International Journal of Obesity Supplements (2020) 10:14–26
https://doi.org/10.1038/s41367-020-0015-3

REVIEW ARTICLE

Cardiovascular effects of antiobesity drugs: are the new medicines all the same?

Mauro Cataldi[1] · Angelo Cignarelli[2] · Francesco Giallauria[3] · Giovanna Muscogiuri[4] · Luigi Barrea[4] · Silvia Savastano[4] · Annamaria Colao[4] · on behalf of Obesity Programs of nutrition, Education, Research and Assessment (OPERA) Group

Abstract

Waiting for a definite answer from well-designed randomized prospective clinical trials, the impact of the new antiobesity drugs -liraglutide, bupropion/naltrexone, phentermine/topiramate and lorcaserin- on cardiovascular outcomes remains uncertain. What has been learned from previous experience with older medicines is that antiobesity drugs may influence cardiovascular health not only causing weight reduction but also through direct actions on the cardiovascular system. Therefore, in the present review, we examine what is known, mainly from preclinical investigations, about the cardiovascular pharmacology of the new antiobesity medicines with the aim of highlighting potential mechanistic differences. We will show that the two active substances of the bupropion/naltrexone combination both exert beneficial and unwanted cardiovascular effects. Indeed, bupropion exerts anti-inflammatory effects but at the same time it does increase heart rate and blood pressure by potentiating catecholaminergic neurotransmission, whereas naltrexone reduces TLR4-dependent inflammation and has potential protective effects in stroke but also impairs cardiac adaption to ischemia and the beneficial opioid protective effects mediated in the endothelium. On the contrary, with the only exception of a small increase in heat rate, liraglutide only exerts favorable cardiovascular effects by protecting myocardium and brain from ischemic damage, improving heart contractility, lowering blood pressure and reducing atherogenesis. As far as the phentermine/topiramate combination is concerned, no direct cardiovascular beneficial effect is expected for phentermine (as this drug is an amphetamine derivative), whereas topiramate may exert cardioprotective and neuroprotective effects in ischemia and anti-inflammatory and antiatherogenic actions. Finally, lorcaserin, a selective $5HT_{2C}$ receptor agonist, does not seem to exert significant direct effects on the cardiovascular system though at very high concentrations this drug may also interact with other serotonin receptor subtypes and exert unwanted cardiovascular effects. In conclusion, the final effect of the new antiobesity drugs on cardiovascular outcomes will be a balance between possible (but still unproved) beneficial effects of weight loss and "mixed" weight-independent drug-specific effects. Therefore comparative studies will be required to establish which one of the new medicines is more appropriate in patients with specific cardiovascular diseases.

Introduction

The approval of four new antiobesity medicines -liraglutide, bupropion/naltrexone, topiramate/phentermine and lorcaserin- has been enthusiastically welcomed because they

On February 13, 2020, after the present manuscript completed its review process, FDA requested the withdrawal of lorcaserin from the market because of evidence from the CAMELLIA-TIMI 61clinical trial that poteintial risk of cancer could outweigh benefits.

✉ Mauro Cataldi
cataldi@unina.it

[1] Department of Neuroscience, Reproductive Sciences and Dentistry, Division of Pharmacology, Federico II University of Naples, Naples, Italy

[2] Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy

[3] Department of Translational Medical Sciences, Internal Medicine (Metabolic and Cardiac Rehabilitation Unit), Federico II University of Naples, Naples, Italy

[4] Department of Clinical Medicine and Surgery, Unit of Endocrinology, Federico II University Medical School of Naples, Via Sergio Pansini 5, 80131 Naples, Italy

could lower the body weight in patients not responding to diet and physical exercise. Achieving a good control of weight is considered a primary objective of obesity treatment as high BMI values are associated with an increase in all-cause mortality [1] that can be reduced by weight loss [2]. The role of cardiovascular disorders in this scenario is still controversial. In fact, while obesity is associated with a higher prevalence of hypertension and other major cardiovascular risk factors, and coronary heart disease and stroke are among the main causes of death in obese patients [1], there is also some evidence that moderate obesity could, instead, reduce the severity of cardiac failure and coronary artery disease, the so-called "obesity paradox" [3]. Despite the positive results of some studies, the clinical evidence accumulated so far does not show any clear benefit that body weight reduction improves cardiovascular outcomes [4].

When dealing with antiobesity drugs the situation turns out to be even more complicated because these medicines may exert direct effects on the cardiovascular system independent from their anorexigenic activity. The relevance of the problem dramatically emerged with medicines such as sibutramine that was withdrawn from the market because of dangerous effects on the cardiovascular system. The lesson learned was that antiobesity drugs are not necessarily beneficial for cardiovascular health as, in some circumstances, they can also be very dangerous. Therefore, in the present review, we will examine what is known about the cardiovascular pharmacology of these new medicines with the aim of highlighting potential mechanistic differences in their expected cardiovascular effects. We will show that, though all of the drugs lower body weight, the new medicines are very different from each other as far as their cardiovascular effects are concerned. This suggests that their final effect on cardiovascular outcomes will be a balance between possible (but still unproved) beneficial effects of weight loss and "mixed" weight-independent drug-specific effects. Therefore comparative studies are eagerly awaited in order to establish which one of the new therapies is more appropriate in patients with specific cardiovascular diseases.

Methods

To prepare the present review we used the Pub Med (https://www.ncbi.nlm.nih.gov/pubmed) and Semantics Scholar (www.semanticscholar.org) search engines by crossing the drug names liraglutide, bupropion/naltrexone, topiramate/phentermine and lorcaserin with the following keywords: cardiovascular, heart, myocardial infarction, stroke, blood pressure, hypertension, plasma lipids, atherogenesis, endothelial dysfunction and endothelium. No specific limit was put in the time interval to be covered by our search.

Bupropion-Naltrexone

The Bupropion/Naltrexone combination (BUP/NAL) is approved for use in obesity both in the US and in the EU. Bupropion and Naltrexone both possess central anorexigenic properties, though quite weak in the case of naltrexone. They have been combined in a single medicine to take advantage of their synergism as naltrexone may antagonize compensatory opioidergic mechanisms that limit bupropion efficacy. As discussed in the next sections, both Bupropion and Naltrexone may exert relevant cardiovascular effects independent of body weight decrease.

The question whether BUP/NAL is safe for the cardiovascular system or even decreases cardiovascular risk continues to be open even though evidence from a randomized clinical trial, the LIGHT trial, has already been published [5]. This trial was, indeed, prematurely stopped by the FDA because of serious confidentiality breaches that led to the disclosure of preliminary findings suggesting a positive effect on cardiovascular outcomes. Nevertheless, the results of the LIGHT trial including those collected at the time 25 and 50% of the planned major cardiovascular events (MACE) (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) had occurred and when the study was stopped, were published in 2016 [5]. Whereas the results at 25% MACE actually suggested some cardiovascular benefit from the medicine, those collected at 50% of MACE only showed noninferiority vs placebo at the limit of 2.0 but not of 1.4, as planned (Table 1). Data at 64% MACE, when the study was closed, indicated a worse safety profile with a higher prevalence of nonfatal stroke in the BUP/NAL. As the trial was not completed and given the different results of the analyses performed at different time points, no definite conclusion can be drawn on cardiovascular safety of this drug combination.

Bupropion

Bupropion is an atypical antidepressant that blocks presynaptic recapture of dopamine and noradrenaline hence enhancing dopaminergic and noradrenergic neurotransmissions both centrally and peripherally, also including the cardiovascular system. Even though bupropion has a mechanism of action similar to cocaine it is considered safer for the cardiovascular system because of its lower potency both on dopamine and on noradrenaline transporters. Nevertheless, significant cardiovascular effects have been described for this drug as detailed in the following paragraphs.

Table 1 Clinical trials with new antiobesity drugs on cardiovascular outcomes.

	LIGHT[a]			LEADER trial			SCALE TRIALS[b]			CAMELLIA–TIMI 61		
Treatment (*n*)	Bup/Nal (4455)	Placebo (4450)	HR (CI)	Liraglutide (4668)	Placebo (4672)	HR (CI)	Liraglutide (3384)	Placebo (2036)	HR (CI)	Lorcaserin (6000)	Placebo (6000)	HR (CI)
MACE (*n*, %)	90 (2.0)	102 (2.3)	0.88 (0.57–1.34)	608 (13)	694* (14.9)	0.87 (0.78–0.97)	8 (0.002)	10 (0.04)	0.42 (0.17–1.08)	364 (6.1)	369 (6.9)	0.99 (0.85–1.14)
CV Death (*n*, %)	17 (0.4)	34 (0.8)	0.50 (0.21–1.19)	219 (4.7)	278* (6.02	0.78 (0.66–0.93)	2 (0.0006)	2 (0.001)	0.56 (0.08–4.08)	90 (1.5)	86 (1.4)	1.04 (0.78–1.40)
Nonfatal Stroke (*n*, %)	21 (0.5)	19 (0.4)	1.10 (0.44–2.78)	159 (3.4)	177 (3.8)	0.89 (0.72–1.11)	3 (0.0009)	3 (0.001)	0.47 (0.09–2.32)	84 (1.4)	98 (1.6)	0.86 (0.64–1.15)
Nonfatal MI (*n*, %)	54 (1.2)	54 (1.2)	1.00 (0.57–1.75)	281 (6.0)	317 (6.8)	0.88 (0.75–1.03)	4 (0.001)	5 (0.002)	0.44 (0.12–1.68)	225 (3.8)	227 (3.8)	0.99 (0.82–1.19)

Note that inclusion criteria of the mentioned studies were different. Specifically, patients with obesity and high cardiovascular risk were enrolled in the LIGHT and the CAMELLIA-TIMI 61 trials, whereas the LEADER trial was performed in obese and non-obese diabetic patients with high cardiovascular risk and the SCALE TRIALS in patients with obesity not selected for a specific severity of the cardiovascular risk.

