



Personalized management of angina and heart failure in clinical practice in the Middle East: a narrative review

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More interventions that better manage cardiovascular disease are urgently needed in the Middle East. To discuss this issue, we held a symposium at the Heart Masters Middle East 2023 congress (Dubai, UAE; May 2023) on personalized management of angina and heart failure (HF). This narrative review summarizes the content of our symposium. Many patients with chronic stable angina have ongoing symptoms and poor quality of life (QoL) despite beta-blocker + calcium-channel blocker therapy and revascularization. Further, angina is often under-recognized in clinical practice. Clinicians should consider adding newer antianginal agents (long-acting nitrates, ranolazine, trimetazidine, ivabradine) to beta-blockers + calcium-channel blockers based on patient risk factors. Individualized therapy is recommended because several mechanisms can cause angina. Agents that act at a cellular level (e.g., trimetazidine) can prevent ischemia in cardiomyocytes. Trimetazidine provides early and sustained antianginal effects, with improvements in myocardial metabolism and exercise capacity. In our view, trimetazidine may be considered as second-line therapy for angina that is suboptimally controlled on first-line therapy, and could be added to first-line therapy for angina occurring after myocardial infarction or revascularization, and comorbid with diabetes. Ivabradine reduces elevated heart rate and, when added to beta-blockers, improves angina symptoms, exercise capacity and QoL. Few patients with HF with reduced ejection fraction receive medications at target doses. Guidelines suggest rapid initiation of first-line agents from four drug classes, with a simultaneous strategy favored over a sequential one. In patients with HF with reduced ejection fraction in sinus rhythm and elevated heart rate, ivabradine should be added to maximum tolerated doses of beta-blockers. Adding ivabradine to first-line therapy improves heart rate control and QoL, and reduces HF-related hospitalization and mortality.

Plain language summary: Improving personalized care in patients with angina and/or heart failure in the Middle East

What is this article about? This article summarizes discussions from a workshop on the treatment of cardiovascular disease (CVD) in the Middle East. Ischemic heart disease, which reduces the heart's ability to pump blood, is a common type of CVD and often causes heart failure (HF). Chest pain (or angina) is a frequent symptom of ischemic heart disease and is caused by reduced blood flow to the heart.

What methodology is described? A group of specialists in CVD gave presentations based on evidence from the literature and clinical experience, and provided their recommendations for improving personalized care in patients with angina and/or HF.

What was discussed? Many patients with angina have ongoing symptoms despite standard therapy with beta-blockers and calcium-channel blockers, and procedures to restore the heart's blood flow. However, other drugs can be added to standard therapy to improve symptoms. For example, trimetazidine improves blood flow and prevents heart muscle damage, and ivabradine reduces heart rate and improves angina symptoms when added to beta-blockers.

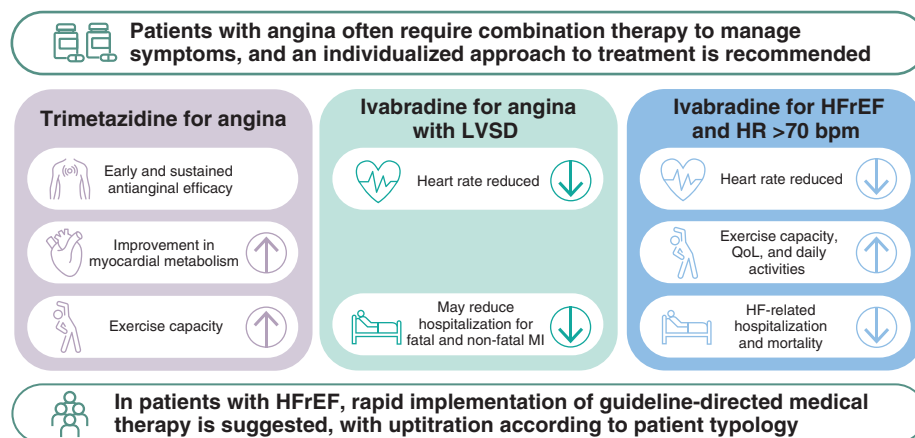
Why is this important? Patients with HF should receive early treatment with multiple medications started together rather than starting one drug class after another, but many patients do not receive appropriate doses of these medications. In patients with HF and an elevated heart rate, addition of ivabradine to standard therapy improves heart rate control and reduces the need for hospitalization due to worsening HF or cardiovascular-related mortality.

Shareable abstract: This article discusses strategies for addressing the unmet need for better personalized management of angina and heart failure in the Middle East, including the benefits of newer antianginal agents in this setting; #trimetazidine, #ivabradine.

Graphical abstract:

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HF: Heart failure; HFrEF: Heart failure with reduced ejection fraction; LVSD: Left ventricular systolic dysfunction; QoL: Quality of life.

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Keywords: angina • chronic coronary syndromes • heart failure • ivabradine • Middle East • personalized management • trimetazidine

Cardiovascular disease (CVD) is the leading cause of death in the Middle East and North Africa region [1]. It is responsible for more than a third of all deaths in the region or 1.4 million people every year [1]. The prevalence of CVD in the Middle East is 10.1%, and is accelerated by the presence of key risk factors, such as dyslipidemia (prevalence 43.3%), hypertension (21.7–26.2%), obesity (24.5%), diabetes (10.5–16.0%) and smoking (12.4–15.6%) [2,3]. Smoking is more common in men than women, but obesity and hypertension are more common in women [3]. Multifaceted interventions are urgently needed for the primary prevention of CVD in this region [2].

Ischemic heart disease (IHD) is the most common CVD worldwide and can lead to heart failure (HF) [4]. In the Middle East and North Africa, IHD accounted for 0.8 million deaths in 2019 [5]. The estimated prevalence of HF in the Middle East is 3.75 million, and the mean age of individuals with HF in this region is at least 10 years younger than that of their Western counterparts [6]. Registry data from the Middle East show that 41–71% of patients with HF also have hypertension, 32–64% have comorbid diabetes, 13–30% have chronic kidney disease and 12–25% have atrial fibrillation [6]. Angina is a common symptom of IHD [7], and the presence of anginal symptoms in daily life can cause worsening of prognosis in patients with chronic coronary syndrome (CCS) [8]. In the Gulf CARE registry of patients with acute HF from seven Gulf countries, patients from this region were younger than those in Western countries, had a high prevalence of HF with reduced ejection fraction (HFrEF) and comorbid diabetes, and had high rates of re-hospitalization [9]. Based on a preliminary report from the ongoing Program for

the Evaluation and Management of the Cardiac Events (PEACE) registry, patients with acute myocardial infarction (MI) and acute HF have a high prevalence of cardiovascular risk factors, as well as poor education levels and low socioeconomic status [10]. Similarly, preliminary data from the Middle East and Africa cohort of the iCaReMe registry highlighted the high prevalence of cardiovascular comorbidities in patients with HF across all levels of left ventricular ejection fraction (LVEF) [11].

