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The Role of Nicorandil in the Management of Chronic Coronary Syndromes in the Gulf Region

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ABSTRACT

Chronic coronary syndromes (CCS) and stable angina are a growing clinical burden worldwide. This is of particular concern in the Gulf region given its high prevalence of cardiovascular risk factors, especially diabetes mellitus and smoking. Despite recommendations on the use of first- and second-line anti-anginal medication, management challenges remain. Current guidelines for pharmacologic treatment are not determined by the range of pathophysiological mechanisms of ischaemia and consequent angina, which may occur either in isolation or co-exist. In this article, we highlight the need to improve knowledge of the epidemiology of chronic coronary syndromes in the Middle East and Gulf region, and the need for studies of stratified pharmacologic approaches to improve symptomatic angina and quality of life in the large and growing number of patients with coronary artery disease from this region. We discuss the role of nicorandil, currently recommended as a second-line anti-anginal drug in CCS patients, and suggest that this may be a particularly useful add-on therapy for patients in the Gulf region.

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Key Summary Points
CCS is a growing clinical burden worldwide, particularly in the Gulf region.
Current guideline recommendations for anti-anginal escalation have a limited evidence base.
Nitrates are frequently used for the treatment of CCS but have their limitations.
Nicorandil is a useful therapeutic option offering vasodilatory and cardioprotective effects.
Nicorandil has a contemporary randomised evidence base and a favourable clinical profile.

DIGITAL FEATURES

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INTRODUCTION

Chronic coronary syndromes (CCS) and symptomatic stable angina pectoris are a growing clinical burden worldwide. This is especially the case in the Gulf region due to the high prevalence of coronary artery disease (CAD) making the use of optimal anti-anginal therapy of paramount importance in this population. Despite evidence showing that anti-anginal therapy improves quality of life, physicians often encounter challenges with individualising anti-anginal medication choices, especially when guideline-directed algorithms either inadequately control symptoms or are not tolerated. This may in part be addressed by adopting an approach of stratifying treatment choices according to the mechanism(s) of ischaemia operating in individual patients. In this review, we discuss the high burden of cardiovascular disease, current treatment landscape in the Middle East and Gulf region in the context of current international guidelines. We focus on the management of patients with symptomatic stable angina pectoris as a major subgroup of CCS, and highlight the potential benefits of nicorandil in managing CCS in this region.

CLINICAL PRESENTATION

The 2019 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of CCS sought to capture the dynamic nature of stable CAD and its varied clinical presentations. The guidelines differentiate six categories of patients with suspected or established CCS [1]:

- Patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea
- Patients with new onset heart failure or left ventricular dysfunction and suspected CAD
- Asymptomatic and symptomatic patients with stabilised symptoms < 1 year after acute coronary syndrome (ACS) or with recent revascularisation
- Patients with angina and suspected vasospastic or microvascular disease
- Asymptomatic patients in whom CAD is detected at screening

This review will focus on patients who are symptomatic with 'stable' anginal symptoms in the setting of epicardial CAD, coronary microvascular dysfunction and vasospastic angina. Patients with stable angina pectoris experience episodes of reversible mismatch of myocardial oxygen supply and demand, usually in association with exercise, emotion or other stressors [2]. Patients with symptomatic stable angina pectoris need to be differentiated from those with unstable angina [1].

EPIDEMIOLOGY

High Burden of Cardiovascular Disease

Cardiovascular disease (CVD) remains the leading cause of death globally. The World Health Organization (WHO) estimated that, in 2016, 17.9 million people died from CVD, accounting for 31% of all mortality worldwide. Atherosclerotic diseases account for $\sim 85\%$ of CVD mortality, principally due to myocardial infarction and stroke [3]. The Global Burden of Disease 2015 study estimated that there were 422.7 million cases of CVD worldwide, with ischaemic heart disease (IHD) the leading cause of death (8.9 million deaths) [4].

The burden of CVD is rising, particularly in low- and middle-income countries in which 75% of global CVD mortality occurs [5]. In low- and middle-income countries in particular, mortality is disproportionately high due to larger population sizes and the increasing prevalence of traditional cardiovascular risk factors, such as poor diet, physical inactivity, obesity,

tobacco use, diabetes mellitus (DM), hypertension and hyperlipidaemia.

The Gulf region bears a particularly heavy healthcare burden from CAD. A community-based study of 17,232 participants in Saudi Arabia found a CAD prevalence of 5.5% [6]. The WHO estimated that, of the total mortality from non-communicable diseases in the countries within the Gulf Cooperation Council, CVD accounted for 23–49% [7]. The Middle East has the lowest age for first presentation with acute myocardial infarction (median age 51 years) and the highest proportion of acute myocardial infarction under 40 years of age (11.2%) [8]. This median age of presentation is 12 years lower than in Western Europe. Systematic reviews have confirmed the high prevalence of cardiovascular risk factors in the Middle East, in particular, obesity (24.5%), DM (10.5%), hypertension (21.7%) and smoking (15.6%) [9, 10]. Of note, while smoking has declined in most Western countries from the late 1980s and 1990s, tobacco consumption has increased in the majority of Middle Eastern countries and is expected to rise further, particularly in young men [11]. The association between high rates of smoking in younger men and premature ACS has already been demonstrated in the Middle East and North Africa [12]. As a result, the number of patients with CCS and symptomatic angina pectoris can be expected to rise.

Need For Gulf Region-Specific Data on CCS

There are few data reporting the prevalence of CCS in the Middle East, with most estimates of disease burden extrapolated from ACS cohorts. The contemporary prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) provides the most recent regional data [13]. CLARIFY enrolled 32,105 patients with CCS from 45 countries worldwide between 2009–2010 and followed them for 2 years. It included 1511 patients from the Middle East and Gulf region. These patients experienced the highest prevalence of DM and elevated body mass index, despite a low prevalence of positive family history of CAD. Rates of anti-anginal use

were as follows: β-blockers, 87.5%; calcium channel blockers, 23.9%; ivabradine, 5.2%; nitrates or other anti-anginal drug, 32.8%.