MACE major adverse cardiovascular events, *MI* myocardial infarction, *Bup/Nal* Bupropion/Naltrexone.

*$P < 0.05$

[a]Only the results of the 50% interim analysis are reported here because they are the last data collected at a scheduled time point before the study was closed by FDA for confidentiality breaches. The cited paper (ref. [5].) also reports the data collected at the previous time point (25% of MACE) and at the time the study was stopped (64% of MACE-unscheduled time point). See text for more details.

[b]The data here reported are from the merged results of the four SCALE trials as reported in ref. [52].

Cardiac effects

Bupropion exerts positive inotropic effects as demonstrated by its ability to increase the contractile response elicited in vitro by noradrenaline in rat ventricular strips [6] and by electrical stimulation in strips from human atrial trabeculae [7]. Bupropion also weakly blocks IKs (hERG) with an IC_{50} of 34 μM, and QT prolongation but not torsades de points has been observed during acute intoxication with this drug [8]. In addition, bupropion widens the QRS complex and delays action potential propagation possibly by decreasing the electrical coupling among cardiomyocytes [8]. The increased response to noradrenaline and the conduction disturbances caused by bupropion could imply an increased risk of myocardial ischemia and arrhythmias similar to what happens with cocaine. Sparse reports of these adverse events after bupropion ingestion have been published and according to the French Pharmacovigilance Database 10.1% of all patients taking bupropion suffered ischemic cardiac events [9].

Effect on blood pressure

Bupropion increased the pressor response to intravenously-injected noradrenaline in anesthetized rats [6]. In humans, acute treatment with rapidly acting oral bupropion caused a small but significant increase in arterial blood pressure both when used for smoking cessation and for the treatment of depression [10]. Evidence that bupropion could affect blood pressure was obtained also in volunteers with mild hypertension treated with the extended release formulation of this drug for 4 weeks [11]. In most of cases a bupropion-induced hypertensive effect is considered not clinically relevant even though the drug may be responsible for hypertensive crisis with tachycardia in the setting of overdosage [12].

Effect on plasma lipids and atherogenesis

Recent evidence shows that bupropion like other antidepressants reduces TNFα release and has anti-inflammatory properties [13]. Whether these anti-inflammatory effects could impact on the development of atherosclerotic plaques is still unknown. Tsai et al. [14] showed that in monocytic THP-1 cells stimulated in vitro with LPS, bupropion suppressed the release of the interferon-γ-inducible protein 10 (IP-10), a cytokine associated with the development of atherosclerotic lesions. However, this drug did not decrease intima/media thickness ratio or enhance acetylcholine-induced relaxation in the thoracic aorta from rats on a high fat diet [15], and no association between markers of subclinical atherosclerosis and the use bupropion or other antidepressants was observed in the 10-year follow-up of the Multi-Ethnic Study of Atherosclerosis (MESA) study [16].

Naltrexone

Naltrexone is a non-selective opioid receptor blocker with about tenfold higher affinity for μ than for κ or δ receptors. This effect is stereospecifically exerted only by the (−) enantiomer whereas the (+) enantiomer is ineffective. A wealth of data shows that endogenous opioids and opiate drugs affect the cardiovascular system acting both on the blood vessels and on the heart, which have been shown to express opioid receptors [17], and, on the brain [18]. The scenario that emerges from these studies is that endogenous opiates have a role in the adaption to acute cardiovascular events that could be attenuated by the use of their antagonists such as naltrexone though with uncertain clinical consequences.

Effect on the heart

Endogenous opioids protect the myocardium from ischemic damage and reduce the occurrence of ischemia-induced arrhythmias [19]. This effect of opioids was originally observed in the context of the so called *ischemic preconditioning,* i.e., in the cardioprotection against major ischemia afforded by repeated episodes of subthreshold ischemic episodes. More specifically, it was shown that preconditioning is abolished by the non-specific opioid antagonist naloxone and reproduced by repeated morphine administration [20]. Likewise opioids have a role in ischemic postconditioning [21], i.e., the protection against reperfusion damage afforded by brief bouts of ischemia delivered after a major myocardial ischemia. Evidence has been reported that that endogenous opioid cardioprotection towards ischemic damage also occurs in humans [22].

Opioid preconditioning largely depends on the activation of cardiac opioid receptors by endogenous opioids, both circulating and locally synthesized in the ischemic myocardium, even though the activation of central opioidergic pathways may contribute as well [23]. The direct cardiac preconditioning effect of opioids is exerted through δ receptors, whose activation has been unequivocally shown to be protective, and κ opioid receptors whose role has been more controversial [24]. Conversely, μ opioid receptors do not seem to be implicated in preconditioning by direct cardiac effect but they could cooperate with δ and κ opioid receptors in mediating the effects of preconditioning that are exerted in the CNS [23]. Opioids are implicated also in other forms of cardioprotection that could be abrogated by naltrexone such as the cardioprotection elicited by the chronic exposure to moderate hypoxia [25]. In addition, through the stimulation of κ opioid receptors endogenous opioids mediate both remote ischemic pre- and post-conditioning, i.e., the reduction of myocardial ischemic damage induced by brief episodes of ischemia delivered to peripheral organs (e.g., a limb) respectively before [26] or after an episode of major myocardial ischemia [27].

Opioids also play a role in chronic heart failure. In particular, in the failing heart there is a significant increase in the cardiac expression of endogenous cardiac opioids and of δ and κ and, in some experimental models of heart failure, also of μ opioid receptors [28]. The functional consequences of the activation of the opioidergic system in heart failure are complex and may vary with the receptors involved and the animal species considered. In the normal heart, opioids decrease cardiomyocyte contractility and this effect may be enhanced in heart failure as demonstrated in a hamster model of hypertrophic cardiomyopathy [29]. Moreover, the opioid antagonists naloxone and naltrexone have beneficial hemodynamic effects and improve the baroreflex sensitivity in dogs with experimental heart failure [30]. While these data suggest that opioid antagonists could have beneficial effects in heart failure it has also to be considered that endogenous opioids may exert cardioprotective effects in the failing myocardium [28] that could be lost upon opioid receptor blockade. It is presently unclear how these findings from preclinical models translate to the evolution of heart failure in humans. In fact, whereas in patients with chronic heart failure, high plasma concentrations of proenkephalins are predictive of cardiovascular-related hospitalization and death [31], in a very small series of patients with NYHA class III/IV chronic heart failure the acute administration of naloxone did not modify hemodynamic parameters or clinical symptoms [32]. Therefore, in the absence of larger studies the effect of opioid antagonists and, in particular, of naltrexone in chronic heart failure remains uncertain.

Effect in stroke receptors

Opioid antagonists may protect the brain from ischemic damage. This was initially suggested by the report of two human patients with stroke who experienced a significant clinical improvement after the administration of naloxone [33], and has been confirmed in experimental animal models [34]. Importantly, protective effects were demonstrated also for other opioid antagonists including naltrexone [35]. The mechanism responsible for ischemic neuroprotection by opioid antagonists is still uncertain. The decrease in blood brain permeabilization and edema [36], the preservation of cerebral blood flow, an antiseizure effect [37], an antiapoptotic effect mediated by the inhibition of the NIK/IKKα/NF-κB pathway [38] may all have a role. A major determinant of opioid antagonist-dependent neuroprotection is, however, the ability of these compounds to reduce microglial activation and neuroinflammation [39]. These antinflammatory effects are largely independent from the blockade of opioid receptors and may involve the non-stereospecifical inhibition of Toll-like receptors 4 as

demonstrated for naloxone and naltrexone [40]. Whether circulating naltrexone in patients treated with BUP/NAL could exert any protective effect against stroke is at the moment undetermined also considering that clinical trials with naloxone in stroke patients showed no obvious benefit.

Effect on blood pressure and on endothelium

Endogenous opioids regulate arterial blood pressure through central and peripheral mechanisms by causing vasodilation and blunting *baroreceptor reflexes* [17, 41]. These effects have been documented in experimental animals and in humans and are believed to be quite small in physiological conditions. Some evidence has been reported that an opioidergic dysfunction could be involved in the genesis of arterial hypertension as well although the question remains open [41]. On the contrary, opioidergic activation is a major mechanism keeping blood pressure low in shock [42]. Opioid antagonists may reverse the effect on blood pressure of endogenous opiates [43] and an increase in arterial blood pressure is mentioned among the possible unwanted effects in the prescribing information for naltrexone.

