Pharmacological Treatment of Ischemic Heart Disease

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Few things are more distressing to a physician than to stand beside a suffering patient who is anxiously looking to him for that relief from pain which he feels himself utterly unable to afford. His sympathy for the sufferer, and the regret he feels for the impotence of his art, engrave the picture indelibly on his mind, and serve as a constant and urgent stimulus in his search after the causes of the pain, and the means by which it may be alleviated.

—T. Lauder Brunton, July 27, 1867.

1 Introduction

Chronic myocardial ischemia may be a consequence of obstructive coronary artery disease (CAD), secondary to luminal stenosis and reduced coronary flow reserve, and/or of other conditions, such as vasospasm, microvascular dysfunction, and energetic mismatch [1–3]. According to the latest European guidelines, whenever a macro- or microvascular coronary disorder is documented, the clinical condition could be denoted as chronic coronary syndrome (CCS) [1].

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Of note, myocardial ischemia is often but not always accompanied by chest pain or angina. Indeed, angina is only the final clinical manifestation of a series of pathophysiological changes induced by myocardial energetic unbalance and named the "*ischemic cascade*," including diminished left ventricular compliance, decreased contractility, increased left ventricular end-diastolic pressure, and electrocardiographic changes [4]. The threshold of ischemia associated with symptoms may vary among patients and within the same patient, or may also be absent in conditions of neuropathic functional denervation (i.e., diabetes) [5, 6]: therefore, episodes of silent ischemia may occur.

Although observational studies suggested that silent myocardial ischemia could compromise contractile function and electrical stability, with negative hemodynamic consequences [7], and life-threatening arrhythmias [8–11], there is currently no evidence showing a prognostic benefit of anti-ischemic therapies in this context. Therefore, current guidelines discourage functional testing in asymptomatic individuals [1] and highlight that the main aim of medical therapy in CCS is to target angina rather than ischemia [1].

As for symptomatic patients, while meta-analyses show that all antianginal drugs are similarly efficacious in alleviating angina and increasing exercise tolerance, evidence for improvement in event-free survival is generally missing, apart from beta-blockers (BBs) in patients with heart failure and reduced ejection fraction, and nicorandil for angina-related hospitalization [12, 13].

Nonetheless, treating ischemia may prove value in specific subsets (e.g., in the presence of an extensive ischemic burden and/or of left ventricular systolic dysfunction) [1], and this topic still remains a matter of debate [14, 15].

2 Pathophysiological Mechanisms of Ischemia and Potential Targets

As detailed in the chapter "Pathophysiology of Ischemic Syndromes in Coronary Artery Disease", in the last century, a plethora of elegant physiological and pharmacological studies have outlined the heterogenous pathophysiological determinants of myocardial ischemia [16]. Whereas an impaired oxygen/nutrients' supply due to either coronary (e.g., epicardial artery stenosis, vasospasm, microvascular dysfunction) or noncoronary causes (e.g., anemia, hypoxia, toxic and metabolic disorders) and an unbalanced increase in energetic demand (secondary to increased myocardial contractility, wall stress, or heart rate) are key determinants of myocardial ischemia, more subtle abnormalities in cardiomyocyte metabolism have been observed as well [16–19]. Importantly, these mechanisms are not exclusive but could be variously intertwined and declined in the single patient, fostering the research for a tailored and integrated therapeutic approach (Fig. 1) [20, 21].

Beyond its conduit function, coronary circulation is responsible for modulating myocardial blood flow to match energetic demand across a wide spectrum of physiological conditions, through the mechanisms of autoregulation and autonomic control [22, 23]. Accordingly, in conditions of increased myocardial requests (e.g., physical exercise, emo-