Despite the high burden of IHD or coronary heart disease in the Middle East and North Africa, many cardiovascular risk factors remain under-recognized, undertreated and poorly controlled [12]. Furthermore, effective management is difficult due to poor patient awareness, ineffective preventive strategies and limited access to guideline-directed medical therapy (GDMT) [12]. Effective patient support networks are also lacking in this region [13].

There is an urgent unmet need for more interventions that allow for improved management of CVD in the Middle East. Therefore, we held a symposium to discuss the personalized management of angina and HF at Heart Masters Middle East 2023 held in Dubai, UAE in May 2023. This narrative review summarizes the content of that symposium, with the aim of providing an overview of the personalized management of angina and HF in clinical practice in the Middle East, based on the literature and as discussed by the speakers at the symposium. An in-depth analysis of all current literature on the topic and possible related controversial issues (including drug cost, availability and reimbursement) are beyond the scope of this article.

Materials & methods

The content of this review is based on the presentations at the symposium. The speakers (and authors of this review) developed their presentations on the basis of literature identified from searches of PubMed for articles on angina, HF and heart rate, as relevant in particular to the Middle East, in association with key terms for treatment and real-world evidence, and on their clinical expertise in the area. Details of the methodology used to perform the literature search are provided in the [Supplementary Methods](#).

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, with the exception of the information provided in individual case reports. The patients described in the case reports provided consent for their data to be included in this review.

Personalized approach to treating angina

Epidemiology of angina

The prevalence of angina is increasing worldwide due to aging [14] and improved survival after myocardial infarction (MI) [15]. Angina is reportedly experienced by 27% of patients at 1 month after discharge post-MI [15]. Many patients with chronic stable angina have persistent symptoms despite receiving first-line antianginal therapy and undergoing percutaneous coronary intervention (PCI), with 18–37% experiencing ongoing anginal symptoms at 1 year post-PCI [16,17]. Persistent or recurrent angina post-PCI has a multifactorial pathophysiology, with structural and functional changes to coronary circulation and noncardiac mechanisms being implicated [18].

Myocardial ischemia (the underlying cause of angina) is multifactorial in nature ([Figure 1](#)) [19]. Angina or ischemia with no obstructive coronary disease (ANOCA or INOCA), which is characterized by <50% epicardial stenosis, is present in approximately 40% of patients undergoing angiography for stable angina and 24% of those with ischemia [20]. ANOCA/INOCA is also caused by multifactorial mechanisms within the coronary microcirculation and endothelium. Patients with ANOCA/INOCA often have coronary microvascular dysfunction (CMD; categorized as structural or functional) or vasospastic angina that leads to a mismatch between myocardial oxygen demands and blood supply [21,22]. These mechanisms can act simultaneously [19]. Structural CMD, caused by arteriolar remodeling that commonly occurs during structural heart diseases, can lead to increased microvascular resistance and impaired coronary flow reserve [22]. In contrast, functional CMD is caused by endothelial dysfunction and reduced arteriolar vasodilatory response [21]. Cardiac cells (cardiomyocytes) are recognized as a major nonvascular contributor to IHD because of their central involvement in a number of ischemic processes, including impaired myocardial energy metabolism [23]. Vasospastic angina is caused by vascular smooth muscle vasoconstriction in response to stimuli, including stress, medications, smoking, hyperventilation or cold [24]. Consequently, angina is caused by multiple overlapping mechanisms, necessitating a combined treatment approach targeting multiple mechanisms [25].

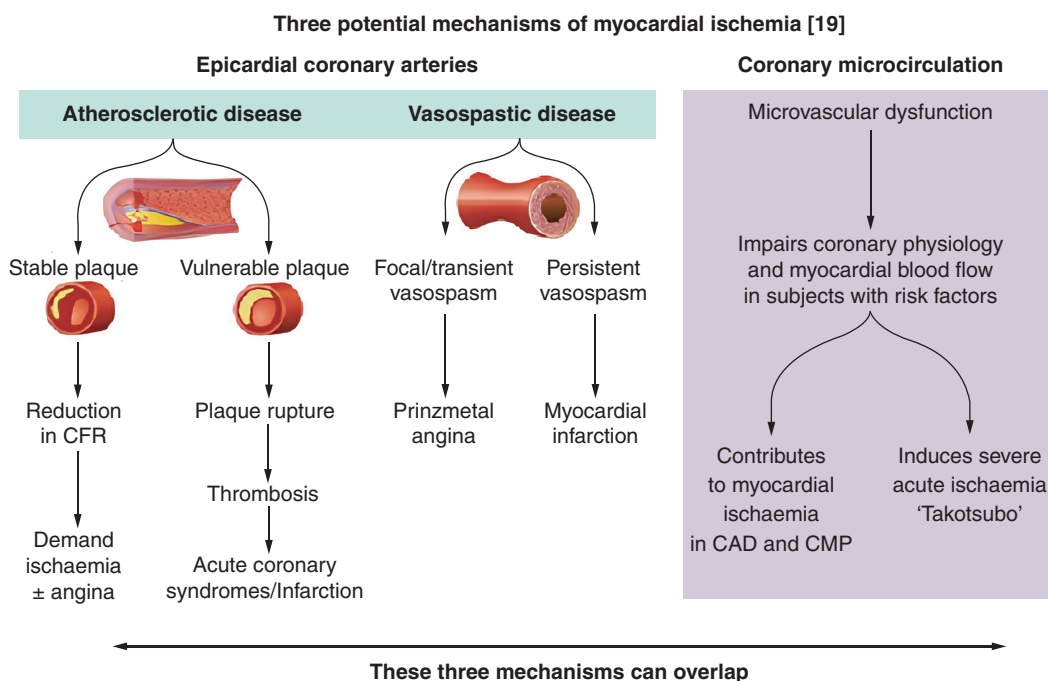


Figure 1. Mechanisms of myocardial ischemia.

Data taken from [19]. Used with permission of the authors Crea F, Camici PG, and Merz CNB., from Coronary microvascular dysfunction: an update, *European Heart Journal* 35(17) (2014). Permission conveyed through Copyright Clearance Center, Inc.

CAD: Coronary artery disease; CFR: Coronary flow reserve; CMP: Cardiomyopathy.