Most of the direct vasodilating effects of opioids depend on pharmacological actions exerted on the endothelium. The presence of μ3 receptors and their coupling to nitric oxide production and vasodilation has been demonstrated in endothelial cells [44]. In addition, κ opioid receptor stimulation with the selective agonist U50,488H causes pulmonary artery vasodilation in rats by inducing NO generation [45]. The effect of opioid agonists on NO synthesis and release could be part of a more complex beneficial role of these peptides in endothelial dysfunction. It has been demonstrated, indeed, that U50,488H protects the aortic endothelium from the oxidative damage due to oxidized lipoprotein accumulation and preserves NO synthesis in rats fed with a high fat diet, by activating the PI3K/Akt signaling pathway [46]. This drug also normalizes vascular tone and reduces thickness and fibrosis of the aortas of rats made diabetic with streptozotocin [47]. Endomorphins, which preferentially bind μ opioid receptors, prevent the decrease in eNOS expression induced in HUVEC cells by the exposure to high glucose concentrations [48] or ox-LDL [49] and inhibit lipid droplet accumulation and foamy cell transformation in monocyte/macrophages cultured in vitro by decreasing the expression of CD36 scavenger receptors [50].

In conclusion, bupropion and naltrexone are expected to exert both positive and detrimental cardiovascular effects. In fact, bupropion, which may increase heart rate and blood pressure by potentiating catecholaminergic neurotransmission, also has beneficial antinflammatory effects, whereas naltrexone is expected to impair cardiac adaption to ischemia and the beneficial protective effects mediated by endogenous opioid in the endothelium, could have a protective effect in stroke and reduce TLR4-dependent inflammation.

Liraglutide

Before being approved for the treatment of obesity, liraglutide has been used for years in diabetic patients (though at a lower dosage) and, therefore, a wealth of data has been collected on its cardiovascular effects. In addition, a controlled, randomized trial, the LEADER trial, performed to assess its safety in people with diabetes with high cardiovascular risk, showed a 13% decrease in MACE [51] (Table 1). A post-hoc analysis of the SCALE trials, the clinical studies that led to liraglutide approval as an anti-obesity drug, showed no detrimental effect and a possible benefit on MACE also in people with obesity [52] (Table 1).

The evidence that GLP1 receptors (GLP1R) are also expressed in the cardiovascular system and in the kidney suggests that GLP1 agonists like liraglutide can exert direct effects on the cardiovascular system [53]. In the next sections we will briefly review the evidence suggesting that liragutide and other GLP1 agonists exert direct anti-ischemic effects on the heart and on the brain, affect blood pressure and heart rate, reduce endothelial dysfunction and have antiatherogenic effects. The effect of GLP1 agonists are not necessarily identical to those of native $GLP1_{7\text{-}36}$ because this peptide partially acts in a GLP1R-independent manner through its degradation product $GLP1_{9–36}$, which is not a GLP1R agonist [54]. The scenario is further complicated by the evidence that important differences could also exist among different GLP1 agonists with some drugs showing clearly positive effects on cardiovascular outcomes (liraglutide, semaglutide and albiglutide) and others not (extended release exenatide and lixisenatide) [55].

Effect in myocardial ischemia and heart failure

The first hint that GLP1 could exert important cardioprotective effects in heart ischemia came from a clinical study in humans that showed a significant improvement in myocardial function in patients with acute myocardial infarction who received the infusion of this hormone after angioplasty [56]. Thereafter, GLP1-induced reductions in infarct size, preservation of contractile function or both were demonstrated in animal models of myocardial infarction [57]. Beneficial effects after acute myocardial infarction were observed also with GLP1 analogs including liraglutide both in experimental animals [58] and in human patients [59]. GLP1 may protect the myocardium from ischemic damage

both when it is given prior to ischemia, i.e., as a pre-conditioning mimetic, or after ischemia at reperfusion [60]. Interestingly, a role has been proposed for GLP1 also in remote pre- or per-conditioning i.e., in the protection elicited when a short-lasting ischemia is induced at distal sites, generally at a limb, before or during the induction of myocardial ischemia [61]. GLP1 protective effects are also observed when experimental ischemia is delivered to the isolated heart or primary cardiomyocyte cultures hence suggesting that they are, at least in part, directly exerted in the heart [62]. Multiple pathways seem to be involved in GLP1-dependent cardioprotection. A first mechanism is the inhibition of the intrinsic apoptosis pathway through the activation of the reperfusion injury salvage kinases, ERKs and PI3K with their downstream effectors mTOR and p70s6k [62]. Recent evidence suggests that liraglutide can also prevent intrinsic apoptosis by enhancing mitophagy through a SIRT-1-Parkin dependent pathway [63] and by promoting the expression of the smooth endoplasmic reticulum Ca^{2+} pump through a PI3K/Akt pathway hence lowering the intracellular Ca^{2+} overload that occurs in ischemia and contributes to mitochondrial dysfunction [64].

The cardioprotective effects of GLP1 and, surprisingly, liraglutide are partly independent from GLP1R activation, being still observed in GLP1R ko mice and partially reproduced by $GLP1_{9–36}$ [54]. The molecular mechanism of these GLP1R-independent responses remains uncertain as no alternative receptor for $GLP1_{9–36}$ has been identified so far. Part of these cardioprotective effects could also be exerted indirectly through an action on the vasculature leading to coronary vasodilation [54]. Evidence has been reported that $GLP1_{7–36}$ and its metabolite $GLP1_{9–36}$ dilate coronary arteries in vivo in humans, a mechanism that can contribute to its protective effect in myocardial ischemia [65]. Finally, the ability of GLP1 and its analogs to promote new vessel formation may also have a role in cardioprotection by promoting tissue repair. Indeed, an increase in new blood vessel formation in the ischemic myocardium has been observed in rats after the intracardiac injection of liraglutide-coated nanoparticles [66]. A recent meta-analysis of the clinical studies on liraglutide in patients with myocardial infarction showed an improvement in left ventricular ejection fraction and a reduction in high-sensitivity C reactive protein, but no change in cardiac death, major adverse cardiovascular events, repeated revascularization or recurrence of MI [67].

GLP1 also exerts positive inotropic effects as indicated by the increase in left ventricular developed pressure in isolated mouse hearts exposed to $GLP1_{7–36}$ [54] and, on the opposite, by the impaired contractile response to inotropic agents observed in GLP1R ko mice [68]. In the rat heart $GLP1_{7–36}$ inotropic effects depend on the activation of GLP1R and are not replicated by $GLP1_{19–36}$ [54]. Experiments performed in isolated human atrial strips showed that exenatide increases the force of isometric contraction through a GLP1/PKA/phospholamban-dependent pathway [69]. The evidence that GLP1 improves left ventricular function in dogs with pacing-induced cardiomyopathy suggested that GLP1 and its analogs could be clinically useful also in heart failure [70]. In mice, liraglutide reduces the contractile dysfunction, inflammation, fibrosis and cardiomyocyte apoptosis induced by obesity and diabetes suggesting that it could improve diabetic cardiomyopathy [71]. These effects are independent from body weight reduction and involve the activation of AMPK and autophagy [71] and the inhibition of endoplasmic reticulum stress-induced apoptosis [72]. In addition, exendin-4 prevents the apoptosis induced by saturated fatty acids, an important mechanism involved in the pathogenesis of diabetic cardiomyopathy [73]. Whether the beneficial effects of GLP1 and its analogs observed in experimental animals also occur in patients with heart failure is still a matter of controversy. In fact, whilst an improvement in hemodynamic parameters has been observed in some studies [74] it has not been confirmed in others including the two randomized trials LIVE and FIGHT [75, 76].

Effect in stroke

Liraglutide and other GLP1 analogs decrease brain damage in experimental brain ischemia in rodents [77] and increase the survival of cultured neurons exposed to hypoxia in vitro [78]. Among the mechanisms that could account for this neuroprotective effect an important role is played by the enhanced expression of anti-apoptotic proteins of the *Bcl_2* family through the activation of the *PI3K/AKT* and *MAPK* pathways and the concomitant decrease of the pro-apoptotic proteins *Bax* and *Bad* [79]. A relevant consequence of the enhanced *Bcl_2* expression is the decrease in mitochondrial ROS generation, which also contributes to neuroprotection [77, 79]. By preserving mitochondrial integrity liraglutide also modulates autophagy in neurons [80]. Enhanced reparative angiogenesis can also have a role [81]. Evidence for the clinical relevance in humans of the neuroprotective effect of liraglutide is still limited and in the LEADER study the prevalence of stroke considered in isolation (i.e., not as part of MACE) was not significantly decreased by liraglutide [51].