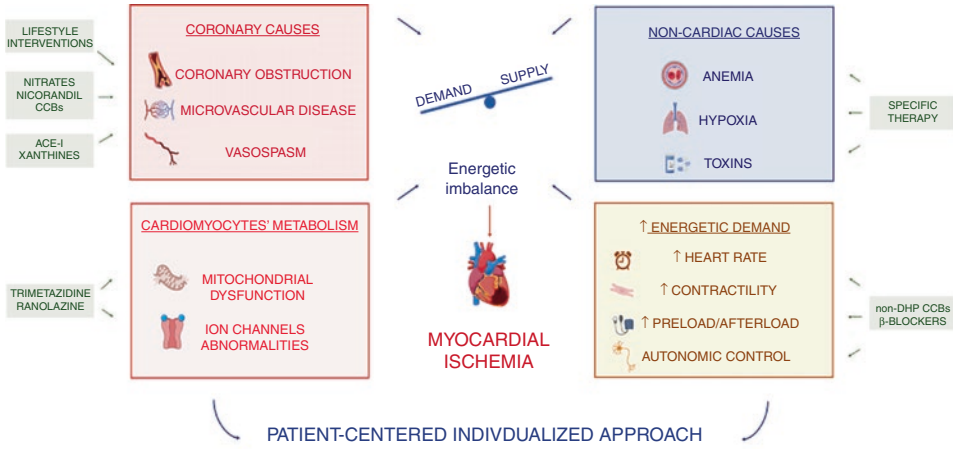

Fig. 1 Pathophysiology-driven pharmacological management of myocardial ischemia. *ACE-i* angiotensin-converting enzyme inhibitors; *CCBs* calcium channel blockers; *DHP* dihydropyridines

tional stress), coronary flow increases proportionally [24]. On the other hand, in the presence of a significant luminal obstruction in an epicardial artery, the downstream flow is usually maintained at rest at the price of exhausting the vasodilatory reserve, so that myocardial ischemia may emerge when a further increase in energetic demand is not adequately counterbalanced [25]. Nevertheless, a certain degree of vasodilation may be obtained through some drugs (e.g., nitric oxide (NO) donors, nicorandil, and calcium channel blockers (CCBs)), which are therefore effective anti-ischemic agents in this setting [26–28].

Although such a hydraulic mechanism has long been considered the fundament of chronic myocardial ischemia and angina, it is nowadays established that this may occur also in the absence of obstructive CAD and persist also after successful revascularization [29–31]. In this regard, vasospasm has been identified as a potential contributor. Although the so-called resting vasospastic or Prinzmetal angina, as originally described [32], represents a rare condition, macro- and/or microvascular spasm may be frequently observed independently of the concomitant atherosclerotic burden [33, 34]. A paradoxical vasoconstrictive response to acetylcholine, which is normally associated with a NO-mediated vasodilation, characterizes coronary vasospasm, implying a pivotal role of endothelial dysfunction [35, 36]. In this context, CCBs (both dihydropyridines—DHP and non-DHP) are a well-established first-line therapy [37, 38], while other vasodilators such as nitrates and nicorandil represent possible alternatives or add-on therapies in refractory cases [39, 40]. On the contrary, BBs are usually not recommended since vasospasm could be exacerbated by the blockage of the "vasodilative" β_2-adrenergic receptors and a paradoxical overstimulation of the "vasoconstrictive" α_1-adrenergic receptors on coronaries' walls [41].

Microvascular disease may underlie myocardial ischemia and angina, also in the absence of detectable epicardial coronary stenosis and vasospasm or other cardiac condi-

tions, due to endothelial and autonomic dysfunction, exaggerated vasoconstrictive and nociceptive responses, and pro-inflammatory signals [3, 42, 43]. Although NO-mediated pathways and Ca^{2+} inflow modulate microvascular tone, too [44], both nitrates and CCBs are poorly effective on microvascular angina [45, 46], particularly when no vasospasm could be detected [47]. Conversely, more promising findings have been obtained for angiotensin-converting enzyme inhibitors, since angiotensin II is a direct modulator of microvascular tone [48] and for xanthines, which may favor flow redistribution toward ischemic areas (by inhibiting the arteriolar vasodilator effects of adenosine) and antagonize adenosine-mediated pain afferents, relieving angina [49].

As anticipated, also the reduction of myocardial energetic demand is an effective strategy to alleviate ischemia and angina and may be achieved by lowering blood pressure and, most importantly, heart rate [50]. Beyond reducing oxygen consumption, a lower heart rate prolongs coronary diastolic perfusion, so that the net effect of negative chronotropic drugs may be an improved contractility of ischemic regions, despite their possible negative inotropic action [51]. Therefore, BBs and non-DHP CCBs play a central role among antianginal therapies [52], while their anti-ischemic efficacy in asymptomatic patients is still controversial [50, 53]. Alternatively, a lower heart rate may be achieved by inhibiting the I_f current with ivabradine, considered a second-line antianginal drug, with no negative inotropic or lusitropic effect [52, 54].

Finally, further targets for anti-ischemic therapies have been identified by shifting the focus on the cardiomyocyte. Indeed, whereas its energetic metabolism is primarily based on mitochondrial oxidation of fatty acids and other substrates (e.g., glucose, ketones) are less utilized in physiological condition [55], in the presence of ischemia, such pathways may be corrupted and anaerobic glycolysis favored, resulting in acidosis, Na^+ and Ca^{2+} overload, and decreased cardiac function [19, 55]. Promoting the shift toward a more efficient energetic asset has therefore emerged as an intriguing strategy and may be achieved by favoring glucose instead of fatty acid utilization. As detailed below in this chapter, two anti-ischemic drugs, i.e., trimetazidine and ranolazine, act in modulating these pathways [56, 57].