Globally, prevalent stable angina has a greater contribution to IHD-associated disability than HF and MI [26]. It also has a significant impact on quality of life (QoL), limiting daily activities and functional status [27]. There is a close relationship between the frequency of angina and patients' perceptions of their QoL and physical activity [28]. This reinforces the importance for clinicians to assess QoL and to optimize medical therapy for its improvement [28]. Furthermore, patients who experience post-PCI angina require repeat PCI, use more healthcare resources, and incur higher costs than those without persistent angina [29]. Under-recognition of angina is common in routine clinical practice (Figure 2) and is associated with less aggressive treatment escalation and poorer angina control [30]. By introducing standardized tools to clinically recognize angina, treatment and outcomes may be improved [30].

Elevated resting heart rate, which causes increased oxygen consumption, is an independent modifiable risk factor for ischemia in patients with stable angina [31,32]. Elevated heart rate also shortens diastole, which causes reduced coronary filling time, oxygen supply and bioavailability of nitric oxide (which is atheroprotective) [32].

Benefits of newer antianginal drugs

Trimetazidine

Antianginal drugs that act at the cellular level can protect cardiomyocytes from ischemic damage, regardless of the causative mechanism [33–35]. As such, combining a drug that directly targets ischemia and angina with standard hemodynamic agents is an attractive therapeutic option [36]. Trimetazidine acts directly on cardiomyocytes to increase adenosine triphosphate levels, reduce acidosis and improve heart function [34,35], and is associated with early antianginal efficacy that is sustained over time [37]. It bypasses the potential mechanisms that cause ischemia and, therefore, may be a suitable medication to combine with first-line antianginal agents [36]. Trimetazidine increases energy supply [35], while beta-blockers reduce energy demand [38]; as such, their combination ensures cell energy balance and provides synergistic antianginal efficacy.

Patients treated with trimetazidine achieve significant improvement in myocardial metabolism and a significant increase in exercise capacity [39,40]. In a double-blind, randomized controlled Greek study in 53 patients with stable angina suboptimally controlled on beta-blockers, the addition of trimetazidine provided superior efficacy at 2 months compared with addition of long-acting nitrates (mean weekly angina attacks reduced by 63% vs 31%;

The Angina Prevalence and Provider Evaluation of Angina Relief (APPEAR) study
155 cardiologists and 1257 outpatients with CAD [30]

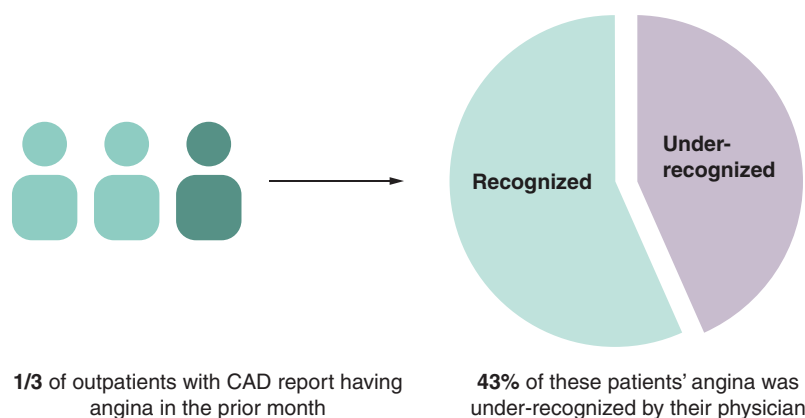


Figure 2. Under-recognition of angina in routine clinical practice.

Data taken from [30].

CAD: Coronary artery disease.

$p = 0.001$) and a reduction in nitroglycerin consumption (69% vs 35%; $p = 0.02$) [41]. Similarly, a randomized, open-label Egyptian study in 200 patients with ischemic LV dysfunction and multivessel coronary artery disease (CAD) receiving standard antianginal therapy reported a greater reduction in the mean frequency of anginal attacks over 24 months with add-on trimetazidine versus placebo (91% vs 22%; $p < 0.05$) [39]. In addition, myocardial metabolism was significantly improved from baseline with trimetazidine (but not with placebo; $p < 0.00001$), and trimetazidine was associated with improved LVEF by 8.3% from baseline at 24 months ($p < 0.05$ vs baseline and $p < 0.0001$ vs placebo) [39]. A meta-analysis of data from 11 randomized controlled trials (total of 545 patients) further confirmed the efficacy of trimetazidine as monotherapy in patients with stable angina, with significantly improved LVEF (mean increase of 7%) and significantly reduced LV end-systolic volume and wall motion score index compared with placebo [42].

Although randomized and controlled clinical trials have inherent advantages over real-world studies, the latter do provide important insights into the everyday management of disorders. Indeed, several real-world studies have shown the benefits of trimetazidine treatment in patients with angina [37,40,43,44]. For example, in the CHOICE-2 study conducted in Russia, add-on trimetazidine therapy significantly decreased the frequency of angina attacks in 741 patients with stable angina, with effects seen as early as week 2 and maintained throughout the 6-month study period ($p < 0.001$; Figure 3) [43]. This trend was observed regardless of background antianginal therapy (beta-blockers alone or beta-blockers combined with calcium-channel blockers [CCBs], long-acting nitrates or CCBs plus long-acting nitrates) [37]. The angina-free walking distance was also significantly improved with trimetazidine ($p < 0.01$) [43]. In the Russian real-world ODA study, add-on trimetazidine 80 mg once daily effectively reduced the frequency of angina attacks and the use of short-acting nitrates after 1 month of treatment, regardless of the patients' duration of stable angina [44]. Another real-world study in 580 patients with angina and diabetes conducted in Spain also reported a reduction in mean weekly angina attacks by 68% and nitroglycerin consumption by 72%, and improved exercise test duration by 50 s at 6 months after addition of trimetazidine to background antianginal therapy ($p < 0.001$ for all) [40].

Despite these encouraging results, the limitations of the available studies of trimetazidine (open-label [37,39,43,44] or observational design [37,44], limited follow-up duration [41,44], small sample size [41]) should be considered when interpreting the results.

Ivabradine

A reduction in heart rate leads to decreased oxygen demand in cardiomyocytes, thereby preserving their viability [45]. At the same time, slowing the heart rate prolongs diastolic perfusion time and improves coronary flow velocity reserve in coronary arteries. These two actions together increase the ischemic threshold, resulting in fewer angina episodes [45]. Ivabradine works by reducing heart rate and myocardial oxygen demand, while increasing