Despite the increasing burden of disease, randomised controlled trials (RCTs) or high-quality registry data for anti-anginal drugs in the Middle East and Gulf region are not available. Health economic analyses of CCS management in the Gulf region are also scarce. A prospective observational study in Saudi Arabia of patients diagnosed or suspected of having IHD estimated the direct medical costs associated with hospitalisation and subsequent diagnosis of stable angina as US$9064 (average length of stay, 6.5 days) [14]. Further studies are needed to address these important and growing unmet clinical needs of patients in the Middle East and Gulf regions.

IMPACT OF DIABETES MELLITUS (DM)

DM is estimated to have a prevalence of 410 million people globally, of whom 90% have type 2 DM. This is a particularly severe issue in the Gulf region where the prevalence is consistently greater than the global average and has been dramatically increasing over the past 20 years, driven predominantly by increasing obesity [15, 16]. The prevalence of type 2 DM in Saudi Arabia has increased from ∼ 4% in the 1980s to ∼ 25% in 2015 and is expected to almost double by 2035 [17]. Diagnosis is often delayed, with 40.3% of patients meeting diagnostic criteria being unaware of the diagnosis, resulting in suboptimal glycaemic control [18] and high rates of complications [15, 19].

The Gulf locals with Acute Coronary Syndrome Events (Gulf COAST) registry, a prospective, multinational, longitudinal, observational cohort study of Gulf citizens admitted with a diagnosis of ACS provides contemporary evidence of the regional burden of DM on cardiovascular mortality [20]: 53.3% of patients with ACS had DM in whom in-hospital, 30-day and 1-year mortality were significantly higher compared to non-diabetics. Patients with angina and concomitant DM also represent a challenging group to manage as they typically have

more diffuse and extensive CAD, coronary microvascular dysfunction, and a greater burden of symptomatic angina than those without DM [21–23]. Given the increasing prevalence of DM and its impact on cardiovascular health in the Gulf region, improved detection, mitigation of cardiovascular risk and anti-anginal treatment are of paramount importance in this high-risk and challenging population.

MANAGEMENT CHALLENGES

Symptomatic angina pectoris may be caused by several ischaemic mechanisms, each of which can coexist. Understanding the relative contributions of each of these mechanisms within an individual patient can provide a rational approach for stratified selection of anti-anginal drug therapy. These include flow limitation due to epicardial coronary stenosis from obstructive CAD, coronary microvascular dysfunction and vasospasm [24–26]. A comprehensive review of anti-anginal drug therapy is beyond the scope of this report and we would refer the reader to current guidelines [1] and contemporary reviews of anti-anginal drugs [24, 25]. In the following sections, we have focussed on the role of nicorandil in the management in the CCS, in particular to highlight features of this drug which may address some of the particular challenges clinicians in the Gulf region face when managing patients with CCS and symptomatic angina pectoris.

Stratified Selection of Anti-anginal Drug Therapy

The choice of anti-anginal drug strategy depends on patient-related factors (mechanisms of ischaemia, haemodynamics, tolerability, drug interactions), physician experience, drug availability and cost [27]. The ESC 2019 CCS guidelines represent a significant advance, but a limitation remains in that they continue to recommend an algorithmic tiered approach to selection of anti-anginal drugs, which is not based on the results of appropriately powered randomised placebo-controlled trials, and further do not explicitly recommend drug choices

based on the mechanism(s) of ischaemia operating in an individual patient [28, 29]. Ferrari et al. have previously argued that classification into first- and second-line drugs is not supported by a definitive evidence base [24, 25]. The recommended algorithm for combining multiple anti-anginal drugs is based predominantly on expert opinion rather than considering a formal stratification according to the underlying mechanism(s) of angina (Table 1). A recent comprehensive systematic review of medical treatment of angina revealed only 72 RCTs comparing two anti-anginals (total $n = 7034$) between 1964 to the present. Only 13 studies evaluated between 100–300 patients with more than 50 patients per group to allow for meaningful comparisons between groups. "Second-line" drugs, however, have a stronger contemporary evidence base [30–32].

Given the lack of robust evidence showing superiority of any given anti-anginal drug, a more rational and personalised approach should be adopted that tailors the use of anti-anginal drug combinations according to physiological factors such as haemodynamics, mechanisms of ischaemia and comorbidities [24]. Recent guidelines also do not explicitly recommend treatment algorithms to be tailored according to the pathophysiological mechanism(s) causing ischaemia and symptoms in any given individual patient. This would seem an intuitive and rational approach, the principle of which is supported by recent studies such as the CorMicA trial [33].

Lack of Improved Cardiovascular Outcomes with Anti-anginals

No anti-anginal drug has been shown to improve cardiovascular mortality in symptomatic stable angina pectoris. Contemporary data from the CLARIFY and REACH registries have failed to demonstrate a reduction in all-cause death in patients on β-blockers [25, 34]. Calcium channel blockers do not improve mortality regardless of history of myocardial infarction. A double-blind placebo-controlled RCT of ivabradine ($n = 19,102$) in stable CAD, in patients without heart failure, did not reduce

Table 1 ESC and ACC/AHA guidelines on anti-ischaemic drugs in stable coronary artery disease [1, 121]

ESC recommendations	Treatment option	Class	Level
First line	β-blockers and/or calcium channel blockers to control heart rate and symptoms	I	A
	If symptoms not controlled on a β-blocker or a calcium channel blocker, the combination of a β-blocker and a dihydropyridine calcium channel blocker should be considered	IIa	C
	Initial first-line treatment with a β-blocker and a dihydropyridine calcium channel blocker should be considered	IIa	B
Second line	Long-acting nitrates should be considered when initial therapy with a β-blocker and/or a non-dihydropyridine calcium channel blocker is contraindicated, poorly tolerated or inadequate in controlling symptoms	IIa	B
	Nicorandil, ranolazine, ivabradine or trimetazidine should be considered to reduced angina frequency and improve exercise tolerance in those who cannot tolerate, have contraindications to, or whose symptoms are not controlled by β-blockers, calcium channel blockers and long-acting nitrates	IIb	B
	In selected patients, the combination of a β-blocker or a calcium channel blocker with second-line drugs (nicorandil, ranolazine, ivabradine and trimetazidine) may be considered for first-line treatment according to heart rate, blood pressure and tolerance		
Other	Short-acting nitrates are recommended for immediate relief of effort angina	I	B
	When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance	IIa	B
	In patients with a low heart rate and blood pressure, ranolazine or trimetazidine may be considered as first-line to reduce angina frequency and improve exercise tolerance	IIb	C
	In selected patients, the combination of a β-blocker or a calcium channel blocker with a second-line drug (nicorandil, ranolazine, ivabradine and trimetazidine) may be considered for first-line treatment according to heart rate, blood pressure and tolerance	IIb	B
	Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy or co-administration with phosphodiesterase inhibitors	III	B