3 Medical Therapy of Ischemic Heart Disease

Historically, the first class of drugs that have been used as antianginal were nitrates, followed almost a century after by BBs, then CCBs, trimetazidine, nicorandil, ivabradine, and, finally, ranolazine [58–64] (Fig. 2).

Considering the number of antianginal drugs now available for clinical use, it may be difficult to identify the optimal treatment. Ideally, the best option should control symptoms, improve quality of life, maximize patient's adherence, and minimize drug-related side effects. Furthermore, as suggested by the current guidelines, the therapeutic choice should also be adapted to the patient's characteristics, such as cardiac and noncardiac

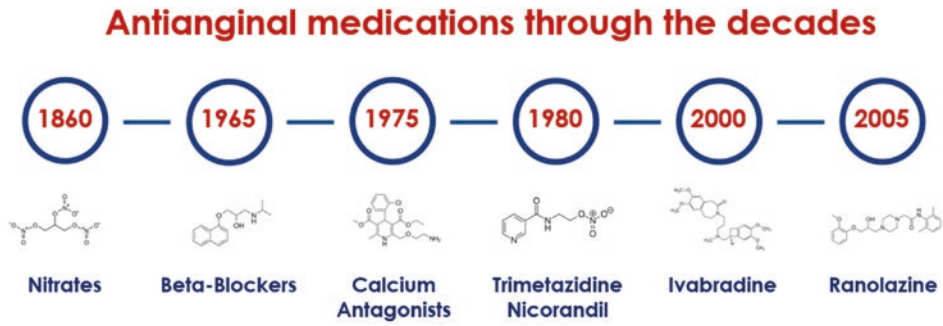

Fig. 2 Antianginal medications through the decades

comorbidities, to improve (soft) outcomes and avoid undesirable side effects [1, 18, 19]. Furthermore, targeting the pathophysiological substrate of myocardial ischemia may further improve therapeutic efficacy [65].

Antianginal drugs are classified as being first-line (BBs, CCBs, and short-acting nitrates on request) or second-line (long-acting nitrates, nicorandil, ivabradine, trimetazidine, and ranolazine) [1]. Second-line medications are usually destinated to patients who have contraindications, do not tolerate, or remain symptomatic despite first-line agents. However, no randomized clinical trial (RCT) has shown superiority of first-line over second-line treatments [1, 21]. A recent systematic review and meta-analysis has also showed that no one antianginal drug is superior to another and that equivalence has only been demonstrated for the use of BBs (atenolol), DHP CCBs (amlodipine, nifedipine), and I_f current inhibitors (ivabradine) [21].

Another meta-analysis supports the combination of DHP CCBs with BBs over monotherapy and to ranolazine added to either BBs or CCBs [66]. According to the same meta-analysis, adding long-acting nitrates and trimetazidine may be effective as well, although the evidence seems more scattered [66]. Similarly, ivabradine was shown to increase exercise time, angina attacks, and use on nitrates when added to BBs in the ASSOCIATE [67] and ADDITIONS [68] trials. There are no significant data for nicorandil as far as combination therapy is concerned [69].

Some authors have also highlighted that each drug/combination may have beneficial or detrimental effects on patients' specific characteristics, and thus a "*diamond*" approach similar to that employed in hypertension (i.e., leaving physician free to choose the most appropriate drug/combination according to patient-specific needs) has been proposed [18]. Considering the mechanisms of action, association of BBs or ivabradine with non-DHP CCBs is not recommended, whereas other combinations (i.e., nitrates/nicorandil with CCBs or ranolazine with trimetazidine) might be partially redundant, unless specific pathophysiology is considered (e.g., vasospastic angina) [18].

3.1 Vasodilators

3.1.1 Nitrates

Short- and long-acting nitrates represent an established class of antianginal drugs, whose effects depend on the release of NO through an enzymatic process (i.e., denitrification) taking place in the vessel walls [70]. By stimulating the soluble guanylyl cyclase of smooth muscle cells, NO promotes the production of cyclic guanosine monophosphate, leading to membrane hyperpolarization and reduction of Ca^{2+} inflow, with consequent vasodilation [70]. Whereas at low doses nitrates act mostly on the venous system (hence reducing preload), arterial vasodilation occurs at higher doses, favoring epicardial coronaries and collateral blood flow perfusion (even in the presence of luminal obstruction) and reducing post-load [71]. Although the potential reduction of myocardial oxygen consumption secondary to reduced pre- and post-load may be partially counterbalanced by an autonomic mediated increase in heart rate, the concomitant use of negative chronotropic drugs (e.g., BBs) may result in synergetic anti-ischemic effect [72]. Furthermore, thanks to their NO-dependent action, nitrates are also effective in relieving vasospastic [73] but not microvascular angina, probably because of the lower sensitivity of resistance arterioles to such signals at clinically used dosages [74].

