signalling system has also been implicated in the development and progression of various forms of shock, cardiovascular collapse, cardiomyopathies, heart failure, atherosclerosis, and restenosis, where peripherally restricted CB_1R antagonists could be beneficial without causing central nervous system-mediated neuropsychiatric adverse effects, which halted the therapeutic development of globally acting CB_1R antagonists.

Accumulating evidence also supports the development of selective CB_2R agonists for the management of

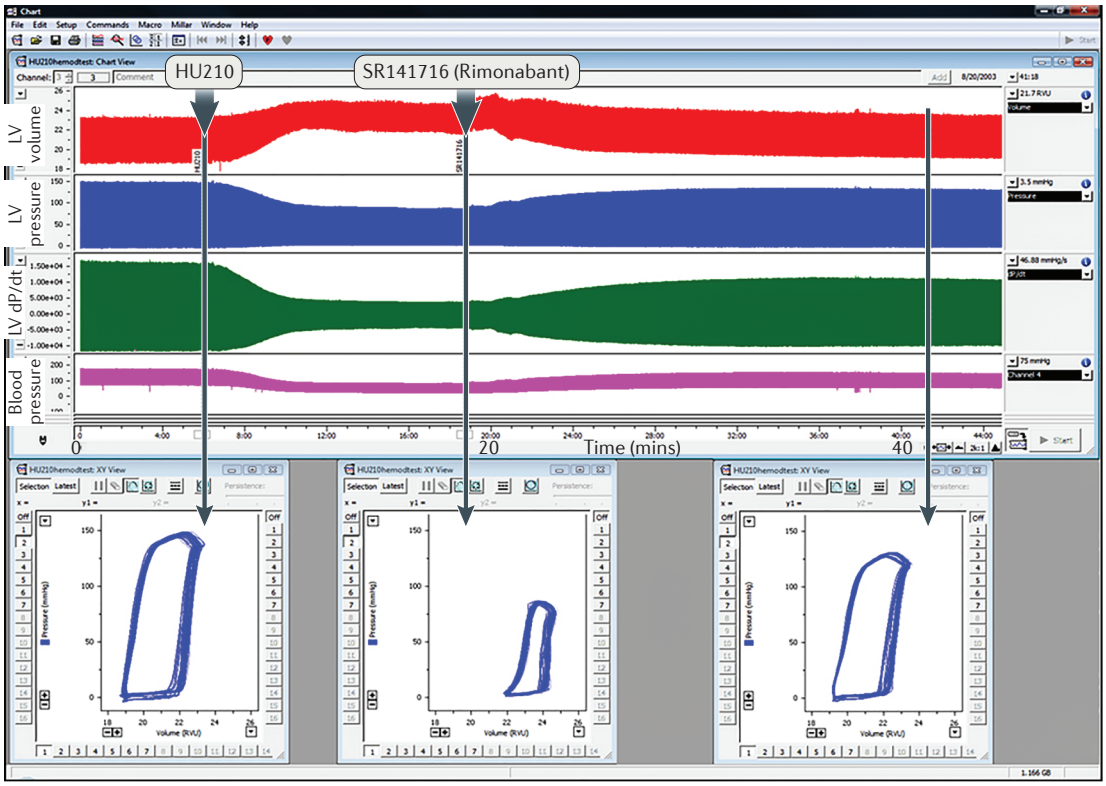

Figure 3 | **Adverse cardiovascular consequences of synthetic cannabinoids.** Cardiovascular effects of potent synthetic cannabinoid receptor 1 (CB_1R) agonist HU210. Intravenous administration of HU210 (0.1 mg/kg) to a rat dramatically decreases left ventricular (LV) pressure (blue trace), LV contractility (+dP/dt; green trace), and blood pressure (purple trace), and shifts pressure–volume loops to the right, indicating decreased cardiac performance. After injection of a CB_1R antagonist, SR141716 (rimonabant; 10 mg/kg), cardiac function and blood pressure largely recover within 20 mins. Reprinted with permission from Pacher, P. *et al.* Measurement of cardiac function using pressure–volume conductance catheter technique in mice and rats. *Nat. Protoc.* **3** (9), 1422–1434 (2008), with permission from Macmillan Publishers Limited.