Effect on arterial blood pressure

GLP1 and GLP1R agonists including liraglutide decrease arterial blood pressure in hypertensive rats [82] and in human patients with diabetes or metabolic syndrome [83]. In randomized clinical trials liraglutide caused a decrease of about 3 mmHg in systolic blood pressure, which tended to

disappear approximately one year from the beginning of the treatment, whereas it had no effect on diastolic blood pressure [83]. The decrease in blood pressure in humans is accompanied by a slight increase in heart rate, which was also observed in rodents and depends both on a direct action on the heart and on the activation of the sympathetic system [84]. Because GLP1 vasorelaxant properties were also observed in vitro in rings from isolated blood vessels it was proposed that GLP1 could directly act on the vasculature as also suggested by the presence of GLP1R on endothelial and vascular smooth muscle cells [54]. The evidence that GLP1-induced vasorelaxation was abrogated by NOS inhibitors [85] or when the vessels were denuded of their endothelium [86] suggested that GLP1, which is known to induce the expression of eNOS in endothelial cells, was acting by enhancing NO release from the endothelium. The blood pressure lowering effect of GLP1 may be part of a more general improvement of endothelial dysfunction [87]. Additional mechanisms can also be in place considering that in other experimental systems GLP1 was still effective after removing the endothelium. In particular, it can relax vascular smooth muscle cells through the PKA-dependent activation of KATP channels [88]. These effects were also replicated by $GLP1_{9–36}$ suggesting that GLP1R was not involved [54, 88]. Contrasting data have been reported about the ability of degradation-resistant GLP1 analogs to trigger GLP1R-independent vasodilation [88]. Liraglutide was ineffective in relaxing endothelium denuded aortic rings in vitro that, instead, was relaxed by the coronary perfusate from the heart of mice treated with this drug [89]. Because liraglutide lowered the blood pressure in $GPL1R^{+/+}$ but not in $GLP1R^{-/-}$ mice and this effect was abolished by the atrial natriuretic peptide (ANP) antagonist anantin, it was concluded that this GLP1 analog lowers blood pressure indirectly by inducing ANP synthesis in the atria through a GLP1R/cAMP/cAMP-activated guanine nucleotide exchange factor pathway [89].

Effect on atherogenesis

GLP1 and its analogs exert anti-atherogenic effects by simultaneously acting on vascular smooth muscle cells, endothelial cells and foamy cells. Endothelial cells are the main target of liraglutide anti-atherogenic effects. GLPR1 agonists preserve viability in endothelial cells exposed to free radicals and prevent their senescence [90], exert anti-inflammatory effects, increase eNOS expression and NO release and decrease the expression of adhesion molecules hence reducing monocyte margination [91]. Notably also TNFα-induced PAI-1 expression is inhibited and this could contribute to decrease the risk of thrombus formation [91]. Importantly, GLP1 agonists improve endothelial dysfunction also in human patients with diabetes [92]. Liraglutide and other GLP1R agonists reduce monocyte margination, their accumulation in the atherosclerotic plaque, their uptake of ox-LDL and foamy cell transformation and the release of proinflammatory cytokines [93]. These effects could be partly dependent on the ability to affect the phenotype of infiltrating cells by enhancing the prevalence of M2 anti-inflammatory relative to M1 pro-inflammatory macrophages [94]. The stimulation of GLP1R in vascular smooth muscle cells elicits antiproliferative and anti-inflammatory effects. In effect, the treatment with exendin-4 reduced myointimal thickening in mice with endothelial denudation injury of the femoral artery [95]. In addition, this GLP1 analog also reduced the proliferation of aortic vascular smooth muscle cells cultured in vitro in the presence of PDGF [95] or angiotensin II [96]. This anti-proliferative effect depends on AMPK activation and contributes to the antiatherogenic effect of liraglutide in ApoE deficient mice [96].

In conclusion, with the only exception of a small increase in heat rate, liraglutide exerts favorable cardiovascular effects by protecting myocardium and brain from ischemic damage, improving heart contractility, lowering blood pressure and reducing atherogenesis.

Phentermine/Topiramate

Phentermine (PHEN) and Topiramate (TPM), two drugs both lowering body weight with different mechanisms, have been combined in a single medicine, fixed dose PHEN/TPM that was approved by FDA in 2012. Limited data are available on the cardiovascular safety of the PHEN/TPM in human patients. The Phase III Registration trial CONQUER and EQUIP and the extension study SEQUEL showed that PHEN/TPM decreased several cardiovascular risk factors including plasma glucose, LDL and triglycerides, systolic and diastolic blood pressure and, obviously, body weight. No prospective randomized controlled trial specifically designed to assess hard cardiovascular endpoints, such as MACE, has been published so far.

Recently, a large retrospective cohort study of real-world US insurance billing data compared the occurrence of MACE in a group of patients taking either TPM, or PHEN or fixed dose PHEN/TPM, before, during and after the end of the treatment and showed that MACE prevalence was lower when patients were taking fixed dose PHEN/TPM or PHEN [97]. By contrast, TPM use was associated with an increase in MACE occurrence [97]. However, this was an uncontrolled, retrospective study with the important limitation of the very short duration of drug exposure (on average 2.1 years). In addition, the safety in patients with cardiovascular diseases was not specifically assessed.

In the following sections we review the evidence that supports the hypothesis that both PHEN and TPM may affect cardiovascular risk independently from their effects on body weight.

Phentermine

Amphetamines are prototypical cardiotoxic agents and the concept that they can induce a whole array of cardiovascular unwanted effects is so well established that it will not be examined in detail in the present review. The point here is instead that PHEN, which is a substituted amphetamine, has been claimed to be less cardiotoxic than the other molecules of this family [98]. Its lesser potency has been proposed as an explanation of this possible higher tolerability [98]. Whilst the few and small randomized trials published so far suggest that PHEN is safe for the cardiovascular system, a few cases of myocardial infarction, stroke, and ventricular arrhythmias [98] have been reported in patients taking this drug. Therefore, the question of PHEN cardiovascular safety remains open in the absence of solid evidence from randomized clinical trials specifically designed to address this issue.

Topiramate

TPM acts on multiple targets blocking voltage-gated ion channels, glutamate AMPA receptors and carbonic anhydrase and activating $GABA_A$ receptors. Even though most of TPM antiobesity effects are exerted centrally through the modulation of hypothalamic neuronal pathways controlling feeding behavior, TPM also acts on its targets peripherally and these peripheral actions may be relevant for cardiovascular risk reduction. More specifically, preclinical evidence suggests that TPM could exert protective effects in ischemic disorders such as stroke and myocardial infarction, decrease atherogenesis, improve insulin sensitivity and preserve endothelial integrity in diabetes.

As with other antiepileptic drugs, TPM reduces the severity of neuronal damage in in vitro [99] and in vivo [100] experimental brain ischemia. The blockade of voltage-gated Na^+ channels and of AMPA receptors is an obvious explanation of TPM-induced neuroprotection because the activation of these ion channels represents a major death mechanism in the ischemic brain. However, more recently, evidence emerged of an additional mechanism depending on the anti-inflammatory effects. TPM, indeed, dose-dependently decreases NFkB activation, the levels of myeloperoxidase and the release of inflammatory cytokines in the brain of rats undergoing experimental subarachnoid hemorrhage [101]. TPM anti-inflammatory effects are not limited to ischemic brain damage as they have been documented also in experimental liver [102] and, notably, cardiac ischemia [103]. TPM acts directly on white blood cells through the modulation of their intrinsic GABAergic system [104]. In effect, monocyte/macrophages and T-lymphocytes synthetize GABA and express GABAergic receptors [104, 105] and GABAergic drugs may affect the evolution of autoimmune diseases such as autoimmune encephalomyelitis by acting on these cells [105]. In mice TPM decreased the cardiac damage induced by the ligation of the coronary artery, reduced the prevalence of heart rupture and increased survival by reducing the percentage of M1/Ly-$6C^{high}$ macrophages, that have proinflammatory and tissue destroying activities, at the same time increasing tissue repairing M2/Ly-$6C^{low}$ macrophages [103]. By modulating the intrinsic GABAergic system in macrophages TPM reduced lipid droplet accumulation and foamy cell transformation in macrophages derived by human monocytes exposed in vitro to oxidized LDL [106]. This effect was dependent on the decrease of the expression of SR-A, CD36 and LOX-1, which are responsible for LDL uptake by macrophages, and on the increase in the expression of ABCA1, ABCG1 and SR-BI, which, conversely, promote cholesterol efflux. Importantly, TPM also caused a decrease in p38MAPK and NF-κB pathway activation and in TNFα production suggesting that it could also reduce inflammation in atherosclerotic plaques. In contradiction to this hypothesis, TPM did not induce any decrease in foamy cell accumulation or atherosclerotic plaque formation in high fat fed apoE-deficient mice [107]. However, these negative results could have been determined by the extremely high plasma lipid levels that are attained in high fat fed apoE-deficient mice. Interestingly, despite the lack of effect on atherosclerotic plaque formation TPM markedly reduced glomerular lipidosis and the related kidney damage.

By blocking carbonic anhydrase TPM protects the blood brain barrier from hyperglycemia-induced damage preventing astrocyte and pericyte loss and the loosening of tight and adherens junctions [108]. Specifically, TPM reduces the generation of $HCO3^-$ which is required for the conversion of pyruvate to oxaloacetate that will be further metabolized in the Krebs cycle with free radical generation.

In conclusion, while no direct cardiovascular beneficial effect is expected for PHEN due to its amphetamine-like properties, TPM may exert cardioprotective and neuroprotective effects in ischemia and anti-inflammatory and anti-atherogenic actions.

Lorcaserin

The synthesis of the selective $5HT_{2C}$ agonist lorcaserin was the result of a program aiming to obtain a drug that could activate $5HT_{2C}$ receptor-dependent anorexigenic pathways

Table 2 Summary of the cardiovascular effects of the new antiobesity drugs.