As recommended by the current guidelines, short-acting nitrates are the first-line therapy to relieve effort angina (class of recommendation (CoR) I, level of evidence (LoE) B), while long-acting nitrates are second-line choices in the long term compared to BBs and non-DHP CCBs (CoR IIa, LoE B) [52]. Indeed, several RCTs have examined the efficacy of nitrates, and in a meta-analysis of 51 studies including a total of 3595 patients with stable angina, their long-term administration was found to be beneficial in preventing angina and improving exercise tolerance but not the overall quality of life [75]. On the other hand, only a few studies have evaluated the survival benefits of chronic nitrate administration in different subsets, yielding substantially neutral results [76–78].

Finally, because of their intense systemic vasodilator action, the use of nitrates may exacerbate various adverse effects, including headache, flushing, and hypotension, while they are not indicated in patients with intraventricular obstruction, severe aortic or mitral stenosis, and constrictive pericarditis, and they should be used with caution in concomitance with other vasodilators [71]. Another limitation for the use of nitrates is the risk of tolerance, with a reduction in their anti-ischemic efficacy [79], so that nitrate-free or low-nitrate intervals are suggested in patients on chronic therapy (CoR IIa, LoE B) [52]. Although the underlying mechanisms are still to be completely clarified, oxidative stress may contribute [79], while the use of alternative molecules may overcome such problem [80].

3.1.2 Nicorandil

Nicorandil is a nicotinamide-nitrate ester holding anti-ischemic properties related to its NO-donor capacity and to a direct stimulation of adenosine triphosphate-sensitive K^+ channels on arterial walls, together leading to vasodilatation, but also to possible metabolic effects [81–83]. Moreover, nicorandil may be effective in alleviating vasospasm [84], and

growing evidence sustains a possible role also in the context of microvascular dysfunction, even though further research seems necessary to confirm such assumption and to clarify the biological mechanisms involved [85, 86].

The use of nicorandil in patients with stable angina has been evaluated in various RCTs, demonstrating good efficacy [20, 52]. Most notably, among 5126 patients with stable angina, nicorandil, compared to placebo, significantly reduced a composite endpoint of cardiovascular events, but not cardiac death or nonfatal myocardial infarction [87]. Therefore, it is considered a second-line treatment to reduce angina frequency and improve exercise tolerance (CoR IIa, LoE B) [52].

Despite the similar mechanisms of action, the use of nicorandil is associated with a lower risk of tolerance than nitrates, whereas nausea, vomiting, mucosal ulcerations, and, most importantly, headache are potential adverse effects, which could affect therapeutic adherence [52, 87].

3.1.3 Dihydropyridine Calcium Channel Blockers

CCBs are a heterogenous class of drugs, characterized by the inhibition of high-voltage-activated L-type Ca^{2+} channels on vascular smooth muscle cells and cardiomyocytes [88]. DHP CCBs (e.g., amlodipine, nicardipine, nifedipine) act more specifically on vascular channels, causing an intense coronary and systemic vasodilation, while they do not act on cardiomyocytes [89].

Beyond vasodilatation, DHP CCBs reduce myocardial oxygen demand by lowering systemic blood pressure (i.e., cardiac post-load) [88, 90] and are effective also in the case of vasospastic [91] and microvascular angina [92, 93], whereas the reflex increase in heart rate could be blunted by the use of BBs, further improving their anti-ischemic efficacy (CoR IIa, LoE B) [52, 94, 95]. In patients with stable angina, the use of nifedipine was associated with a reduced need for coronary angiography and intervention, despite no difference in cardiac death or myocardial infarction [96], while the use of amlodipine reduced the risk of adverse cardiovascular events and of atherosclerosis progression [97].

Although headache, ankle swelling, and hypotension represent possible side effects [89], DHP CCBs are usually well tolerated and represent first-line antianginal therapies (CoR I, LoE A) [52].