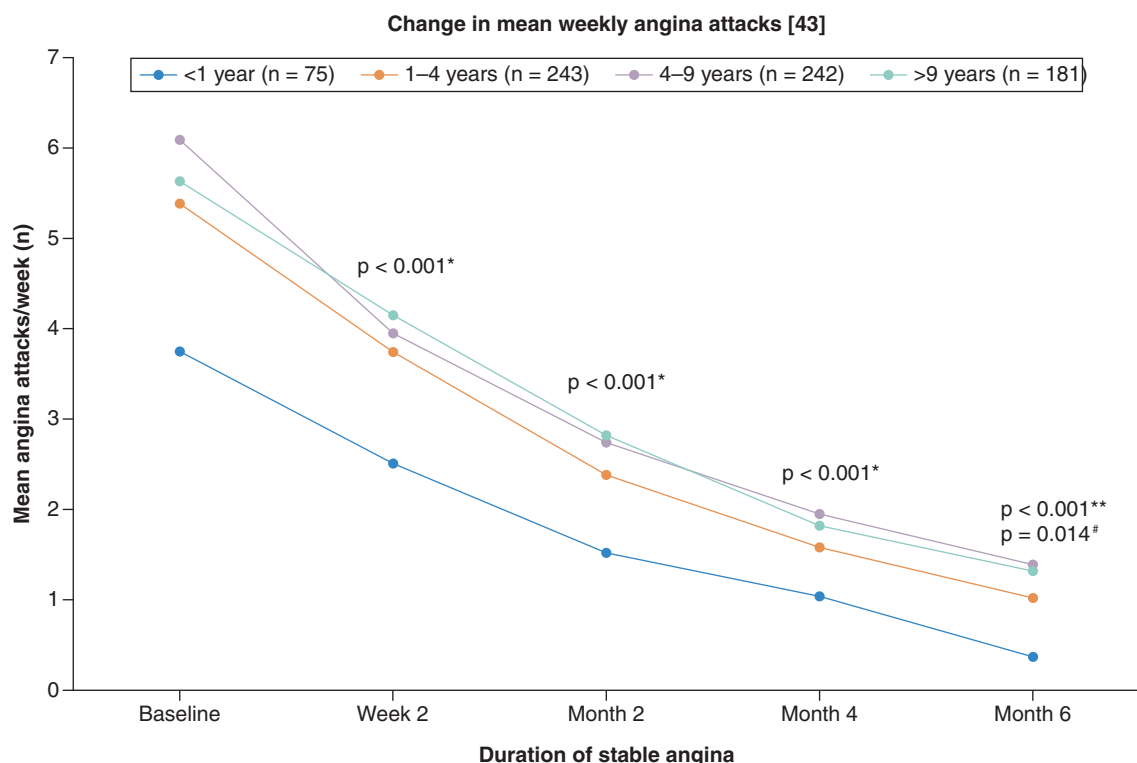


Figure 3. Change in mean weekly angina attacks with trimetazidine treatment by duration of stable angina.

Data taken from [43].

*Versus previous visit in all groups.

**Versus previous visit in the 1-4, 4-9 and >9 years groups.

#Versus previous visit in the <1 year group.

both coronary flow velocity and myocardial metabolism, thus protecting against ischemia and reducing anginal symptoms [46]. Ivabradine also increases coronary flow reserve, even after heart rate correction, demonstrating improved microvascular function [47].

Several randomized and real-world studies have demonstrated the efficacy of ivabradine as an add-on therapy to beta-blockers in patients with angina for improvement of angina symptoms, exercise capacity, QoL and daily activities [48-54].

In a randomized study in 14 patients with stable CAD and heart rate ≥ 70 bpm on background beta-blocker therapy, add-on ivabradine reduced resting heart rate from baseline at 3 weeks ($p = 0.01$ vs placebo) and prolonged diastolic perfusion time by 41% ($p = 0.0005$ vs placebo) [48]. The randomized, open-label, CONTROL-2 study evaluated the efficacy of ivabradine plus beta-blockers in 1104 patients with stable angina and a heart rate ≥ 60 bpm [49]. Compared with beta-blocker up-titration, significantly more patients in the add-on ivabradine group were free from angina at week 16 (34.2% vs 50.6%; $p < 0.001$) and patient health status (measured by a visual analog scale) was significantly better with add-on ivabradine ($p = 0.001$) [49]. A pooled analysis of five randomized controlled trials of 2425 patients with stable angina found that the antianginal efficacy of ivabradine was similar across several different patient subgroups, including those with diabetes, aged ≥ 75 years, or who had previous MI or revascularization [50].

A randomized trial of 889 patients with stable angina receiving beta-blocker therapy (mean heart rate 67 bpm) reported significantly improved total mean exercise duration with add-on ivabradine versus placebo (24.3 vs 7.7 s; $p < 0.001$) [51]. Add-on ivabradine also significantly improved other exercise test criteria compared with placebo, including mean time to limiting angina (26.0 vs 9.4 s), mean time to angina onset (49.1 vs 22.7 s) and mean time to 1 mm ST segment depression (45.7 vs 15.4 s; $p < 0.001$ for all) [51]. Similarly, a randomized study in 29 patients with stable angina, moderate LV dysfunction (LVEF $< 39\%$) and a heart rate > 60 bpm who were receiving

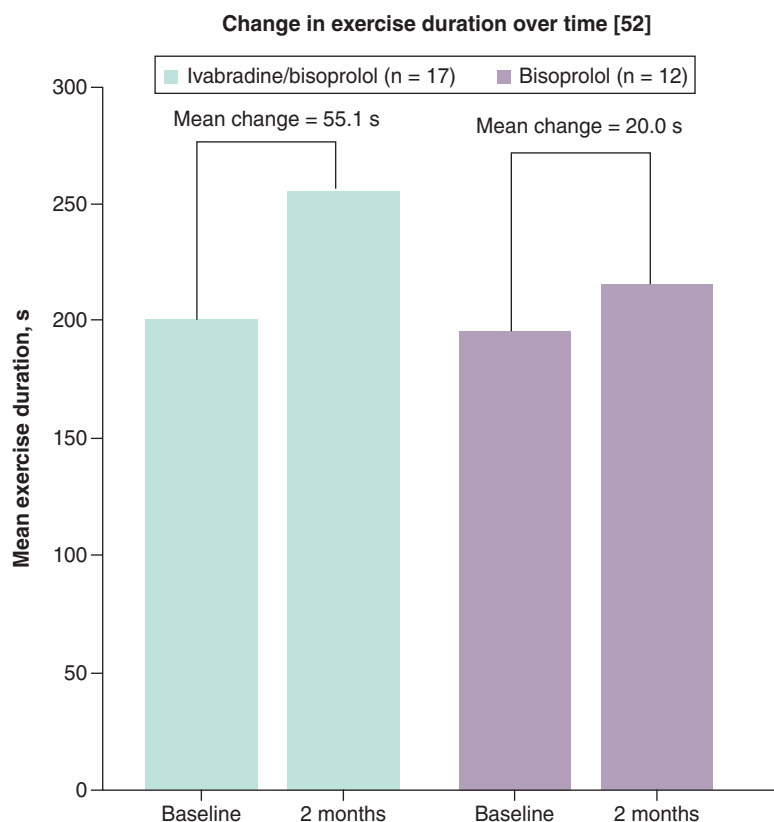


Figure 4. Mean change in exercise duration at 2 months with ivabradine/bisoprolol versus bisoprolol.