	Bupropion	Naltrexone	Liraglutide	Topiramate	Phentermine	Lorcaserin
Effect on myocardial ischemic damage	↑ (9)	↑[a]	↓ (56–67)	↓ (103)	↑ [b]	n.a.
Effect on myocardial contractility	↑ (6,7)	↑ (28,30–32)	↑ (54–76)	n.a.	↑ [b]	n.a
Risk of arrhythmias or conduction disturbances	↑ (8,9)	↑[a]	↑ (53)	n.a.	↑ [b]	n.a.
Effect on ischemic brain damage	n.a.	↓ (33–40)	↓ (77–81)	↓ (99–101)	↑ [b]	n.a.
Effect on arterial blood pressure	↑ (6,10–12)	↑ (42,43)	↓ (82–89)	n.a.	↑ [b]	↑ (?) (112–119)
Effect on endothelial dysfunction	n.a.	↑ [a]	↓ (90–92)	↓ (106–107)	n.a.	n.a.
Effect on inflammation in the atherosclerotic plaque	↑ (13–15)	n.a.	↓ (94)	↓ (102–105)	n.a.	n.a.
Effect on foamy cell formation	n.a.	↑ [a]	↓ (93)	↓ (106–107)	n.a.	n.a.

[a]Expected as a consequence of the reversal of physiological effects of endogenous opioids but not directly demonstrated.

[b]Expected as a class effect of amphetamines although limited evidence suggests that phentermine could be safer than other amphetamines.

in the hypothalamus without stimulating other serotonin receptors (mainly of the $5HT_{2B}$ subtype) which may induce serious unwanted cardiovascular effects. Clinical evidence that lorcasein is, indeed, safe for the cardiovascular system has been reported only at the end of 2018 with the publication of the results of the CAMELLIA–TIMI 61 trial [109] (Table 1). In this study no difference in MACE occurrence was observed in patients with obesity and established atherosclerotic cardiovascular disease or multiple cardiovascular risk factors randomly assigned to receive either lorcaserin or placebo. Of note, while this study showed that lorcaserin is safe it did not report any evidence of a reduction of cardiovascular outcomes.

Though remarkably more selective than other $5HT_{2C}$ agonists, at doses higher than 20 mg/day lorcaserin may still exert effects on $5HT_{2A}$ and $5HT_{2B}$ receptors since the Ki for these receptor subtypes is only about 100-fold higher than for $5HT_{2C}$ receptors. $5HT_{2C}$ receptors are mainly expressed in the central nervous system [110] and therefore, the cardiovascular effects of $5HT_{2C}$ stimulation, if any, are exerted centrally. $5HT_{2C}$ agonists decrease the activity of neurons in the nucleus of tractus solitarius which receive the afferent inputs of cardiac baroreflex arc [111]. In addition, in unstressed rats the intracerebroventricular injection of the $5HT_{2C}$ agonist mCPP caused an increase in mean arterial blood pressure that is initially accompanied by bradycardia and, then, by tachycardia [112]. This effect was prevented by the pretreatment with the 5-HT_{2C} receptor antagonist SDZ SER082 suggesting a role of central $5HT_{2C}$ receptors in the control of heart rate and blood pressure. However, mCPP is far from being specific [113] and SDZ SER082 also blocks $5HT_{2B}$ receptors [114]; these considerations cast doubts on the real involvement of $5HT_2$ receptors in the aforementioned effect also considering that no cardiovascular abnormality has been observed in $5HT_{2C}$ receptor ko mice [115]. Although $5HT_{2C}$ receptors have been traditionally considered as not present the cardiovascular system, a few studies suggested that $5HT_{2C}$ receptor activation could induce vasoconstriction in specific vascular beds such as the perfused hindquarter in anesthetized rats [116] or the mesenteric vascular bed [117]. While these results were obtained with agonists whose specificity could be questioned, Zhang et al. [118] showed that in rats that developed pulmonary hypertension because of exposure to chronic hypoxia the expression of $5HT_{2C}$ receptors evaluated with Western blots, immunocytochemistry and RT-PCR did increase in smooth muscle cells of the pulmonary artery. Importantly, siRNA against these receptors lowered the proliferation of pulmonary smooth muscle cells in vitro. Likewise, Morán et al. [119] supported their hypothesis that mCPP-induced vasoconstriction in the in situ autoperfused kidney from normotensive rats was due to the activation of $5HT_{2C}$ receptors by demonstrating the expression of this receptor type in renal arteries by Western blot experiments. If confirmed, these results could deserve some attention because they suggest that lorcaserin could exert unwanted vasoconstricting activity in critical vascular beds such as the renal and pulmonary ones.

In conclusion, lorcaserin does not seem to exert significant direct effects on the cardiovascular system though at very high concentrations it could lose some of its specificity and start acting on $5HT_{2A}$ and $5HT_{2B}$ receptors, which, conversely, have a relevant role in cardiovascular pathophysiology.

Conclusions

We performed a review of the literature on the cardiovascular effects that are exerted independently from the decrease in body weight by the active substances contained in the four recently approved antiobesity medicines. Relevant differences emerged among these drugs since some of them show unequivocal cardioprotective or antiatherogenic effects whereas others could detrimentally impact on cardiovascular risk (Table 2). Therefore their final effect on

cardiovascular risk will be the combined result of the benefits of body weight lowering and of drug-specific effects. In this perspective, future comparative studies also considering gender differences [120] are mandatory to establish whether any of the antiobesity drugs do offer advantages as compared with the others and, importantly whether in terms of precision medicine prescription, specific subgroups of patients should better be treated with one particular antiobesity medicine rather than with another.

An important note of caution is that many of the studies that we reviewed were performed in animal models or in human patients without obesity and therefore they could not be immediately translatable to patients with obesity. Accordingly, it is important to mention that cardiovascular disorders could be different from a pathophysiological point of view in patients with and without obesity as observed, for instance, in the case of arterial hypertension.

Acknowledgements Obesity Programs of nutrition, Education, Research and Assessment (OPERA) group members served as collaborators and approved the final version of the manuscript: Colao Annamaria, Savastano Silvia, Barrea Luigi, Muscogiuri Giovanna, Alviggi Carlo, Angrisani Luigi, Annunziata Giuseppe, Beguinot Francesco, Belfiore Annamaria, Belfiore Antonino, Bellastella Giuseppe, Biondi Bernadette, Bonaduce Domenico, Bordoni Laura, Brasacchio Caterina, Capaldo Brunella, Caprio Massimiliano, Cataldi Mauro, Cignarelli Angelo, Cittadini Antonello, Conforti Alessandro, Cuomo Rosario, De Placido Giuseppe, De Siena Marina, Di Carlo Costantino, Di Luigi Luigi, Di Nisio Andrea, Di Renzo Laura, Di Somma Carolina, Docimo Ludovico, Donini Lorenzo Maria, Federici Massimo, Foresta Carlo, Gabbianelli Rosita, Gambineri Alessandra, Gastaldelli Amalia, Giallauria Francesco, Giardiello Cristiano, Gnessi Lucio, Guida Brunella, Laudisio Daniela, Lenzi Andrea, Macchia Paolo Emidio, Manno Emilio, Marzullo Paolo, Migliaccio Silvia, Muratori Fabrizio, Musella Mario, Nardone Gerardo, Nicasto Vincenzo, Piazza Luigi, Pilone Vincenzo, Pivari Francesca, Pivonello Rosario, Pugliese Gabriella, Riccardi Gabriele, Ritieni Alberto, Salzano Ciro, Sanduzzi Alessandro, Sbraccia Paolo, Sesti Giorgio, Soldati Laura, Taglialatela Maurizio, Trimarco Bruno, Tuccinardi Dario.

Funding The 2019 OPERA meeting was organized by Panta Rei Srl and sponsored by Novo Nordisk, Therascience, Bruno Pharma, Merck, Savio Pharma Italia Srl, IBSA Institut Biochimique SA, Bioitalia Srl, Cohesion Pharmaceutical, and Specchiasol Srl. Publication of this article as part of a supplement was sponsored by Panta Rei Srl, Naples, Italy. The meeting sponsors and organizer did not have access to the manuscripts and the authors maintained control of the content.

Author contributions The authors' responsibilities were as follows: MC, AC, and FG: were responsible for the concept of this paper and drafted the manuscript; GM, LB, SS and AC: provided a critical review of the paper. OPERA Group members participated to the revision of the manuscript. All authors and OPERA Group Members contributed to and agreed on the final version of the manuscript.

Compliance with ethical standards

Conflict of interest AC received lecture fees from Eli Lilly, Novo Nordisk, Sanofi Aventis, Astra Zeneca, Bruno farmaceutici, Roche. The remaining authors have nothing to disclose.