AHA recommendations	Treatment option	Class	Level
First line	β-blocker	I	B
	Long-acting non-dihydropyridine calcium channel blocker (e.g. verapamil or diltiazem)	IIa	B
Second line	Calcium channel blocker/long-acting nitrates when β-blockers contraindicated or unacceptable side effects	I	B
	Addition of calcium channel blocker/long-acting nitrates if β-blocker unsuccessful alone	I	B
	Ranolazine can be used as a substitute if initial treatment with a β-blocker is ineffective, contraindicated or not tolerated	IIa	B
	Addition of ranolazine if initial treatment with β-blocker unsuccessful	IIa	A
Other	Sublingual nitroglycerin for immediate relief of angina	I	B

the composite primary endpoint of cardiovascular death or non-fatal myocardial infarction [35]. Similarly, the BEAUTIFUL trial of ivabradine in patients with CAD and left ventricular systolic dysfunction did not demonstrate improvements in the primary composite endpoint of cardiovascular death, hospitalisation for acute MI, or hospitalisation for new or worsening heart failure [36]. A Cochrane Review of ranolazine similarly did not find any reduction in cardiovascular death [37]. However, ranolazine significantly reduced glycated haemoglobin levels (HbA_{1c}) in patients with stable angina enrolled in the MERLIN trial, thought due to β-cell preservation, inhibition of glucose secretion and enhanced insulin secretion [38].

Should Long-Acting Nitrates be the First Choice Second-Line Agent?

Long-acting nitrates are the most commonly prescribed class of anti-anginal worldwide and their utilisation in the Middle East and Gulf Region is high. They are metabolised to produce vasoactive nitric oxide and, at low doses, venodilate to reduce preload, venous return, ventricular volume and myocardial tension leading to reduced myocardial oxygen demand. At higher doses, they vasodilate coronary arteries, improve subendocardial perfusion, decrease ventricular diastolic pressure and lower blood pressure. Short-acting nitrates have a Class I Level B recommendation for the immediate relief of angina in the 2019 ESC guidelines. Long-acting nitrates have been upgraded and are now recommended if β-blocker or calcium channel blocker therapy is unsuccessful. However, while they are frequently prescribed, their use is not supported by a high-quality evidence base with no new supporting evidence that they provide significant added anti-anginal effects on top of first-line drugs [28, 29]. In meta-analyses, long-acting nitrates are not superior to other anti-anginals at improving symptoms and exercise outcomes [39–41]. Other studies have suggested that long-acting nitrates cause endothelial dysfunction from mechanisms such as the production of reactive oxygen species

[42, 43]. Furthermore, nitrate tolerance also remains a significant real-world problem. Extended-release nitrates should be dosed with a nitrate-free interval of at least 8 h. In patients who develop nitrate tolerance, there have been increasing concerns regarding adverse cardiovascular outcomes with the long-term use of nitrates due to the accumulation of free radicals, increased vasoconstriction and rebound angina [43–46]. Pseudo-tolerance may also develop, which is thought to be due to counter-regulatory responses from activation of the renin–angiotensin–aldosterone system, increased circulating catecholamines and vasopressin, sodium retention and expansion of plasma volume [47].

In registry data, long-term nitrate therapy (18 months) in patients with healed myocardial infarction was associated with increased recurrent coronary events [48]. The Japanese Coronary Artery Disease (JCAD) Study of patients who had significant stenosis in at least one coronary artery, and who were followed-up for an average of 2.7 years, found that nitrates had an approximately 15% increase in adverse outcomes ($p = 0.005$). In vasospastic angina, there is an indication of increased risk of major adverse cardiac events in those on long-term nitrates and when combined with nicorandil [49–51].

Nicorandil

Nicorandil may be a useful option especially if considering a nitric oxide donor for treatment of symptomatic angina. It may be particularly helpful in the Middle East given the high prevalence of DM and its association with coronary microvascular dysfunction [52], a condition in which nicorandil has shown benefit [53, 54]. In addition to its vasodilatory effects, it is also cardioprotective and has properties that mimic ischaemic preconditioning (Fig. 1). Furthermore, it does not induce endothelial dysfunction or significant tolerance, and can mediate vasodilatation at a microcirculatory level. It has favourable characteristics compared to long-acting nitrates and other nitric oxide donors such as molsidomine [55]
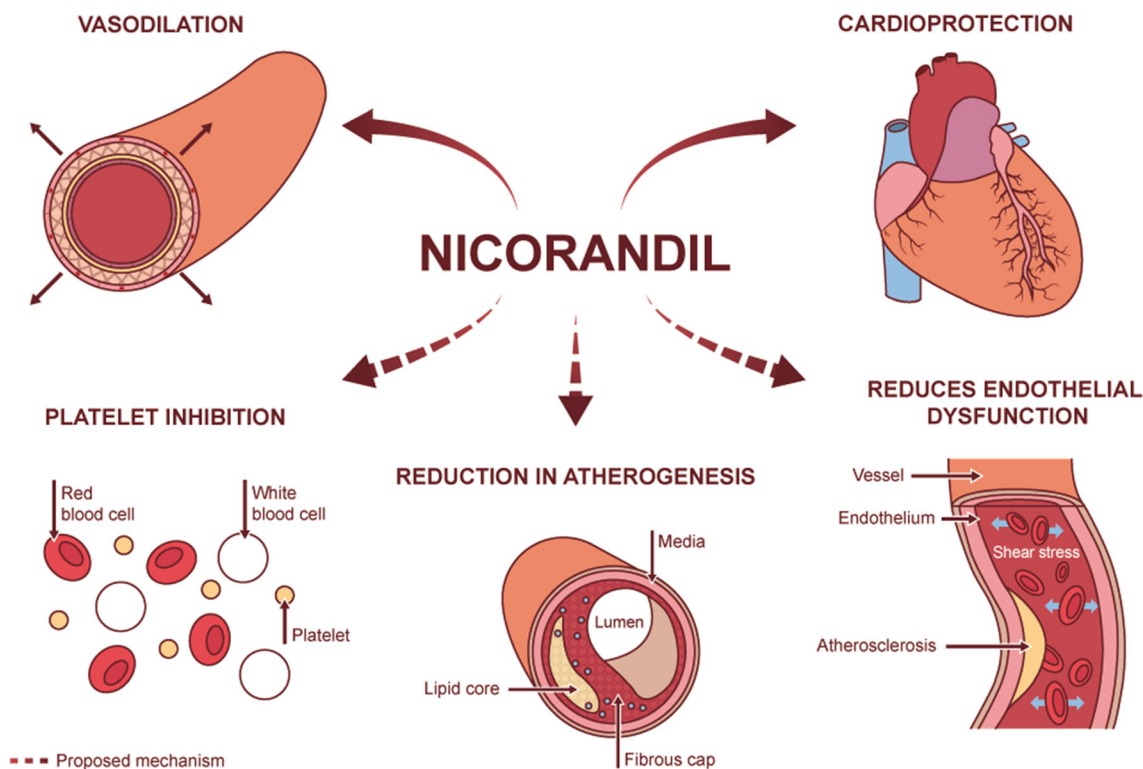
Fig. 1 Pharmacodynamic effects of nicorandil