Data taken from [52].

s: Second.

beta-blocker therapy showed an increase in mean exercise duration with add-on ivabradine versus beta-blocker up-titration after 2 months of treatment (55.1 vs 20.0 s; [Figure 4](#)) [52].

The randomized BEAUTIFUL study examined the efficacy of ivabradine on cardiovascular outcomes in patients with stable CAD and LV systolic dysfunction with limiting angina (n = 1507) [53]. In a subgroup analysis of 712 patients with a resting heart rate ≥ 70 bpm, add-on ivabradine was associated with significantly fewer hospitalizations for fatal and nonfatal MI than placebo ([Figure 5](#)). Hospitalization for MI was reduced by 73% (hazard ratio [HR] 0.27; 95% confidence interval [CI] 0.11, 0.66), coronary revascularization was reduced by 59% (HR: 0.41; 95% CI: 0.17, 0.99), and overall, cardiovascular mortality or hospitalization for fatal and nonfatal MI or HF was reduced by 24% (HR: 0.76; 95% CI: 0.58, 1.00) with add-on ivabradine treatment [53].

A real-world study conducted in Germany of 8555 patients with stable angina and heart rate ≥ 60 bpm showed that ivabradine (either alone or added to beta-blockers) significantly reduced the frequency of weekly angina attacks and use of short-acting nitrates from baseline after 1 and 4 months of treatment ($p < 0.0001$ vs baseline) [54]. Ivabradine was also associated with significantly improved clinical status, with most patients (67%) rated as Canadian Cardiovascular Society class I at 4 months ($p < 0.0001$). The proportion of patients with activity-limiting angina (Canadian Cardiovascular Society class $\geq$ II) was reduced from 73% at baseline to 33% at 4 months, and QoL scores were significantly improved at 4 months ($p < 0.0001$). The effectiveness of ivabradine remained consistent across all analyzed subpopulations, including patients with previous MI or PCI, diabetes and those aged ≥ 75 years [54].

Again, when interpreting the data on ivabradine, the study limitations should be considered (e.g., open label study design [49], small sample size [48,52], short duration of follow-up [52,54], post-hoc/subgroup analysis [53]).

Time to event curves for hospitalization for fatal and nonfatal myocardial infarction [53]

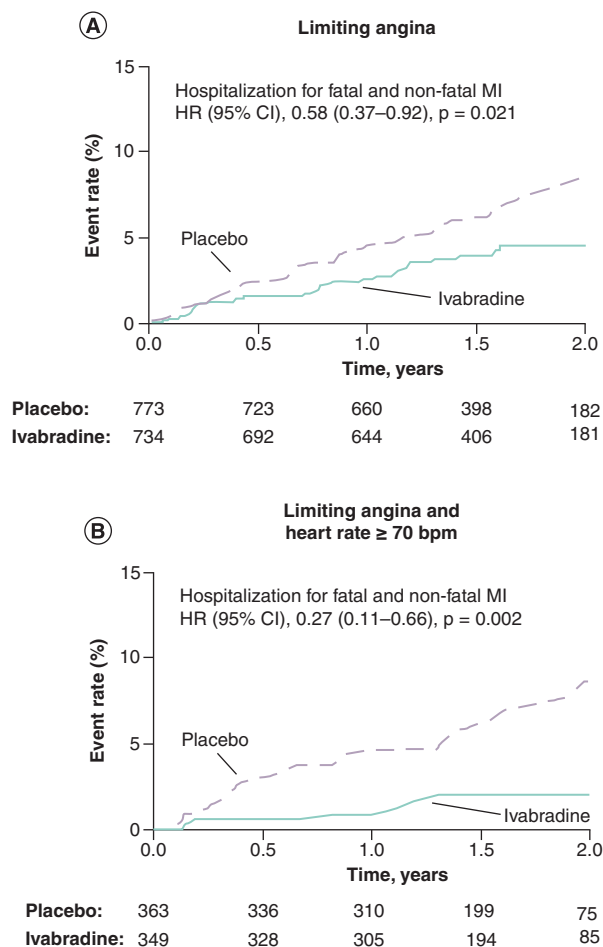


Figure 5. Kaplan–Meier time-to-event curves by treatment group for the secondary end point of hospitalization for fatal and nonfatal myocardial infarction in patients. (A) Limiting angina at baseline and (B) limiting angina and resting heart rate ≥ 70 bpm at baseline.

Data taken from [53].
HR: Hazard ratio; MI: Myocardial infarction.
Used with permission from Fox K, Ford I, Steg PG, Tendera M, Robertson M and Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial. *Eur. Heart J.* 2009; 30:2337-45 with permission of Oxford University Press.

Guidelines for use of newer antianginal drugs

The Saudi Heart Association (SHA) for the management of patients with CCS include trimetazidine and (in some cases) ivabradine among the suggested second-line or add-on treatment options [55], similar to the recommendations from the European Society of Cardiology (ESC) 2024 guidelines [22]. Based on evidence from a meta-analysis of 46 studies, trimetazidine provides benefits for most clinical outcomes, although these data were more heterogeneous than those for beta-blockers or CCBs [56]. The ESC guidelines also recommend trimetazidine as part of initial treatment in properly selected patients, including those with intolerance or contraindications to beta-blockers and/or CCBs or those with microvascular angina [22]. Combination antianginal therapy that includes trimetazidine may also be considered in patients with low heart rate and low blood pressure (BP), and in patients with obstructive CAD [22].

The SHA guidelines state that add-on ivabradine therapy should be limited to patients with HF and uncontrolled heart rate despite treatment with beta-blockers [55]. Similarly, the ESC guidelines recommend considering add-on ivabradine in patients with LV dysfunction (LVEF < 40%) and inadequate control of symptoms, or as part of

initial treatment in appropriately selected patients, but do not recommended it in patients without HF or an LVEF > 40% [22]. In patients with HFrEF, ivabradine may be considered as add-on to standard therapy or an alternative to beta-blockers (when contraindicated or not tolerated), or as additional antianginal therapy in patients with normal sinus rhythm and elevated heart rate (>70 bpm) [22].

Of note, while the 2024 ESC guidelines for the management of CCS recommend a combination strategy that considers patients' comorbidities when selecting potential drug combinations [22], the approved indications for trimetazidine and ivabradine in Europe have not changed.