References

1. Di Angelantonio E, Bhupathiraju ShN, Wormser D, Gao P, Kaptoge S. Global BMI Mortality Collaboration et al. Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet.2016;388:776–86.
2. Ma C, Avenell A, Bolland M, Hudson J, Stewart F, Robertson C, et al. Effects of weight loss interventions for adults who are obese on mortality, cardiovascular disease, and cancer: systematic review and meta-analysis. BMJ. 2017;359:j4849.
3. Carbone S, Lavie CJ, Arena R. Obesity and heart failure: focus on the obesity paradox. Mayo Clin Proc. 2017;92:266–79.
4. LeBlanc EL, Patnode CD, Webber EM, Redmond N, Rushkin M, O'Connor EA. Behavioral and pharmacotherapy weight loss interventions to prevent obesity-related morbidity and mortality in adults: an updated systematic review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018. AHRQ Publication No. 18-05239-EF-1 September 201, https://www.ncbi.nlm.nih.gov/books/NBK532379/pdf/Bookshelf_NBK532379.pdf.
5. Nissen SE, Wolski KE, Prcela L, Wadden T, Buse JB, Bakris G, et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. JAMA. 2016;315:990–1004.
6. Killian LM, Docherty JR. Cardiovascular stimulant actions of bupropion in comparison to cocaine in the rat. Eur J Pharmacol. 2014;735:32–7.
7. Cremers B, Schmidt KI, Maack C, Schäfers HJ, Böhm M. Catecholamine release in human heart by bupropion. Eur J Pharmacol. 2003;467:169–71.
8. Caillier B, Pilote S, Castonguay A, Patoine D, Ménard-Desrosiers V, Vigneault P, et al. QRS widening and QT prolongation under bupropion: a unique cardiac electrophysiological profile. Fundam Clin Pharmacol. 2012;26:599–608.
9. Beyens MN, Guy C, Mounier G, Laporte S, Ollagnier M. Serious adverse reactions of bupropion for smoking cessation: analysis of the French Pharmacovigilance Database from 2001 to 2004. Drug Saf. 2008;31:1017–26.
10. Martins LC, Ferreira-Melo SE, Sabha M, Coelho OR, Yugar-Toledo JC, Quinaglia T, et al. Acute effects of pharmacotherapies in blood pressure in normotensive moderate smokers. Blood Press. 2009;18:255–60.
11. Thase ME, Haight BR, Johnson MC, Hunt T, Krishen A, Fleck RJ, et al. A randomized, double-blind, placebo-controlled study of the effect of sustained-release bupropion on blood pressure in individuals with mild untreated hypertension. J Clin Psychopharmacol. 2008;28:302–7.
12. Balit CR, Lynch CN, Isbister GK. Bupropion poisoning: a case series. Med J Aust. 2003;178:61–3.
13. Brustolim D, Ribeiro-dos-Santos R, Kast RE, Altschuler EL, Soares MB. A new chapter opens in anti-inflammatory treatments: the antidepressant bupropion lowers production of tumor necrosis factor-alpha and interferon-gamma in mice. Int Immunopharmacol. 2006;6:903–7.
14. Tsai JH, Kuo CH, Yang P, Cheng KH, Wang PW, Chen CC, et al. Effects of antidepressants on IP-10 production in LPS-activated THP-1 human monocytes. Int J Mol Sci. 2014;15:13223–35.

15. Ahmed M, El-Bakly WM, Zaki AM, abd Alzez LF, El serafi O. Bupropion effects on high-fat diet-induced steatohepatitis and endothelial dysfunction in rats: role of tumour necrosis factor-alpha. J Pharm Pharmacol. 2014;66:793–801.
16. Camacho Á, McClelland RL, Delaney JA, Allison MA, Psaty BM, Rifkin DE, et al. Antidepressant use and subclinical measures of atherosclerosis: the multi-ethnic study of atherosclerosis. J Clin Psychopharmacol. 2016;36:340–6.
17. Wittert G, Hope P, Pyle D. Tissue distribution of opioid receptor gene expression in the rat. Biochem Biophys Res Commun. 1996;218:877–81.
18. Holaday JW. Cardiovascular effects of endogenous opiate systems. Annu Rev Pharmacol Toxicol. 1983;23:541–94.
19. Tanaka K, Kersten JR, Riess ML. Opioid-induced cardioprotection. Curr Pharm Des. 2014;20:5696–705.
20. Schultz JE, Hsu AK, Gross GJ. Morphine mimics the cardioprotective effect of ischemic preconditioning via a glibenclamide-sensitive mechanism in the rat heart. Circ Res. 1996;78:1100–4.
21. Tong G, Sun Z, Wei X, Gu C, Kaye AD, Wang Y, et al. U50,488H postconditioning reduces apoptosis after myocardial ischemia and reperfusion. Life Sci. 2011;88:31–8.
22. Tomai F, Crea F, Gaspardone A, Versaci F, Ghini AS, Ferri C, et al. Effects of naloxone on myocardial ischemic preconditioning in humans. Am Coll Cardiol. 1999;33:1863–9.
23. Li R, Wong GT, Wong TM, Zhang Y, Xia Z, Irwin MG. Intrathecal morphine preconditioning induces cardioprotection via activation of delta, kappa, and mu opioid receptors in rats. Anesth Analg. 2009;108:23–9.
24. Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning and morphine induced cardioprotection involve the delta (d)-opioid receptor in the intact rat heart. J Mol Cell Cardiol. 1997;29: 2187–95.
25. Maslov LN, Naryzhnaia NV, Tsibulnikov SY, Kolar F, Zhang Y, Wang H, et al. Role of endogenous opioid peptides in the infarct size-limiting effect of adaptation to chronic continuous hypoxia. Life Sci. 2013;93:373–9.
26. Zhang SZ, Wang NF, Xu J, Gao Q, Lin GH, Bruce IC, et al. κ-opioid receptors mediate cardioprotection by remote preconditioning. Anesthesiology. 2006;105:550–6.
27. Xu YC, Li RP, Xue FS, Cui XL, Wang SY, Liu GP, et al. κ-Opioid receptors are involved in enhanced cardioprotection by combined fentanyl and limb remote ischemic postconditioning. J Anesth. 2015;29:535–43.
28. He SF, Jin SY, Yang W, Pan YL, Huang J, Zhang SJ, et al. Cardiac μ-opioid receptor contributes to opioid-induced cardioprotection in chronic heart failure. Br J Anaesth. 2018;121: 26–37.
29. Bolte C, Newman G, Schultz Jel J. Kappa and delta opioid receptor signaling is augmented in the failing heart. J Mol Cell Cardiol. 2009;47:493–503.
30. Yatani A, Imai N, Himura Y, Suematsu M, Liang CS. Chronic opiate-receptor inhibition in experimental congestive heart failure in dogs. Am J Physiol. 1997;272(1 Pt 2):H478–84.
31. Arbit B, Marston N, Shah K, Lee EL, Aramin H, Clopton P, et al. Prognostic usefulness of proenkephalin in stable ambulatory patients with heart failure. Am J Cardiol. 2016;117:1310–4.
32. Oldroyd KG, Gray CE, Carter R, Harvey K, Borland W, Beastall G, et al. Activation and inhibition of the endogenous opioid system in human heart failure. Br Heart J. 1995;73:41–8.
33. Baskin DS, Hosobuchi Y. Naloxone reversal of ischaemic neurological deficits in man. Lancet. 1981;2:272–5.
34. Hosobuchi Y, Baskin DS, Woo SK. Reversal of induced ischemic neurologic deficit in gerbils by the opiate antagonist naloxone. Science. 1982;215:69–71.
35. Baskin DS, Hosobuchi Y, Grevel JC. Treatment of experimental stroke with opiate antagonists. Effects on neurological function, infarct size, and survival. J Neurosurg. 1986;64:99–103.
36. Yang L, Wang H, Shah K, Karamyan VT, Abbruscato TJ. Opioid receptor agonists reduce brain edema in stroke. Brain Res. 2011;1383:307–16.
37. Gooshe M, Abdolghaffari AH, Aleyasin AR, Chabouk L, Tofigh S, Hassanzadeh GR, et al. Hypoxia/ischemia a key player in early post stroke seizures: modulation by opioidergic and nitrergic systems. Eur J Pharmacol. 2015;746:6–13.
38. Wang X, Sun ZJ, Wu JL, Quan WQ, Xiao WD, Chew H, et al. Naloxone attenuates ischemic brain injury in rats through suppressing the NIK/IKKα/NF-κB and neuronal apoptotic pathways. Acta Pharmacol Sin. 2019;40:170–9.
39. Anttila JE, Albert K, Wires ES, Mätlik K, Loram LC, Watkins LR, et al. Post-stroke intranasal (+)-naloxone delivery reduces microglial activation and improves behavioral recovery from ischemic injury. eNeuro. 2018;18:5. pii: ENEURO.0395-17.2018.
40. Wang X, Zhang Y, Peng Y, Hutchinson MR, Rice KC, Yin H, et al. Pharmacological characterization of the opioid inactive isomers (+)-naltrexone and (+)-naloxone as antagonists of toll-like receptor 4. Br J Pharmacol. 2016;173:856–69.
41. Cozzolino D, Sasso FC, Cataldo D, Gruosso D, Giammarco A, Cavalli A, et al. Acute pressor and hormonal effects of beta-endorphin at high doses in healthy and hypertensive subjects: role of opioid receptor agonism. J Clin Endocrinol Metab. 2005;90:5167–74.
42. Faden AI, Holaday JW. Opiate antagonists: a role in the treatment of hypovolemic shock. Science. 1979;205:317–8.
43. Schobel HP, Oren OM, Mark AL, Ferguson DW. Naloxone potentiates cardiopulmonary baroreflex sympathetic control in normal humans. Circ Res. 1992;70:172–83.
44. Stefano GB, Hartman A, Bilfinger TV, Magazine HI, Liu Y, Casares F, et al. Presence of the mu3 opiate receptor in endothelial cells. Coupling to nitric oxide production and vasodilation. J Biol Chem. 1995;270:30290–3.
45. Sun X, Ma S, Zang YM, Lu SY, Guo HT, Bi H, et al. Vasorelaxing effect of U50,488H in pulmonary artery and underlying mechanism in rats. Life Sci. 2006;78:2516–22.
46. Tian F, Zheng XY, Li J, Zhang SM, Feng N, Guo HT, et al. κ-Opioid receptor stimulation improves endothelial function via Akt-stimulated NO production in hyperlipidemic rats. Sci Rep. 2016;6:26807.
47. Zhou X, Wang D, Zhang Y, Zhang J, Xiang D, Wang H. Activation of κ-opioid receptor by U50,488H improves vascular dysfunction in streptozotocin-induced diabetic rats. BMC Endocr Disord. 2015;15:7.
48. Liu J, Wei S, Tian L, Yan L, Guo Q, Ma X. Effects of endomorphins on human umbilical vein endothelial cells under high glucose. Peptides. 2011;32:86–92.
49. Zhao J, Zhang Q, Liu J, Tian L, Huang W, Quan J, et al. Effect of Endomorphins on HUVECs Treated by ox-LDL and Its Related Mechanisms. J Diabetes Res. 2016;2016:9741483.
50. Chiurchiù V, Izzi V, D'Aquilio F, Vismara D, Carotenuto F, Catanzaro G, et al. Endomorphin-1 prevents lipid accumulation via CD36 down-regulation and modulates cytokines release from human lipid-laden macrophages. Peptides. 2011;32:80–5.
51. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375:311–22.
52. Davies MJ, Aronne LJ, Caterson ID, Thomsen AB, Jacobsen PB, Marso SP, et al. Liraglutide and cardiovascular outcomes in adults with overweight or obesity: A post hoc analysis from SCALE randomized controlled trials. Diabetes Obes Metab. 2018;20:734–9.

53. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation. 2017;136:849–70.
54. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways. Circulation. 2008;117:2340–50.
55. Lim S, Kim KM, Nauck MA. Glucagon-like peptide-1 receptor agonists and cardiovascular events: class effects versus individual patterns. Trends Endocrinol Metab. 2018;29:238–48.
56. Nikolaidis LA, Mankad S, Sokos GG, Miske G, Shah A, Elahi D, et al. Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. Circulation. 2004;109:962–5.
57. Bose AK, Mocanu MM, Carr RD, Brand CL, Yellon DM. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. Diabetes. 2005;54:146–51.
58. Noyan-Ashraf MH, Momen MA, Ban K, Sadi AM, Zhou YQ, Riazi AM, et al. GLP1R agonist liraglutide activates cytoprotective pathways and improves outcomes after experimental myocardial infarction in mice. Diabetes. 2009;58:975–83.
59. Chen WR, Chen YD, Tian F, Yang N, Cheng LQ, Hu SY, et al. Effects of liraglutide on reperfusion injury in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Imaging. 2016;9:e005146.
60. Bose AK, Mocanu MM, Carr RD, Yellon DM. Glucagon like peptide-1 is protective against myocardial ischemia/reperfusion injury when given either as a preconditioning mimetic or at reperfusion in an isolated rat heart model. Cardiovasc Drugs Ther. 2005;19:9–11.
61. Basalay MV, Mastitskaya S, Mrochek A, Ackland GL, Del Arroyo AG, Sanchez J, et al. Glucagon-like peptide-1 (GLP1) mediates cardioprotection by remote ischaemic conditioning. Cardiovasc Res. 2016;112:669–76.
62. Bose AK, Mocanu MM, Carr RD, Yellon DM. Myocardial ischaemia-reperfusion injury is attenuated by intact glucagon like peptide-1 (GLP1) in the in vitro rat heart and may involve the p70s6K pathway. Cardiovasc Drugs Ther. 2007;21(Aug):253–6.
63. Qiao H, Ren H, Du H, Zhang M, Xiong X, Lv R. Liraglutide repairs the infarcted heart: The role of the SIRT1/Parkin/mitophagy pathway. Mol Med Rep. 2018;17:3722–34.
64. Zhang Y, Zhou H, Wu W, Shi C, Hu S, Yin T, et al. Liraglutide protects cardiac microvascular endothelial cells against hypoxia/reoxygenation injury through the suppression of the SR-Ca(2+)-XO-ROS axis via activation of the GLP1R/PI3K/Akt/survivin pathways. Free Radic Biol Med. 2016;95:278–92.
65. Clarke SJ, Giblett JP, Yang LL, Hubsch A, Zhao T, Aetesam-Ur-Rahman M, et al. GLP1 is a coronary artery vasodilator in humans. J Am Heart Assoc. 2018;7:e010321.
66. Qi Q, Lu L, Li H, Yuan Z, Chen G, Lin M, et al. Spatiotemporal delivery of nanoformulated liraglutide for cardiac regeneration after myocardial infarction. Int J Nanomedicine. 2017;12:4835–48.
67. Yang X, Liang Z. Efficacy of liraglutide intervention in myocardial infarction: a meta-analysis of randomized controlled trials. Herz. 2018. https://doi.org/10.1007/s00059-018-4748-5.
68. Gros R, You X, Baggio LL, Kabir MG, Sadi AM, Mungrue IN. et al. Cardiac function in mice lacking the glucagon-like peptide-1 receptor. Endocrinology.2003;144:2242–52.
69. Wallner M, Kolesnik E, Ablasser K, Khafaga M, Wakula P, Ljubojevic S, et al. Exenatide exerts a PKA-dependent positive inotropic effect in human atrial myocardium: GLP1R mediated effects in human myocardium. J Mol Cell Cardiol. 2015;89:365–75.
70. Nikolaidis LA, Elahi D, Hentosz T, Doverspike A, Huerbin R, Zourelias L, et al. Recombinant glucagon-like peptide-1 increases myocardial glucose uptake and improves left ventricular performance in conscious dogs with pacing-induced dilated cardiomyopathy. Circulation. 2004;110:955–61.
71. Noyan-Ashraf MH, Shikatani EA, Schuiki I, Mukovozov I, Wu J, Li RK, et al. A glucagon-like peptide-1 analog reverses the molecular pathology and cardiac dysfunction of a mouse model of obesity. Circulation. 2013;127:74–85.
72. Ji Y, Zhao Z, Cai T, Yang P, Cheng M. Liraglutide alleviates diabetic cardiomyopathy by blocking CHOP-triggered apoptosis via the inhibition of the IRE-α pathway. Mol Med Rep. 2014;9:1254–8.
73. Leonardini A, D'Oria R, Incalza MA, Caccioppoli C, Andrulli, Buccheri V, et al. GLP1 receptor activation inhibits palmitate-induced apoptosis via ceramide in human cardiac progenitor cells. J Clin Endocrinol Metab. 2017;102:4136–47.
74. Arturi F, Succurro E, Miceli S, Cloro C, Ruffo M, Maio R, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. Endocrine. 2017;57:464–73.
75. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hänselmann A, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail. 2017;19:69–77.
76. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2016;316:500–8.
77. Briyal S, Shah S, Gulati A. Neuroprotective and anti-apoptotic effects of liraglutide in the rat brain following focal cerebral ischemia. Neuroscience. 2014;281:269–81.
78. Wang MD, Huang Y, Zhang GP, Mao L, Xia YP, Mei YW, et al. Exendin-4 improved rat cortical neuron survival under oxygen/glucose deprivation through PKA pathway. Neuroscience. 2012;226:388–96.
79. Zhu H, Zhang Y, Shi Z, Lu D, Li T, Ding Y, et al. The neuroprotection of liraglutide against ischaemia-induced apoptosis through the activation of the PI3K/AKT and MAPK pathways. Sci Rep. 2016;6:26859.
80. Ma X, Lin W, Lin Z, Hao M, Gao X, Zhang Y, et al. Liraglutide alleviates H2O2-induced retinal ganglion cells injury by inhibiting autophagy through mitochondrial pathways. Peptides. 2017;92:1–8.
81. Chen Y, Zhang X, He J, Xie Y, Yang Y. Delayed administration of the glucagon-like peptide 1 analog liraglutide promoting angiogenesis after focal cerebral ischemia in mice. J Stroke Cerebrovasc Dis. 2018;27:1318–25.
82. Yu M, Moreno C, Hoagland KM, Dahly A, Ditter K, Mistry M, et al. Antihypertensive effect of glucagon-like peptide 1 in Dahl salt sensitive rats. J Hypertens. 2003;21:1125–35.
83. Zhao X, Huang K, Zheng M, Duan J. Effect of liraglutide on blood pressure: a meta-analysis of liraglutide randomized controlled trials. BMC Endocr Disord. 2019;19:4.
84. Baggio LL, Ussher JR, McLean BA, Cao X, Kabir MG, Mulvihill EE, et al. The autonomic nervous system and cardiac GLP1 receptors control heart rate in mice. Mol Metab. 2017;6:1339–49.
85. Golpon HA, Puechner A, Welte T, Wichert PV, Feddersen CO. Vasorelaxant effect of glucagon-like peptide-(7-36)amide and amylin on the pulmonary circulation of the rat. Regul Pept. 2001;102:81–6.
86. Richter G, Feddersen O, Wagner U, Barth P, Göke R, Göke B. GLP1 stimulates secretion of macromolecules from airways and relaxes pulmonary artery. Am J Physiol. 1993;265:L374–L381.