(see Table 2). In the following sections, we review the pharmacological and clinical profile of nicorandil and place its role in the context of current angina management.

Pharmacology and Physiology

Nicorandil (*N*-[2-(Nitro-oxy) ethyl]-3 pyridine carboxamide) is a nitrate derivative of nicotinamide that has a dual mechanism of action where it acts as an adenosine-sensitive potassium-channel (K^{+ATP}) opener as well as a nitric oxide donor (Fig. 2). Via nitric oxide-mediated signalling pathways in vascular smooth muscle cells, it acts as a balanced coronary and peripheral vasodilator reducing both preload and afterload as well as improving coronary blood flow [56–58]. Therefore, it affects several of the main haemodynamic determinants of oxygen demand without affecting myocardial conduction or contractility [59]. Early studies in the late 1980s investigated the physiology, efficacy, dose response and duration of action of nicorandil. After administration of 20 mg or 40 mg of nicorandil, coronary diameter was measured in the major epicardial arteries of patients undergoing cardiac catheterisation for suspected CAD [60]. Increases in mean diameter were demonstrated in the proximal, midpoint and distal segments, as well as in stenotic segments. Myocardial oxygen consumption also decreased 14% and 22% at doses of 20 mg and 40 mg, respectively. Nicorandil dilates the coronary arteries without producing coronary steal, exacerbation of myocardial ischaemia or abrupt withdrawal syndrome [61].

In cardiac mitochondria, nicorandil activates potassium-ATP channels (K^{+}_{ATP}) whose downstream pathways are cytoprotective, thus mimicking ischaemic preconditioning (Fig. 2) [62, 63]. Although the precise mechanism by which this occurs is unknown, several theories have been proposed. By activating sarcolemmal K^{+}_{ATP} channels, nicorandil is thought to stabilise the resting membrane potential and markedly shorten the duration of the action potential, reducing calcium overload and

**Table 2** Comparison of nitrates, nicorandil and molsidomine

	Long-acting nitrates	Nicorandil	Molsidomine
Evidence for benefit in stable angina	Yes	Yes	Yes [102–104]
Randomised evidence	Yes [105]	Yes	Yes [104]
Comparison against placebo	Yes [105]	Yes	Yes [104]
Benefit as add-on to first line therapy	Yes, although poor-quality evidence [37]	Yes	Yes
Benefit in microvascular dysfunction	No [106, 107]	Yes, but limited evidence	No evidence
Concerns about tolerance and endothelial dysfunction	Yes	No	Evidence unclear [102, 108]
Cost for 28 days treatment [109]	Isosorbide mononitrate 25 mg modified-release capsules; NHS prescription price: £9	Nicorandil (20 mg twice a day); NHS prescription price: £9	Molsidomine tablets (2 mg); NHS prescription price: £9.00
	Isosorbide mononitrate MR tablets (60 mg); Basic NHS price: £10.50	Nicorandil (20 mg twice a day); Basic NHS price: £4.59	
	Isosorbide dinitrate (20 mg four times a day): £29.04	Nicorandil (10 mg; 30 tablets): 30 Saudi Riyal	
	Isosorbide dinitrate (10 mg; 30 tablets): 25 Saudi Riyal; (20 mg; 30 tablets): 45 Saudi Riyal	Nicorandil (20 mg; 30 tablets): 60 Saudi Riyal	

cellular energy demands [64, 65]. Increasing evidence, however, has suggested the involvement of other mechanisms. Nicorandil opens the mitochondrial K^+_{ATP} channel, which is thought to inhibit activation of the mitochondrial permeability transition pore, a protein in the mitochondrial inner membrane that forms in conditions of stress to allow cell death [63, 66, 67]. Nicorandil has also been implicated in suppressing other apoptotic pathways (such as the endoplasmic PI3K/Akt pathway in a model of myocardial ischaemia reperfusion injury) and in activating others (e.g. Nrf2/HO-1

signalling pathway in a model of coronary microembolisation) to prevent cell death [68, 69].