Based on the ESC guidelines and consensus statements, a stepwise, patient-tailored, individualized approach to the management of angina is recommended [22,25,57]. This strategy recognizes that angina is caused by several overlapping mechanisms [19,25]. In addition, the ESC guidelines recommend a multifaceted approach, including lifestyle modifications, risk factor management and GDMT, as first-line treatment to reduce symptoms and improve prognosis in patients with CCS [22]. Patients should undergo revascularization if these measures are unsuccessful [22]. Despite a lack of data when considering GDMT, the ESC guidelines have moved away from the traditional first-/second-line approach of prescribing antianginal agents. This shift acknowledges that there is no robust evidence showing superiority of any one antianginal agent over another for symptom relief [22]. Therapy should be tailored to each patient's hemodynamic profile, comorbidities, concomitant medications, treatment tolerability and underlying pathophysiological mechanisms, while also considering local drug availability and cost [22]. The guidelines offer a practical framework by introducing the 'diamond' scheme, which assists clinicians in individualizing therapy when selecting drug combinations, enabling the optimal selection of medications based on comorbidities and risk factors [22].

Patients with angina often have comorbid conditions, including prior MI (52%), PCI (38%) or diabetes (33%) [8]. In our opinion, patients with these comorbidities are an important group to focus on. According to the SHA guidelines, modifiable cardiovascular risk factors, including diabetes, hypertension, obesity, dyslipidemia and smoking, are highly prevalent in Saudi Arabia [55].

Clinical scenarios

An example of the usefulness of the addition of trimetazidine to standard treatment for angina is best illustrated by the case of a typical patient post-PCI. This patient was a 54-year-old male ex-smoker with a history of dyslipidemia who had previously undergone successful PCI to the right coronary artery. At the time of presentation, the patient was receiving beta-blockers, combination lipid-lowering therapy (a statin plus ezetimibe) and aspirin. However, he had persistent anginal chest pain and stress echocardiography was positive for inferior ischemia; angiography showed no significant coronary in-stent re-stenosis. The patient's heart rate was 65 bpm, BP was 115/75 mmHg, and low-density lipoprotein-cholesterol was 55 mg/dl. In our opinion, add-on trimetazidine therapy should be considered for this patient.

Our clinical experience also concurs with the published data of the benefits of ivabradine in patients with angina. Our patient was a 59-year-old male with a 20-year history of diabetes and hypertension, and a 12-year history of IHD. He was also an ex-smoker with chronic obstructive pulmonary disease (COPD). His angina had been reasonably controlled until 1 year before, when he started experiencing symptoms upon exertion. Coronary angiography showed proximal occlusions and diffuse distal vessel disease, and the cardiology team considered he was not suitable for revascularization. He had an LVEF of 55%, a heart rate of 88 bpm, and a BP of 124/86 mmHg. At this time, his medications included an angiotensin-converting enzyme inhibitor (ACEi) and a CCB; add-on beta-blocker therapy was initiated. Two weeks later, the patient's heart rate was 74 bpm and his BP was 108/78 mmHg, but he experienced COPD exacerbation and intermittent dizziness. Beta-blockers were then down-titrated and add-on ivabradine therapy was started. A further 2 weeks later, his heart rate and BP had decreased to 62 bpm and 116/82 mmHg, respectively, his COPD symptoms had improved, and his angina has reduced from functional class III to class II.

Personalized approach to treating HF

Guideline-directed medical therapy

Many patients with HFrEF do not receive GDMT, and among those treated, few receive target doses [58,59]. Certain physiological factors, such as BP, heart rate, serum potassium levels and renal function, may account for most gaps in treatment, although up to 20% of the undertreated patients are still unaccounted for [60].

Patients with HF who receive a higher number of GDMT have a reduced risk of mortality, as demonstrated by a nested case-control study of 4128 patients from the IMPROVE HF registry, where an increasing survival benefit was observed with each additional GDMT (up to four agents) [61]. In a comparative analysis of three randomized controlled trials in patients with HFrEF, GDMT was associated with an additional 1.4–6.3 years' survival and 2.7–8.3 years' free from cardiovascular death or HF-related hospitalization, compared with ACEi or angiotensin receptor blocker (ARB) plus beta-blocker therapy [62].

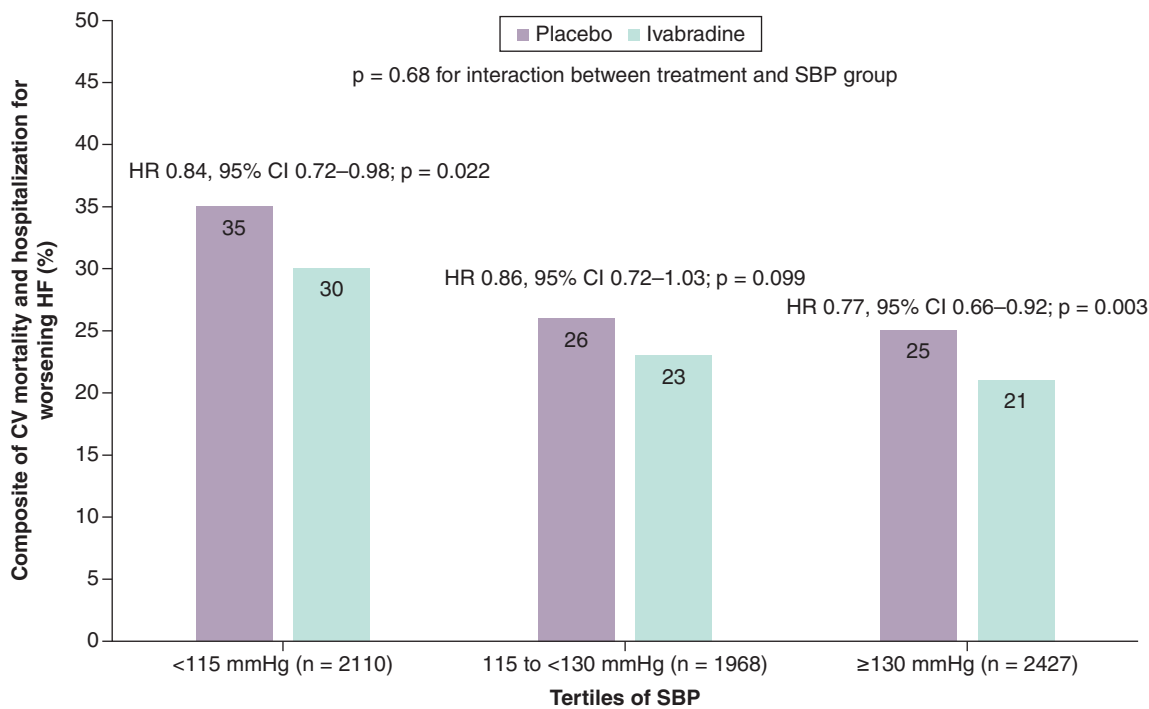
Based on a proposed investment framework for sequencing and intensification of GDMT in patients with HF, the sequence of GDMT should consider how each medication draws upon reserves in various physiological and psychosocial domains, to minimize short-term harm and maximize long-term return on investment [63]. For this framework, the key domains are BP, heart rate, serum creatinine, serum potassium and treatment complexity. This approach may help promote tailored treatment intensification in patients with HFrEF to reduce patient burden and treatment-related adverse events [63].