3.2 Drugs Reducing Myocardial Oxygen Consumption

3.2.1 Non-dihydropyridine Calcium Channel Blockers

Differently from DHP CCB, diltiazem and verapamil (i.e., non-DHP CCB) show a higher selectivity for myocardial than for vascular Ca^{2+} channels, and their anti-ischemic efficacy mostly relies upon the reduction of myocardial oxygen demand secondary to a negative inotropic and heart rate-dependent chronotropic effects [88, 89, 98]. The use of these drugs is therefore recommended to control heart rate and symptoms in patients with stable effort angina (CoR I, LoE A) [1], while they are routinely used also in patients with vaso-

spastic angina [99] and may be effective in the case of microvascular dysfunction [100], where ongoing studies (e.g., NCT04777045) are expected to confirm such findings.

Although generally safe, RCTs failed to show any survival benefit with the use of diltiazem [101], while verapamil was shown to reduce adverse events only in patients after myocardial infarction and without heart failure [102]. Moreover, they share similar side effects with DHP CCBs, and they should be used with caution in patients at risk of sinus bradycardia or atrioventricular blocks and in those with systolic dysfunction [52, 88, 89].

3.2.2 Beta-Blockers

BBs are very effective antianginal therapies, as demonstrated by the high rate of patients free from anginal events after optimization of medical therapy in both the COURAGE (87% receiving BBs) [103] and the ORBITA (77% receiving BBs) [104] trials, and thus represent a first-line treatment to control heart rate and symptoms in patients with stable effort angina (CoR I, LoE A) [1].

Similarly to non-DHP CCBs, BBs' antianginal action mainly relies on the reduction of myocardial oxygen demand [19]. Their primary action is to decrease heart rate and thus to increase diastolic duration and coronary perfusion, in particular blood flow per heartbeat [105]. Although BBs have negative inotropic effects (less than non-DHP CCBs), by decreasing oxygen consumption in the healthy myocardium, they may increase perfusion to the post-stenotic myocardium and also its regional contractility [106, 107], but only if heart rate reduction is achieved [51]. However, they may also favor coronary vasoconstriction by blocking *β2*-adrenergic receptors, so *β1*-selective compounds, or BBs with vasodilatation capability, such as carvedilol—an *α*-*β*-blocker [108] [109]—or nebivolol, through NO release [110], are usually preferred in the treatment of CCS, unless a vasospastic component is hypothesized. In that case, BBs should be used with caution (i.e., low dose or adding a vasodilator) or avoided, similarly to other conditions such as asthma, baseline bradycardia, or evidence of atrioventricular conduction abnormalities.

Although several studies have investigated the prognostic effects of BBs, according to the main RCTs and meta-analyses [111], this seems limited to patients receiving BBs early after myocardial infarction [112] or with left ventricular systolic dysfunction [113].

3.2.3 Ivabradine

As non-DHP CCBs and BBs, also ivabradine's antianginal capacity derives from a reduction of heart rate. This is obtained through a selective inhibition of the I_f (or "funny," inward Na^+-K^+) current of the sinoatrial node [114, 115], which has a key role in the generation of spontaneous depolarization of pacemaker cells and in mediating the autonomic control of heart rate [116]. By inhibiting I_f current, ivabradine causes a decrease in the slope of depolarization, lowering heart rate [105] and promoting a proportionate improvement in ischemic regional blood flow and contractile function [117].

The risk of bradycardia with ivabradine is low, since its effect is heart rate dependent by acting on open channels [118]. Furthermore, ivabradine does not affect myocardial work or vascular tone, favoring its use when such effects would be undesirable (i.e., patients with hypotension) [119].

Despite those premises, the increased risk of cardiovascular death and nonfatal myocardial infarction observed in patients with CCS treated with ivabradine in the SIGNIFY trial [120] raised some concerns, which could have been at least partially explained by the concomitant use of non-DHP CCBs (which may inhibit the ivabradine-metabolizing cytochrome p450, i.e., CYP3A4) causing bradycardia in a relevant proportion of patients. Hence, this association should be avoided. On the contrary, no safety concerns were observed when administering ivabradine with BBs, in the BEAUTIFUL trial, in which ivabradine was however shown not to improve outcome in patients with CCS and left ventricular systolic dysfunction [121], apart from decreasing the risk of hospitalization for myocardial infarction or coronary revascularization in patients with a heart rate ≥70 bpm.

Of note, ivabradine may also be useful in improving symptoms in patients with microvascular dysfunction [122], even though future studies should confirm such findings. Finally, outside the CCS scenario, ivabradine was found to decrease the combined outcome of cardiovascular mortality and hospitalization (mainly driven by reduced hospitalizations for worsening heart failure) in patients with heart failure and reduced ejection fraction (89% on BBs) [123].