In patients with stable angina, intravenous nicorandil was able to induce a pre-conditioning effect compared to control (intravenous isosorbide dinitrate) as measured by ST segment change on balloon inflation during percutaneous transluminal coronary angioplasty [62]. Other effects of nicorandil have been proposed, such as reduced atherosclerosis and plaque necrosis [70], anti-platelet properties and protection against long-term endothelial
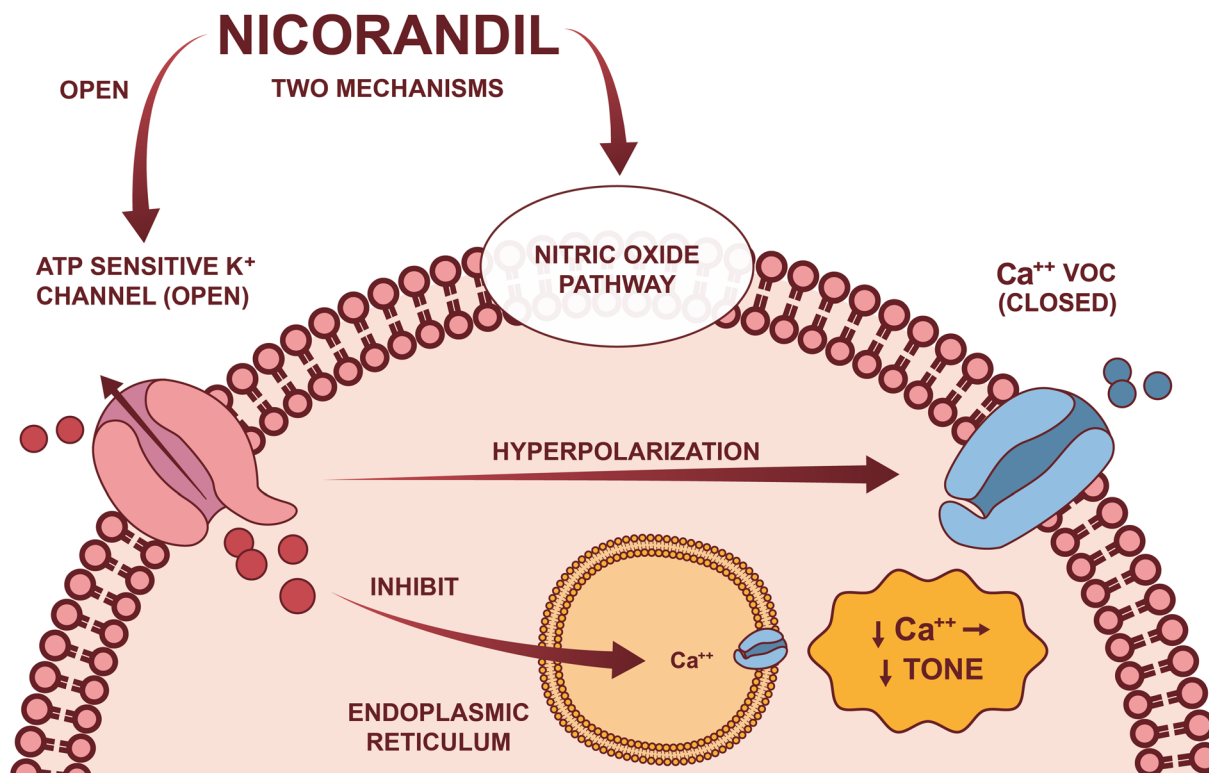
Fig. 2 Mechanism of action of nicorandil

dysfunction (Fig. 1) [71, 72]. However, such data are preliminary.

PHARMACOKINETICS AND DOSAGE

Nicorandil has good oral bioavailability (> 75%) with rapid and almost complete absorption via the gastrointestinal tract. It is not significantly metabolised by the liver, avoiding first-pass metabolism, and has a linear dose-to-plasma concentration, reaching peak plasma concentration after 30–60 min and a steady state after approximately 96–120 h (4–5 days) (Table 3) [41, 73, 74]. During repeated dosing of nicorandil 20 mg twice a day, steady-state plasma concentrations of ∼ 250–300 μm/L occur within 4 days of the first dose [65]. Food delays the absorption rate of nicorandil but has a minimal effect on bioavailability or peak plasma concentration.

Nicorandil is extensively metabolised, undergoing denitration and then metabolism along the nicotinamide/nicotinic acid pathway. It is almost fully eliminated via the kidney (< 2% of dose excreted via biliary tract) with more than 60% of the administered dose eliminated in the urine 24 h after dosing. It is eliminated as the denitrated compound (2-nicotinamidoethanol) and its derivates (nicotinuric acid, nicotinamide, N-methylnicotinamide and nicotinic acid). Only 1% of nicorandil is excreted unchanged in the urine. It has a half-life of 1–2 h for the main phase of elimination and is almost entirely eliminated from plasma within 8 h. Most nicorandil metabolites are excreted within 1 day of dosing, while some are excreted more slowly as nicotinamide derivatives. Pharmacokinetics are not significantly different in the elderly or those with chronic renal or hepatic impairment [74, 75].

Nicorandil is recommended to be prescribed as a twice daily regimen as its clinical effects, including improvements in time to angina or

Table 3 Summary of characteristics of nicorandil

Mechanism of action	Absorption	Peak dose	Half-life	Metabolism	Elimination	Prescribing considerations	Adverse effects
Nitric oxide donor	> 75% oral bioavailability	30–60 min	1–2 h	Extensive hepatic metabolism	Mainly renal	Twice-daily dosing	Hypotension; Dizziness; Headache; Vasodilation and flushing
Activates adenosine-sensitive potassium-channel (K^+_{ATP})	Almost complete enteral absorption; Avoids first-pass metabolism	Linear dose-to-plasma concentration	Mostly eliminated from plasma within 8 h	Predominantly denitration followed by subsequent nicotinamide metabolism	More than 60% of administered dose eliminated in urine 24 h after dosing; Only 1% excreted unchanged in urine	No specific dosing in the elderly or in patients with chronic renal or hepatic impairment	Weakness, nausea and vomiting, haemorrhage; Rarely skin, mucosal, gastro-intestinal and eye ulceration

1 mm ST depression, persists for ∼ 12 h [76]. Approved dosages may vary between countries. In the UK, the British National Formulary advises that nicorandil should be initiated at 5–10 mg twice daily, then increased if tolerated to 40 mg twice daily [77]. A usual dose of 10–20 mg twice daily, to which most patients respond, is recommended. For patients susceptible to headaches, a lower initial dose should be used. Dose reduction in the elderly is not required. Nicorandil is not licenced by the Food and Drug Administration for use in the US.

CLINICAL EFFICACY

Several small placebo-controlled studies in the late 1980s first demonstrated clinical efficacy with nicorandil [78–81]. At doses of 20 mg, 40 mg and 60 mg, time to onset of angina on treadmill improved by 58, 96 and 125 s over baseline ($p < 0.01$), with improvements in exercise capacity maintained at 6 h compared to placebo [80]. Plasma concentrations of nicorandil correlated with reductions in blood pressure at 2 h after administration. Dose-dependent effects on blood pressure were noted (2 of 6 patients experienced severe dizziness at 60 mg dose), while adverse events were dose-related. Other studies have shown nicorandil to have equivalent anti-anginal effects to long-term nitrates [82–86], β-blockers [87–90] and calcium channel blockers [91–94] in terms of time to angina, exercise duration and time to 1 mm segment depression (Table 4) [65].