87. Wei R, Ma S, Wang C, Ke J, Yang J, Li W, et al. Exenatide exerts direct protective effects on endothelial cells through the AMPK/Akt/eNOS pathway in a GLP1 receptor-dependent manner. Am J Physiol Endocrinol Metab. 2016;310:E947–E957.
88. Green BD, Hand KV, Dougan JE, McDonnell BM, Cassidy RS, Grieve DJ. GLP1 and related peptides cause concentration-dependent relaxation of rat aorta through a pathway involving KATP and cAMP. Arch Biochem Biophys. 2008;478:136–42.
89. Kim M, Platt MJ, Shibasaki T, Quaggin SE, Backx PH, Seino S, et al. GLP1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. Nat Med. 2013;19:567–75.
90. Oeseburg H, de Boer RA, Buikema H, van der Harst P, van Gilst WH, Silljé HH. Glucagon-like peptide 1 prevents reactive oxygen species-induced endothelial cell senescence through the activation of protein kinase A. Arterioscler Thromb Vasc Biol. 2010;30:1407–14.
91. Gaspari T, Liu H, Welungoda I, Hu Y, Widdop RE, Knudsen LB, et al. A GLP1 receptor agonist liraglutide inhibits endothelial cell dysfunction and vascular adhesion molecule expression in an ApoE−/− mouse model. Diab Vasc Dis Res. 2011;8:117–24.
92. Nystrom T, Gutniak MK, Zhang Q, Zhang F, Holst JJ, Ahren B, et al. Effects of glucagon-like peptide-1 on endothelial function in type 2 diabetes patients with stable coronary artery disease. Am J Physiol Endocrinol Metab. 2004;287:E1209–E1215.
93. Dai Y, Dai D, Wang X, Ding Z, Li C, Mehta JL. GLP1 agonists inhibit ox-LDL uptake in macrophages by activating protein kinase A. J Cardiovasc Pharmacol. 2014;64:47–52.
94. Bruen R, Curley S, Kajani S, Crean D, O'Reilly ME, Lucitt MB, et al. Liraglutide dictates macrophage phenotype in apolipoprotein E null mice during early atherosclerosis. Cardiovasc Diabetol. 2017;16:143.
95. Goto H, Nomiyama T, Mita T, Yasunari E, Azuma K, Komiya K, et al. Exendin-4, a glucagon-like peptide-1 receptor agonist, reduces intimal thickening after vascular injury. Biochem Biophys Res Commun. 2011;405:79–84.
96. Jojima T, Uchida K, Akimoto K, Tomotsune T, Yanagi K, Iijima T, et al. Liraglutide, a GLP1 receptor agonist, inhibits vascular smooth muscle cell proliferation by enhancing AMP-activated protein kinase and cell cycle regulation, and delays atherosclerosis in ApoE deficient mice. Atherosclerosis. 2017;261:44–51.
97. Ritchey ME, Harding A, Hunter S, Peterson C, Sager PT, Kowey PR, et al. Cardiovascular safety during and after use of phentermine and topiramate. J Clin Endocrinol Metab. 2019;104:513–22.
98. Rothman RB, Hendricks EJ. Phentermine cardiovascular safety. Am J Emerg Med. 2009;27:1010–3.
99. Noh MR, Kim SK, Sun W, Park SK, Choi HC, Lim JH, et al. Neuroprotective effect of topiramate on hypoxic ischemic brain injury in neonatal rats. Exp Neurol. 2006;201:470–8.
100. Yang Y, Shuaib A, Li Q, Siddiqui MM. Neuroprotection by delayed administration of topiramate in a rat model of middle cerebral artery embolization. Brain Res. 1998;804:169–76.
101. Tian Y, Guo SX, Li JR, Du HG, Wang CH, Zhang JM, et al. Topiramate attenuates early brain injury following subarachnoid haemorrhage in rats via duplex protection against inflammation and neuronal cell death. Brain Res. 2015;1622:174–85.
102. Cure E, Cure MC, Tumkaya L, Kalkan Y, Aydin I, Kirbas A, et al. Topiramate ameliorates abdominal aorta cross-clamping induced liver injury in rats. Saudi J Gastroenterol. 2014;20:297–303.
103. Wang Z, Huang S, Sheng Y, Peng X, Liu H, Jin N, et al. Topiramate modulates post-infarction inflammation primarily by targeting monocytes or macrophages. Cardiovasc Res. 2017;113:475–87.
104. Dionisio L, Jose De Rosa M, Bouzat C, Esandi Mdel C. An intrinsic gabaergic system in human lymphocytes. Neuropharmacology. 2011;60:513–9.
105. Bhat R, Axtell R, Mitra A, Miranda M, Lock C, Tsien RW, et al. Inhibitory role for GABA in autoimmune inflammation. Proc Natl Acad Sci USA. 2010;107:2580–5.
106. Yang Y, Lian YT, Huang SY, Yang Y, Cheng LX, Liu K. GABA and topiramate inhibit the formation of human macrophage-derived foam cells by modulating cholesterol-metabolism-associated molecules. Cell Physiol Biochem. 2014;33:1117–29.
107. Manzini S, Busnelli M, Parolini C, Minoli L, Ossoli A, Brambilla E, et al. Topiramate protects apoE-deficient mice from kidney damage without affecting plasma lipids. Pharmacol Res. 2018;141:189–200.
108. Salameh TS, Shah GN, Price TO, Hayden MR, Banks WA. Blood-brain barrier disruption and neurovascular unit dysfunction in diabetic mice: protection with the mitochondrial carbonic anhydrase inhibitor topiramate. J Pharmacol Exp Ther. 2016;359:452–9.
109. Bohula EA, Wiviott SD, McGuire DK, Inzucchi SE, Kuder J, Im K, et al. Cardiovascular safety of lorcaserin in overweight or obese patients. N Engl J Med. 2018;379:1107–17.
110. Julius D, MacDermott AB, Axel R, Jessell JM. Molecular characterization of a functional cDNA encoding the serotonin 1C receptor. Science. 1988;241:558–64.
111. Jordan D. Vagal control of the heart: central serotonergic (5-HT) mechanisms. Exp Physiol. 2005;90:175–81.
112. Ferreira HS, Oliveira E, Faustino TN, Silva Ede C, Fregoneze JB. Effect of the activation of central 5-HT2C receptors by the 5-HT2C agonist mCPP on blood pressure and heart rate in rats. Brain Res. 2005;1040:64–72.
113. Hamik A, Peroutka SJ. 1-(m-chlorophenyl)piperazine (mCPP) interactions with neurotransmitter receptors in the human brain. Biol Psychiatry. 1989;25:569–75.
114. Nozulak J, Kalkman HO, Floersheim P, Hoyer D, Schoeffter P, Buerki HR. (+)-cis-4,5,7a,8,9,10,11,11a-octahydro-7H-10-methylindolo[1,7- bc][2,6]-naphthyridine: a 5-HT2C/2B receptor antagonist with low 5-HT2A receptor affinity. J Med Chem.1995;38:28–33.
115. Tecott LH, Sun LM, Akana SF, Strack AM, Lowenstein DH, Dallman MF, et al. Eating disorder and epilepsy in mice lacking 5-HT2c serotonin receptors. Nature. 1995;374:542–6.
116. Calama E, Morán A, Ortiz De Urbina AV, Martin ML, San Roman L. m-CPP, a 5-HT2C receptor agonist that modifies the perfusion pressure of the hindquarter vascular bed of anesthetized rat. Pharmacology. 2005;73:70–5.
117. Fernández MM, Morán A, Martín ML, San Román L. Mesenteric vasoconstrictor responses to 5-hydroxytryptamine in the in situ blood autoperfused rat mesentery:involvement of 5-HT2B and/or 5-HT2C receptor activation. Eur J Pharmacol. 2000;40:221–7.
118. Zhang B, Liu Y, Luo Y, Niu W, Li ZC. Alteration of serotonin 2C receptor expression in the aorta and the pulmonary artery in rats exposed to hypoxia. Chin J Physiol. 2008;51:338–47.
119. Morán A, Ortiz de Urbina AV, Martín ML, García M, Rodriguez-Barbero A, Dorado F, et al. Characterization of contractile 5-hydroxytryptamine receptor subtypes in the in situ autoperfused kidney in the anaesthetized rat. Eur J Pharmacol. 2008;592:133–7.
120. Cataldi M, Muscogiuri G, Savastano S, Barrea L, Guida B, Taglialatela M, et al. Gender-related issues in the pharmacology of new anti-obesity drugs. Obes Rev. 2019;20:375–84.