3.3 Myocyte Metabolism Modulators

3.3.1 Trimetazidine

Trimetazidine increases cellular tolerance to ischemia by decreasing fatty acid metabolism through the inhibition of 3-ketoacyl CoA thiolase, shifting myocardial metabolism toward pyruvate oxidation [56, 61]. Trimetazidine also stimulates glucose metabolism and insulin sensitivity [124].

The antianginal/anti-ischemic effects of trimetazidine are similar to those obtained with BBs or CCBs [125]. Of note, the absence of relevant hemodynamic consequences [126] prompts the use of this molecule as a second-line treatment in patients that do not tolerate, have contraindications to, or whose symptoms are not adequately controlled by BBs, CCBs, and long-acting nitrates (CoR IIa, LoE B) [1]. When used in combination with metoprolol, trimetazidine was shown to decrease angina and increase exercise duration and time to ST-segment depression compared to metoprolol alone in 426 patients with stable, effort-induced angina and documented CAD (TRIMPOL II trial) [127]. Similar findings were obtained adding trimetazidine to atenolol in the VASCO trial [128] or to diltiazem [129]. The overall beneficial effect of trimetazidine on anginal attacks, daily use of nitrates, exercise duration, and time to ST-segment depression has been confirmed also in three meta-analyses [130–132]. Trimetazidine prolonged exercise time and time to ST depression also in patients with microvascular angina in a small placebo-controlled RCT [133]. On the contrary, ranolazine seems ineffective on major cardiovascular adverse events or angina recurrence in patients who have undergone successful percutaneous coronary intervention from the ATPCI trial (n = 6007) [134]. Trimetazidine remains contraindicated in Parkinson's disease and motion disorders, such as tremor (shaking), muscle rigidity, walking disorders, and restless leg syndrome [1].

3.3.2 Ranolazine

Ranolazine, similarly to trimetazidine, is a metabolic antianginal agent, which inhibits fatty acid oxidation in the mitochondria and favors glucose metabolism [135]. Its main mechanism of action is however to increase myocardial relaxation by reducing Ca^{2+} overload caused by inhibition of late Na^{+} currents [136]. Like trimetazidine, also ranolazine does not affect heart rate or blood pressure and therefore may be used in patients with hypotension or bradycardia [137, 138].

The antianginal properties of ranolazine have been evaluated in several RCTs. In patients with CCS, the use of ranolazine was associated with fewer angina episodes and longer exercise duration compared to placebo [138], in both patients without other antianginal therapies or already on standard treatment [139–141]. Ranolazine was shown to improve angina and use of nitrate in patients with diabetes compared to placebo [142], but did not reduce angina, need for repeated revascularization, or angina-related hospitalizations in patients with incomplete revascularization: a high nonadherence to the drug may partly explain such findings [143]. Likewise, ranolazine seems ineffective in patients with microvascular disease [144]. An exception seems to be represented by women with microvascular angina, in whom ranolazine was shown to improve angina and myocardial ischemia, albeit only in those with reduced coronary flow reserve [145]. Ranolazine seems to be also not beneficial in patients with acute coronary syndrome as shown in the MERLIN-TIMI trial [146], even though a possible antiarrhythmic effect has been observed in this scenario [147].

In 2017, a Cochrane systematic review and meta-analysis on the use of ranolazine in patients with CCS has been published, highlighting the positive effect of ranolazine on angina (moderate quality of data), some evidence of increased risk of nonserious side effects (low quality of data), and an uncertain effect on both overall and cardiovascular mortality (low quality of data) [148].

Side effects of ranolazine, such as dizziness, nausea, and constipation, are dose dependent [149]. The inhibition of late sodium currents, together with its effect on delayed rectifier potassium currents, also causes prolongation of QT interval [149], and thus ranolazine should be avoided in patients with long QT interval or already taking QT-prolonging drugs. However, no significant increase in life-threatening arrythmias has been noticed in multiple safety studies [150].

4 Novel Perspectives from Animal Models and Human Studies

Therapeutic efficacy, safety profile, and cost-effectiveness are essential factors to be considered when designing a novel drug [151]. Standing this premise, several anti-ischemic compounds are on the pipeline. Novel vasodilators, metabolic modulators, as well as angiogenetic factors and cell therapies represent possible opportunities, especially for patients with refractory angina (Fig. 3).