Treatment of HFrEF should target five pathways (angiotensin II, norepinephrine, aldosterone, neprilysin, sodium-glucose cotransporter-2 [SGLT2]) using four drugs (angiotensin receptor-neprilysin inhibitors [ARNIs], beta-blockers, mineralocorticoid receptor antagonists [MRAs] and SGLT2 inhibitors [SGLT2is]) [64]. All five pathways should be targeted as early as possible, preferably within 4 weeks, while also considering patient safety [64,65]. Lower doses of all drug classes are preferable rather than maximizing the dose of one class before initiating another [64]. Early initiation of quadruple GDMT also maximizes collective medication tolerability in patients with HF [66]. Of note, three additional agents have been shown to improve outcomes in specific populations: ivabradine (in patients with normal sinus rhythm and heart rate ≥ 70 bpm), hydralazine/isosorbide dinitrate (Black people) and vericiguat (worsening HF) [64].

Benefits of ivabradine

An elevated heart rate (≥ 70 bpm) is a predictor of mortality in patients with HF [67], whereas a lower heart rate is associated with improved survival and a reduction in HF-related hospitalizations in patients with HFrEF and sinus rhythm [68]. In the abovementioned proposed framework for GDMT in patients with HF [63], ivabradine is the only agent that reduces heart rate and has no effect on BP. Furthermore, a meta-analysis of 23 beta-blocker HF trials ($n = 19,209$) indicated that the survival benefits of beta-blockers were significantly associated with the amount of heart rate reduction achieved ($p = 0.006$), rather than the beta-blocker dose administered [69].

The randomized controlled Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT) study and subsequent subgroup analyses have demonstrated the efficacy of add-on ivabradine therapy in patients with HFrEF and elevated heart rate (median follow-up 22.9 months) [70–76]. In the SHIFT study in 6558 patients with HFrEF in sinus rhythm (heart rate ≥ 70 bpm), ivabradine added to background therapy (beta-blockers in 89–90% of patients) was associated with improved HF outcomes [70]. Patients in the ivabradine group had an 18% reduction in the primary composite end point (cardiovascular death or hospitalization for worsening HF) compared with those in the placebo group ($p < 0.0001$), and reported significant improvements in QoL ($P \leq 0.0011$) [70]. Various subgroup analyses of the SHIFT study have been conducted; although these post-hoc analyses consider subpopulations and parameters that were not defined in the original study protocol and for which the study may not have been powered, they do provide important insights into the potential benefits of ivabradine. The benefits of add-on ivabradine therapy in the SHIFT study were analyzed in subgroups defined by baseline heart rate (≥ 75 vs < 75 bpm) [71]. In this subgroup analysis, ivabradine reduced the risk of the primary composite end point (HR: 0.76, 95% CI: 0.68, 0.85; $p < 0.0001$), all-cause mortality (HR: 0.83, 95% CI: 0.72, 0.96; $p = 0.0109$), cardiovascular mortality (HR: 0.83; 95% CI: 0.71, 0.97; $p = 0.0166$), HF death (HR: 0.61; 95% CI: 0.46, 0.81; $p = 0.0006$) and hospitalization for worsening HF (HR: 0.70; 95% CI: 0.61, 0.80; $p < 0.0001$) compared with placebo in patients with a baseline heart rate ≥ 75 bpm, but there was no significant difference in these outcomes for patients in the < 75 bpm subgroup [71]. When data from the SHIFT study were analyzed according to baseline systolic BP (SBP), add-on ivabradine was associated with a similar relative risk reduction of the primary composite end point regardless of baseline SBP (< 115 , ≥ 115 to < 130 , or ≥ 130 mmHg; $p = 0.68$ for treatment interaction; Figure 6) [72]. The benefits of ivabradine observed with regard to the primary composite end point in the SHIFT study were also maintained in patients with or without renal dysfunction at baseline ($p = 0.89$ for treatment interaction) [73]. A *post hoc* analysis of the SHIFT study also demonstrated that ivabradine treatment reduced the incidence of all-cause hospitalizations compared with placebo during the post-discharge phase following hospitalization for HF

Treatment effect on the composite of cardiovascular mortality and hospitalization for worsening heart failure [72]**Figure 6. Effect of ivabradine on cardiovascular death or heart failure-related hospitalization in the SHIFT population according to tertiles of systolic blood pressure.**

Data taken from [72].

CV: Cardiovascular; HF: Heart failure; HR: Hazard ratio; SBP: Systolic blood pressure.

(incidence rate ratio at 3 months of 0.79; 95% CI: 0.63, 0.99; $p = 0.04$) [74]. Of note, the magnitude of heart rate reduction with ivabradine therapy, rather than background beta-blocker dose, was the main determinant of clinical outcomes in the SHIFT study [75]. Lastly, an echocardiographic subanalysis of SHIFT found that ivabradine could reverse cardiac remodeling compared with placebo [76]. Ivabradine was associated with a greater reduction in LV end-systolic volume index versus placebo (-7.0 vs -0.9 ml/m², $p < 0.001$), with similar improvements observed for the end-diastolic volume index (-7.9 vs -1.8 ml/m², $p = 0.002$) and LVEF ($+2.4\%$ vs -0.1% ; $p < 0.001$) [76].

Notwithstanding their inherent limitations, real-world studies have also confirmed the benefits of ivabradine in patients with HF [77,78]. A study in 289 patients with acute decompensated HF conducted in Italy showed that ivabradine therapy (with or without beta-blockers) was associated with lower event rates at 6 months post-discharge for the composite end point (rehospitalization for HF or cardiovascular mortality), for all-cause mortality, and cardiovascular mortality compared with no ivabradine therapy [77]. Likewise, a real-world Taiwanese study in patients with HFrEF who were clinically indicated for ivabradine plus sacubitril/valsartan therapy reported that simultaneous administration of these two medications led to significantly lower rates of cardiovascular death and/or HF-related re-hospitalization than sequential administration (16.9 vs 25.7 per 100-person years; HR: 0.64, 95% CI: 0.46, 0.90; $p = 0.01$) [78].