Table 1 | **Cardiovascular effects of endocannabinoids, marijuana, and synthetic cannabinoids**

Substance	Good	Bad	Ugly
Endocannabinoids	• CB_2R-mediated tissue-protective and anti-inflammatory effects • Potential source of anti-inflammatory and beneficial vasoactive mediators via metabolism to arachidonic acid	• CB_1R-mediated metabolic, cardiovascular, pro-inflammatory, pro-oxidant, and profibrotic effects • Potential source of pro-inflammatory mediators via metabolism to arachidonic acid or oxidation by cyclooxygenase	• Potential source of vasoconstrictor mediators (for example, thromboxane A_2) via metabolism to arachidonic acid or oxidation by cyclooxygenase
Marijuana (partial agonist)	• Low dose of THC in marijuana might exert CB_2R-mediated and unrelated tissue-protective and anti-inflammatory effects • THC is a fairly weak partial CB_1R agonist; therefore, the acute cardiovascular and CNS effects are often mild and reversible • Marijuana can contain various nonpsychoactive constituents that do not activate CB_1R and might exert beneficial anti-inflammatory and antioxidant effects (for example, cannabidiol, tetrahydrocannabivarin, terpenoids, β-caryophyllene)	• THC can exert CB_1R-mediated metabolic, cardiovascular, pro-inflammatory, pro-oxidant, and profibrotic effects (the cardiovascular effects are dose-dependent) • THC exerts CB_1R-mediated psychoactive effects • Marijuana smoke can be as harmful as tobacco smoke • Marijuana can accumulate pesticides and heavy metals	• In rare cases, life-threatening cardiovascular effects can develop (for example, arrhythmias, profound hypotension, myocardial infarction, ischaemic stroke)
Synthetic cannabinoids (for example, spice); commonly a mixture of very potent and efficacious CB_1R agonists (some several hundred times more potent than THC) with long half-lives	NA	NA	• Can induce very severe and fatal cardiovascular, CNS, and kidney complications, also very addictive • Can contain organic solvents (masking mass spectrometry detection) and other unknown drugs

CB_1R, cannabinoid receptor 1; CB_2R, cannabinoid receptor 2; CNS, central nervous system; NA, not applicable; THC, Δ^9-tetrahydrocannabinol.

acute tissue injury associated with inflammation (such as myocardial infarction, stroke, or organ transplantation). Therapeutic targeting of the endocannabinoid-degrading enzymes FAAH and MGL can be a double-edged sword owing to amplification of not only therapeutically desirable, but also adverse endocannabinoid effects, indicating the need for further research.

The clinical indication for marijuana or marijuana-based products (such as extracts, synthetic THC, or analogues: dronabinol, nabilone, and nabiximols) is still very limited and includes chemotherapy-induced nausea and vomiting, and promotion of appetite in wasting disorders such as AIDS or tumour cachexia. Although these indications might be expanded to include various forms of chronic pain, evidence so far suggests that these drugs are not sufficiently effective on objective measures or scales of pain in controlled clinical trials, even though they are effective by many subjective measures.

Despite a dearth of evidence for a substantial cardiovascular risk of marijuana use until the past few years, evidence now indicates an alarming rise in the incidence of severe and sometimes fatal cardiovascular adverse effects, which has paralleled the dramatic increase in the THC content of recreational marijuana as well as the appearance of a variety of synthetic or 'designer' cannabinoids, whose potency and efficacy far exceed those of THC. These warning signs cannot be ignored and have to be further studied to assess their public-health implications.

The efficacy and probable approval of cannabidiol for therapeutic use in treatment-resistant epilepsy is exciting, and might open a new avenue for exploratory clinical trials in other diseases, including diabetes and diabetic complications, graft-versus-host disease, and cardiovascular diseases in which preclinical data support the therapeutic potential of cannabidiol. To this end, limiting or even eliminating THC from cannabis extracts used in the management of such disorders would make sense.

We are in the era of widespread legalization of marijuana for medicinal, and even recreational, use. We can also download hundreds of marijuana-related applications to our phone to pick our favourite marijuana varieties or learn how to start a marijuana business, which is growing into a multibillion industry. The medicinal use of marijuana and its constituents is likely to lead to important therapeutic opportunities to ease human suffering. These opportunities might be risked by ignoring the clear and present danger posed by the spread of marijuana containing high levels of THC, and designer drugs containing superpotent synthetic cannabinoids, which have been linked to severe cardiovascular, kidney, and central nervous system toxicity. Given the clustering of cannabis-related toxicity in multiple states, the repurposing of rimonabant as an antidote for such poisonings should be seriously considered. Physicians should also be very vigilant to recognizing these effects and their underlying cause. TABLE 1 summarizes the effects of endocannabinoids, marijuana, and synthetic cannabinoids relevant to cardiovascular outcomes and pathology. Further research is warranted to inform the regulatory measures that are needed to curb the spread of synthetic cannabinoids and to keep the risk–benefit ratio of the medicinal use of marijuana and related cannabinoids as low as possible.

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