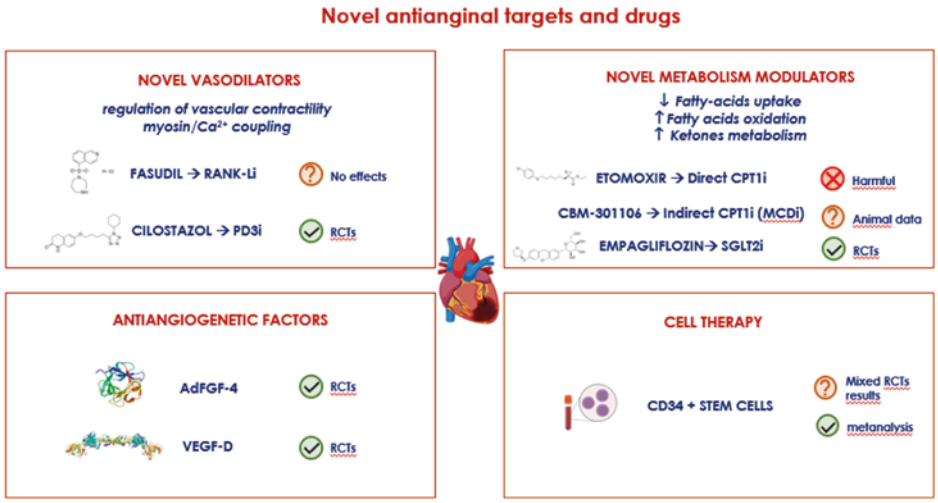

Fig. 3 Novel antianginal targets and drugs. *CPT1i* inhibitor of carnitine palmitoyltransferase I; *FGF* fibroblast growth factor; *MCDi* inhibitor of malonyl-CoA decarboxylase; *PDE3i* inhibitor of phosphodiesterase 3; *RANKL-i* inhibitor of the receptor activator of nuclear factor kappa-B ligand; *RCTs* randomized controlled trials; *SGLT2i* inhibitor of sodium glucose transporter 2; *VEGF* vascular endothelial growth factor

4.1 Novel Compounds with Vasodilatory Effects

The small guanosine triphosphatase RhoA and its downstream effector Rho-kinase are involved in the regulation of vascular contractility, leading through inhibition myosin light-chain phosphatase to Ca^{2+} sensitization in response to vasoconstrictor stimuli [152]. Fasudil, a Rho-kinase inhibitor approved in Japan for the prevention of cerebral artery vasospasm in the setting of subarachnoid hemorrhage [153], has been tested in animal studies and in small trials in patients with microvascular spasm [154] and in patients with stable angina [155]. While fasudil intracoronary infusion was shown to prevent Ach-mediated vasoconstriction [153], fasudil oral administration only increased time to ST depression and had no effect on symptoms in humans [155]. To date, no Rho-kinase inhibitor has been approved for the treatment of vasospastic angina, and more clinical evidence is needed.

A selective phosphodiesterase-3-inhibitor, cilostazol, has also been shown to be efficacious in vasospastic angina in small clinical trials [156, 157], although its mechanism of action remains to be elucidated. In 49 patients with vasospastic angina, cilostazol decreased weakly angina episodes, proportion of angina-free period of angina severity compared to placebo, at the cost of increased rate of headache [157]. Still, its efficacy, dosage, and safety should be confirmed in larger RCTs.

4.2 Novel Modulators of Myocardial Metabolism

Since alterations in myocardial substrate preference contribute to energetic inefficiency, contractile dysfunction, and severity of ischemia, novel drugs inhibiting fatty acid oxidation or increasing the coupling of glycolysis to glucose oxidation represent promising approaches in CCS [158].

Decreasing myocardial fatty acid uptake may be obtained by acting on CD-36 (a sarcolemmal transporter responsible for up to 50% of cardiac fatty acid uptake) [159], and sulfo-N-succinimidyl-oleate was shown to inhibit fatty acid uptake in vitro in various cell lines including cardiomyocytes [160]. Interestingly, its infusion increased the glycolytic rate by 46% and pyruvate-dehydrogenase activity by 53%, while it decreased lactate efflux rate by 56% in the hearts of diabetic rats during hypoxia, compared with untreated rats, preventing cardiac dysfunction in hypoxic conditions. Although promising, whether this compound might be beneficial in CCS is still to be demonstrated.

The rate of cardiac fatty acid oxidation is regulated by the activity of carnitine palmitoyltransferase-I. While the use of direct inhibitors (e.g., etomoxir, perhexiline, oxfenicine, teglicar) may be burdened by hepatotoxic and cardiotoxic effects due to unspecific mitochondrial effects [161], an indirect inhibition of this pathway by malonyl-CoA may be a promising approach. CBM-301106 inhibits malonyl-CoA decarboxylase, which catalyzes degradation of malonyl-CoA converting it to acetyl-CoA and thus decreases long-chain fatty acid metabolism [161]. This molecule reduced fatty acid oxidation and lactate production during demand-induced ischemia in various rat and pig models of ischemic heart disease [162–164], but it has to be tested in humans.