In 2002, the landmark Impact of Nicorandil in Angina (IONA) RCT was reported, and it remains the sole large-scale RCT of nicorandil to date [32]. This study sought to investigate the effect of nicorandil compared with placebo on the frequency of adverse coronary events in patients with stable angina pectoris secondary to epicardial CAD. The investigators recruited 5126 patients who were randomised to receive either 20 mg nicorandil twice a day ($n = 2565$), initially 10 mg twice a day and then increased to 20 mg after 2 weeks, or placebo ($n = 2561$) on top of standard anti-anginal treatment. Those in the nicorandil group had concomitant use of anti-anginals as follows: β-blockers 57%, calcium-channel blockers 55%, and nitrates 87%. For secondary prevention, 56% also took statins, 89% aspirin/antiplatelets, and 29% angiotensin-converting enzyme inhibitors. A significant improvement in the primary composite endpoint (coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest pain) was shown [398 (15.5%) events in the placebo group vs. 337 (13.1%) in the nicorandil group (hazard ratio 0.83, 95% CI 0.72–0.97; $p = 0.014$)] (Fig. 3). Cardiovascular mortality and myocardial infarction were not significantly different, with the benefit mainly due to a reduction in unplanned hospitalisation for unstable angina. Although there was no significant difference in the rate of the secondary endpoint (coronary heart disease death or non-fatal myocardial infarction), nicorandil reduced the rate of ACS (hazard ratio 0.79; $p = 0.028$) and of all cardiovascular events (hazard ratio 0.86; $p = 0.027$). All-cause mortality was no different. The majority of patients were established on concomitant nitrate therapy (87% in both nicorandil and placebo groups) suggesting that the observed beneficial effect may have been mediated through the action of nicorandil on mitochondrial potassium-ATP channels [95]. Subgroup analyses confirmed the benefit was observed across a range of cardiovascular risk factors, baseline anti-anginal medications, and in those with the highest risk of recurrent events [96, 97].

In 2010, the JCAD study, a multi-centre prospective observational study ($n = 2558$), investigating cardiovascular outcomes in patients with stable angina, reported that nicorandil improved all-cause mortality by 35% ($p = 0.0008$) compared to a propensity score-matched control population [92]. There was a consistent and significant reduction in the main secondary endpoints in patients treated with nicorandil, in particular cardiac death (56%), fatal myocardial infarction (56%), cerebral or vascular death (71%) and congestive cardiac failure (33%). A meta-analysis of 17 RCTs found that the addition of nicorandil significantly reduced cardiovascular events, but there were no significant differences in all-cause mortality or repeat revascularisation [98]. The prevention

Table 4 Studies on the clinical efficacy of nicorandil in angina

| Author and date	Study size and treatment duration	Study design	Dosing and comparator	Outcome
Nicorandil vs. placebo				
IONA study group 2002 [95]	$n = 5126$ Median 1.6 years $\pm$ 0.5	Multicentre placebo-controlled RCT	20 mg nicorandil twice daily vs. placebo	Significant improvement in reduction in major coronary events:15.5% vs. 13.1% (hazard ratio 0.83, 95% CI 0.72–0.91, $p = 0.068$) of primary composite endpoint (coronary heart disease death, non-fatal myocardial infarction, unplanned hospitalisation for angina)
Comparison with long-acting nitrates				
Döring et al. 1992 [83]	$n = 129$ 4–6 weeks	Multicentre RCT Two double-blind studies: 1. Comparison with isosorbide mononitrate in crossover design 2. Nicorandil and isosorbide dinitrate administered to two parallel groups	1. 20 mg nicorandil vs. 20 mg mononitrate twice daily 2. 10 mg three times a day for 2 weeks, then 20 mg three times a day for 4 weeks	Equally effective in treatment of stress-induced angina Prolonged bicycle exercise tolerance, reduced ST-segment depression and reduced weekly angina attack rates No significant difference between groups No development of tolerance to nitrates
Falcone et al. 1993 [85]	$n = 41$	Double-blind RCT	Nicorandil 10–20 mg twice daily	Significant increases in time to angina and maximum ST depression
Ciampricotti et al. 2000 [82]	$n = 194$ Elderly patients $\geq$ 65 years with stable angina and positive exercise test ($\geq$ 0.1 mV ST-segment depression) 4 weeks	Multicentre, double-blind, double-dummy controlled	10 mg twice daily nicorandil ISMN	Significant postponement of onset of ischaemia compared with baseline No differences between nicorandil and ISMN

Table 4 continued

Author and date	Study size and treatment duration	Study design	Dosing and comparator	Outcome
Zhu et al. 2007 [86]	n = 232 2 weeks	Double-dummy RCT	Nicorandil 5 mg three times a day vs. ISMN 20 mg twice daily	Nicorandil and ISMN significantly increased time to 1 mm ST segment depression, total exercise time and time to angina onset
				Both reduced number of anginal attacks
				Use of short-acting nitrates significantly reduced only with nicorandil
Comparison with β-blockers				
Hughes et al. 1990 [88]	n = 37 6 weeks	Double-dummy, placebo-controlled parallel RCT	Nicorandil 10–20 mg twice daily vs. atenolol 50–100 mg daily	Improvements in exercise time, time to angina and 1 mm ST depression compared to baseline
				No significant difference between treatment groups
Di Somma et al. 1993 [87]	n = 20 6 weeks	Double-blind parallel RCT	10–20 mg twice daily nicorandil vs. 100 mg metoprolol twice daily	Total exercise duration and time to ischaemia reduced
				Sublingual nitroglycerin use and angina attacks reduced
				Both nicorandil 10 mg and 20 mg twice daily exerted similar effects to that of metoprolol
Meeter et al. 1992 [89]	n = 77 men 6 weeks	Double-blind parallel RCT	Nicorandil 10–20 mg twice daily Propranolol 40–80 mg three times a day	Number of anginal attacks decreased relative to baseline with nicorandil and propranolol ($p < 0.002$)
				Total exercise duration not influenced by either drug
				Delay in occurrence of ischaemia with both