Guidelines for use of ivabradine

The management of HFrEF has evolved over the last 5 years from a lengthy sequential initiation [79] to personalized care with rapid initiation of comprehensive treatment [80]. Guidelines from the National Heart Center (NHC)/SHA, ESC, American Heart Association/American College of Cardiology/Heart Failure Society of America, and Canadian Cardiovascular Society/Canadian Heart Failure Society recommend combined treatment with four medication classes for first-line GDMT in patients with HFrEF (ACEis/ARBs/ARNIs, beta-blockers, MRAs and SGLT2is), with doses titrated as needed to achieve intended outcomes (as tolerated by the individual patient) [80–83]. According to the NHC/SHA guidelines for the management of HF, ivabradine should be considered

in patients with symptomatic HFrEF (LVEF $\leq 35\%$) who have a resting heart rate of >70 bpm and are in sinus rhythm [81]. Ivabradine should not be administered in patients with stable CAD or acute coronary syndrome for the past 2 months, and should not be combined with ranolazine or nicorandil due to unknown safety [81]. Similar to the NHC/SHA guidelines, a 2024 consensus statement from the Saudi Heart Failure group recommends ivabradine therapy to reduce heart rate in patients with HFrEF in sinus rhythm and an elevated heart rate (>75 bpm) [84]. The 2022 ESC guidelines also recommend considering ivabradine in patients with HFrEF (LVEF $\leq 35\%$) in sinus rhythm and an elevated resting heart rate (≥ 70 bpm) despite GDMT [80]. Ivabradine should also be considered in patients who are unable to tolerate or have contraindications to beta-blockers; such patients should also receive an ACEi/ARNI and a MRA [80].

A consensus report from the Heart Failure Association (HFA) of the ESC identified patient profiles that may be relevant for treatment implementation in HFrEF [85]. These profiles take into account heart rate, BP and estimated glomerular filtration rate, as well as the presence of atrial fibrillation, hyperkalemia and cardiac congestion. A tailored approach that adjusts GDMT to the individual patient profile may allow more comprehensive, personalized therapy, rather than forced titration of each drug class before sequential initiation of treatment with the next agent. Using this approach, the consensus report states that ivabradine represents an important therapeutic option, particularly in patients with high heart rate (>70 bpm) and low BP (systolic BP <90 mmHg in patients without CAD), as it lowers heart rate without affecting BP [85]. The report also recommends ivabradine as an addition to beta-blockers in patients who are normotensive (systolic BP > 90 mmHg) but continue to have a HR > 70 bpm in sinus rhythm despite the use of beta-blockers, and in patients with a HR of 60–70 bpm and low BP (systolic BP < 90 mmHg) [85].

Clinical scenarios

In our clinical experience, the following three patient scenarios are most likely to be encountered in routine clinical practice: high heart rate and high BP; high heart rate and low BP and heart rate 60–70 bpm and low BP. Low BP, which is reported in 15–25% of patients with HF, may be associated with severe LV dysfunction or with the use of GDMTs, such as ACEis, beta-blockers, ARBs or diuretics [86]. As a consequence, up-titration of GDMT is often challenging in patients with HF. In addition, patients with low BP are less likely to be receiving target doses of beta-blockers, which has implications for the management of patients with high heart rate and low BP [86]. In clinical scenario (2) above (i.e., high heart rate and low BP), the reduction or discontinuation of beta-blockers may be required after considering withdrawal of any unnecessary BP-lowering agents, based on the consensus report from the HFA of the ESC [85]. In this scenario, ivabradine represents an important therapeutic option as it lowers heart rate without affecting BP; MRAs and SGLT2is have a very modest impact on BP, so their withdrawal is not necessary [85].

Conclusion

There is an urgent need for interventions for the medical management of CVD in the Middle East due to the high prevalence of CVD and its risk factors in the region.

Many patients with chronic stable angina continue to have symptoms despite receiving first-line antianginal therapy and undergoing revascularization, and have a significantly reduced QoL. In addition, angina is commonly under-recognized by physicians in routine clinical practice. Drugs that act directly at the cellular level of cardiac tissue, such as trimetazidine, can protect cardiomyocytes from ischemic damage. Trimetazidine is associated with early antianginal efficacy that is sustained over time, providing significant improvements in myocardial metabolism and significant increases in exercise capacity. In our opinion, trimetazidine should be considered as second-line therapy in patients with angina, and added to first-line therapy as early as possible, particularly in patient who are post-MI, post-PCI or with comorbid diabetes.

Elevated heart rate (≥ 70 bpm) is a trigger for ischemia in patients with stable angina and a risk factor for hospitalization and mortality in patients with HFrEF. Ivabradine reduces heart rate and is effective as an add-on therapy to beta-blockers in patients with angina, providing improvements in angina symptoms, exercise capacity, QoL and daily activities. The antianginal effects of ivabradine remain consistent irrespective of age and comorbidities. In patients with HFrEF, combining ivabradine with standard therapy improves heart rate control and QoL, and reduces HF-related hospitalization and mortality. Patients with HFrEF should also undergo rapid implementation of GDMT, with up-titration according to the individual patient's symptoms.

Summary points

- This symposium, held during the Heart Masters Middle East 2023 congress (Dubai, UAE) discussed how to improve personalized management of angina and heart failure (HF) using newer antianginal agents (trimetazidine and ivabradine).
- Patients with chronic stable angina or HF often require combination therapy to manage symptoms, and an individualized approach to treatment is recommended.
- Drugs acting at a cellular level, like trimetazidine, can prevent ischemic damage in patients with angina.
- Trimetazidine is associated with early and sustained antianginal efficacy, with significant improvements in myocardial metabolism and exercise capacity.
- Trimetazidine may be considered as second-line therapy in patients with persistent anginal symptoms, and added to standard therapy as early as possible, especially for patients who are post-myocardial infarction, post-percutaneous coronary intervention or with comorbid diabetes.
- Elevated heart rate (≥ 70 bpm) can lead to ischemia in patients with angina and is a risk factor for hospitalization and mortality in patients with HF with reduced ejection fraction.
- Ivabradine reduces heart rate in patients with angina and is effective as an add-on therapy to beta-blockers for improvement in symptoms, exercise capacity, quality of life and daily activities.
- In patients with HF with reduced ejection fraction, adding ivabradine to standard therapy improves heart rate control and quality of life and reduces the risk of HF-related hospitalization and mortality.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://becarispublishing.com/doi/epdf/10.57264/cer-2025-0119>

Author contributions

JA Ali was the moderator and scientific chair for the symposium, and read and approved the drafts of the manuscript. B Mittal was a speaker at the symposium and read and approved the drafts of the manuscript. F El Deeb was a speaker at the symposium and read, revised and approved the drafts of the manuscript. C Semaan was a speaker at the symposium and read, revised and approved the drafts of the manuscript. HM Sabbour was a speaker at the symposium and read, revised and approved the drafts of the manuscript. All authors read and approved the final manuscript.

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Ethical conduct of research

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors, with the exception of the information provided in the individual case reports. These patients provided consent for their data to be included in this review.

Data sharing statement

Data sharing is not applicable to this article as no datasets were generated from this symposium.

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