The role of ketones in cardiac energetics may be important in the condition of limited energy supply, as in the case of the failing heart [165]. Whether ketone metabolism may be a "super-fuel," increasing cardiac efficiency or changing fatty acid oxidation or glucose metabolism, is still debated [166, 167]. In this respect, the positive effects of Na^+-glucose-cotransporter-2-inhibitors (SGLT2-i) on cardiovascular outcomes in diabetic patients and in those with heart failure could be partially ascribed to an increased cardiac consumption of ketone bodies [168, 169]. However, the increase in ketone bodies following administration of SGLT2-i is usually mild and higher during fasting (i.e., at night) [169]. Therefore, it is currently unknown whether this may be sufficient to change myocardial metabolism (especially during daily activity), so as to have favorable effects on patients with CCS. Of note, empagliflozin has been recently shown to decrease contractile dysfunction and arrhythmias following ischemia in Langendorff-perfused rabbit heart [170], but the effects on ketone bodies were not assessed. This topic should be then addressed by dedicated studies.

4.3 Angiogenetic Factors

Vascular endothelial growth factors (VEGF) and fibroblast growth factors (FGF) have been tested in a few studies mainly in the setting of refractory angina [171], starting from the pioneering works in rabbit with hindlimb ischemia by Takeshita [172] and in humans by the group of Isner [173]. However, in the setting of RCTs, the percutaneous intracoronary administration or epicardial injection of VEGF (during bypass surgery) via naked plasmid or adenoviral vectors failed to deliver significant clinical effects, although no significant long-term side effect was observed [174].

On the other hand, intracoronary adenoviral mediated FGF-4 delivery improved exercise time in postmenopausal women as shown in a pooled analysis of the AGENT-3 and AGENT-4 trials [171]. The results of two similar trials, the Russian ASPIRE trial (NCT01550614) [174] based on intracoronary administration of Ad5FGF-4 (open-label design, no placebo, completed in 2016) and the AWARE trial [174] based on intracoronary administration of AdFGF-4 only in women with stable angina, have never been published.

Finally, intramyocardial adenoviral delivery of VEGF-D showed promising results in the KAT301 (phase I–IIa, $n = 60$) trial [175], where VEGF-D administration was associated with a significant improvement of myocardial perfusion reserve, reduction of angina, and improvement of quality of life, differently from placebo, especially in patients with high lipoprotein (a) levels. A larger phase IIb multicentric trial on VEFG-D is currently ongoing [171].

4.4 Cell Therapy

Similarly to angiogenetic factors, cell therapy has also been tested in refractory angina [171], but also in myocardial infarction and heart failure [176]. Although bone marrow-derived progenitors do not transform into myocytes, they may exert paracrine effects. Different pro-angiogenic cells were administered in an autologous setting, including unfractionated bone marrow-derived mononuclear cells, selected endothelial progenitors (i.e., CD34+ and CD133+ cells), or mesenchymal stem [177].

In the ACT34-CMI placebo-controlled trial ($n = 167$), patients with refractory angina receiving intramyocardial injection of CD34+ stem cells showed improved exercise tolerance ($p = 0.01$) and angina frequency ($p = 0.02$), also after a 2-year follow-up, where a trend of reduction in major events was observed as well [178]. Conversely, the RENEW trial was prematurely terminated by the sponsor for strategic consideration after enrolling

only 112 of the 444 patients originally planned, showing a borderline reduction ($p = 0.05$) in angina frequency and only a trend toward an increase in exercise time at 3 months ($p = 0.06$), lost at 6 and 12 months. In a meta-analysis [179] including 3 phase II trials and 269 patients, intramyocardial therapy with CD34+ stem cells was superior to placebo in improving angina frequency, increasing exercise time, and decreasing mortality, without significant adverse events, thus supporting future larger trials in refractory angina patients.

5 Conclusions

Various anti-ischemic medications are currently available and extensively used in the routine clinical practice. Although their prognostic benefits are poor or scarcely investigated, they seem to be equally effective in relieving angina and improving quality of life. However, considering the multifactorial pathophysiology of myocardial ischemia and the heterogeneity of patients with CCS, a more rational patient-tailored use of anti-ischemic drugs may yield further benefits. Finally, various promising molecules are emerging from exploratory animal and preliminary clinical studies and may prove their value in the next future.

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