Table 4 continued

Author and date	Study size and treatment duration	Study design	Dosing and comparator	Outcome
Raftery et al. 1993 [90]	n = 37 6 weeks	Double-blind parallel RCT	Nicorandil 10–20 mg twice daily or atenolol 50–100 mg once a day	Significant improvement with both to time to 1 mm ST segment depression, time to angina onset and time to peak exercise compared to baseline
				No significant difference between nicorandil or atenolol
Comparison with calcium channel blockers				
Ulvenstam et al. 1992 [94]	n = 58 8 weeks	Multicentre double-blind RCT	Nicorandil 10–20 mg twice daily vs. nifedipine 20 mg twice daily	Anginal attack rate decreased significantly compared with baseline
				Both treatments significantly increased exercise duration, time to angina onset and time to 1 mm ST depression
				No significant differences between treatment groups
Guermonprez et al. 1993 [91]	n = 123 3 months	Double-blind parallel RCT	Nicorandil 20 mg twice a day vs. diltiazem 60 mg three times a day	Both reduced frequency of anginal attacks and use of nitroglycerin
				Significant improvements in maximum exercise capacity and work required to angina onset
				No significant difference between groups

Table 4 continued

Author and date	Study size and treatment duration	Study design	Dosing and comparator	Outcome
Swan Study Group (Chatterjee et al.) 1999 [93]	n = 121 8 weeks	Multicentre, double-blind, RCT	Nicorandil 10–20 mg twice daily vs. amlodipine 5–10 mg daily	Time to onset of ST-segment depression increased only with amlodipine
				Time to onset of angina and total exercise duration increased with both
				Both reduced magnitude of ST depression at maximal workload, weekly angina attacks and nitroglycerin use
				No differences between treatment groups
Comparison with standard anti-anginal therapy				
Jiang et al. 2016 [99]	n = 402 12 weeks	Multicentre, open-label, RCT	12 weeks of nicorandil (5 mg three times daily) plus current standard anti-anginal therapy vs. current standard anti-anginal therapy	Significantly reduced number of myocardial ischaemic attacks with nicorandil compared to control (adjusted ratio 0.503; 95% CI 0.301–0.840; $p = 0.0086$)
				No significant differences in total myocardial ischaemic burden, maximum ST-depression, longest duration of ST-depression, 6-min walk test or heart rate variability
				11.7% (n = 23) of nicorandil group and 6.3% (n = 13) of control group reported at least treatment adverse event
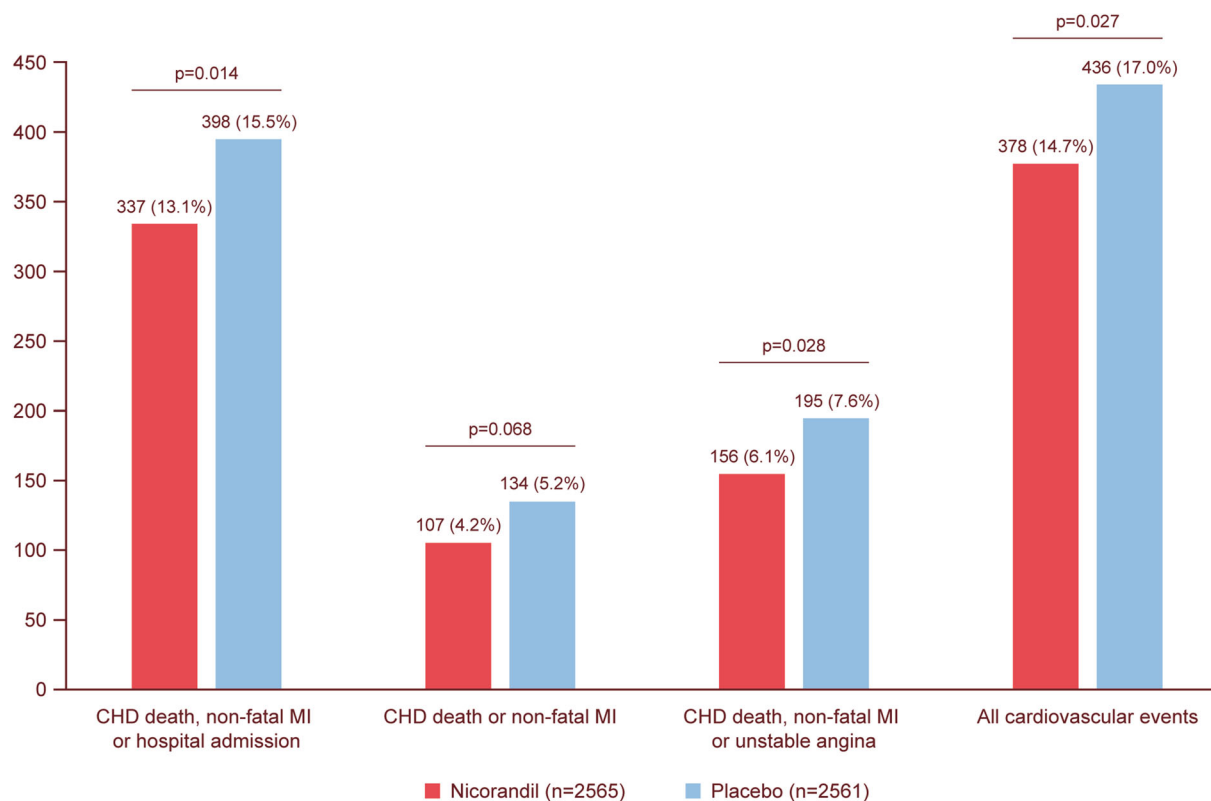
Fig. 3 Major clinical outcomes in the Impact Of Nicorandil in Angina (IONA) trial [32]

of recurrent adverse cardiovascular events, as reported in the literature for nicorandil, remains a major goal of treatment, and has not been demonstrated for other anti-anginal drugs.

Recently, an open label RCT by Jiang et al. (n = 402) evaluated nicorandil in the context of contemporary anti-anginal medications. Patients either received nicorandil 5 mg three times a day for 12 weeks in addition to standard anti-anginal therapy, or continued on their current prescribed anti-anginals. Add-on nicorandil therapy was associated with a lower number of ischaemic episodes on 24 h Holter monitoring, but no significant differences were found in total ischaemic burden, maximum ST-depression, longest duration of ST-depression, 6-min walk test or heart rate variability [99]. Additional adequately-powered RCTs comparing nicorandil against contemporary, maximally tolerated anti-anginal drugs will be needed to further support these results.

Finally, nicorandil has been shown to be effective and is currently recommended in guidelines for the management of vasospastic angina [100, 101]. Nicorandil may also, theoretically, be beneficial in patients with angina secondary to coronary microvascular dysfunction or microvascular spasm, although the evidence base in support of this is limited [102]. Intracoronary administration of nicorandil has been shown to dilate the coronary microcirculation and to decrease microcirculatory resistance in patients having undergone percutaneous coronary intervention (PCI) for stable angina or ST-elevation myocardial infarction [53, 103]. In a small double-blind placebo-controlled crossover RCT of patients with microvascular angina (n = 13), a 2-week course of oral nicorandil significantly improved time to 1 mm ST depression (p = 0.026) and total exercise duration (p = 0.036) compared with placebo [102]. Although a meta-analysis of RCTs of nicorandil in non-obstructive CAD suggested that it did not improve coronary flow reserve, nicorandil was shown to reduce the index of microcirculatory resistance

significantly compared to controls ($p = 0.0004$) [54]. Conversely, nitrates have been shown not to be efficacious in patients with microvascular angina. A study of 53 patients demonstrated that short-acting sublingual isosorbide dinitrate improved results on exercise stress tests for patients with obstructive CAD but not for microvascular angina [104]. Although a recent meta-analysis of RCTs of the effects of nicorandil in patients with unobstructed coronary arteries (24 RCTs; $n = 2323$) suggested that nicorandil may improve anginal symptoms, time to 1 mm ST-segment depression on treadmill, and endothelial dysfunction, the strength of evidence is low and insufficient to draw firm conclusions [105]. The available data support the hypothesis that nicorandil is a plausible drug for treating coronary microvascular dysfunction and vasospasm at both the epicardial and microvascular level. Further studies investigating nicorandil for these indications would be extremely valuable, as the current treatment options for such patients, who can be extremely debilitated by symptoms, is very limited.

FUTURE DIRECTIONS

A significant proportion of patients experience a recurrence of their angina after successful revascularisation. The management of recurrent or persistent angina after revascularisation remains an unmet need. These symptoms may be explained by the presence of persistent ischaemia secondary to coronary microvascular dysfunction [106, 107]. Coronary microvascular dysfunction is thought to play a significant role in the pathophysiology of recurrent angina after PCI. Of note, recent RCTs of ranolazine and trimetazidine in an unselected population of patients undergoing PCI failed to achieve their primary endpoints [108, 109]. However, these studies did not specifically evaluate patients with persistent ischaemia and evidence of coronary microvascular dysfunction. Nicorandil (intravenous or intracoronary) at the time of PCI has been shown to reduce microvascular dysfunction induced by coronary stenting and is suggested to improve cardiovascular outcomes [53, 103, 110, 111]. However,

the long-term use of oral nicorandil to treat residual ischaemia and persistent or recurrent angina in patients with coronary microvascular dysfunction after revascularisation has not been investigated and would appear a fruitful avenue for future investigation.

In addition, given the large and growing burden of DM in the Middle East and Gulf region, the incidence of diffuse small vessel disease and coronary microvascular dysfunction is only expected to rise [112]. Data from the IONA study is limited in this regard, only $\sim 8\%$ of participants had DM and subgroup analysis did not demonstrate any interaction between the benefit observed with nicorandil and DM status [113]. With further adequately-powered studies of its effect on cardiovascular outcomes in patients with stable angina pectoris secondary to coronary microvascular dysfunction, nicorandil may prove to be a plausible drug choice in this population.

SIDE EFFECTS AND CONTRA-INDICATIONS

Side effects of nicorandil include headache, flushing, dizziness, hypotension and, rarely, ulceration, which may be oral, ocular, peri-anal or gastrointestinal. The use of aspirin, non-steroidal anti-inflammatory drugs, or corticosteroids with nicorandil increases the risk of gastrointestinal ulceration, perforations, or haemorrhage, while patients with diverticular disease may be at risk of fistula formation or bowel perforation [56]. In patients who develop serious skin, mucosal and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula or abscess, treatment should be stopped and an alternative considered. The most common side effect of headache, occurring in 30% of patients, can be minimised by starting at a low dose. Importantly, compared to long-acting nitrates, long-term use of nicorandil does not cause significant drug tolerance, endothelial dysfunction or rebound angina [77]. Early animal and clinical studies have demonstrated a lack of development of tolerance; however cross-tolerance with nitroglycerin has been

suggested and one study observed an attenuation of the time-to-1 mm ST segment depression on exercise testing after 2 weeks of treatment with nicorandil [76, 114–116].

Nicorandil is contraindicated in hypotension, left ventricular failure and cardiogenic shock and, as with nitrates, it should not be used with soluble guanylate cyclase stimulators or phosphodiesterase-5 inhibitors due to the risk of severe hypotension. In patients who develop persistent aphthous or severe mouth ulcers, alternative anti-anginals should be considered. In addition, although the combination of nicorandil and long-acting nitrates has not been specifically investigated, it may be safe and able to offer additional clinical benefits. For example, in the IONA study, 87% of patients in both the nicorandil and placebo groups were reported to have received concomitant nitrates, although there is no specification as to whether these were short- or long-acting [32]. Other studies which have used nicorandil together with long-acting nitrates have not reported significant adverse effects and patients with complex CAD not suitable for revascularisation, or who have refractory angina, may benefit from nicorandil in combination with long-acting nitrate therapy [117–120]. Further large-scale studies are needed not only to assess their combination but to allow for head-to-head comparison of efficacy and side effects.

CONCLUSION

Stable symptomatic angina pectoris is a growing population of patients, particularly in the Gulf region, where the prevalence is set to significantly increase in the near future. Given the high and increasing prevalence of obesity, DM and the growing number of patients undergoing revascularisation in the Middle East and Gulf region, coronary microvascular dysfunction is likely a very common mechanism of ischaemia in CCS patients with symptomatic angina in this region. Many of these patients remain symptomatic despite treatment with long-acting nitrates which are very commonly prescribed in the Middle East and Gulf region, the reasons for which have been discussed in this review. Region-specific data on the benefit of pharmacologic treatments, including nicorandil in CCS patients who remain symptomatic with angina, are lacking and much-needed, particularly noting that optimal medical therapy remains the cornerstone of management in this patient group. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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