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Review Article

Clinical use of ivabradine in the acute coronary syndrome: A systematic review and narrative synthesis of current evidence

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ABSTRACT

Heart rate (HR) lowering during acute coronary syndrome (ACS) is beneficial as it reduces myocardial oxygen consumption. However, the role of ivabradine as an HR-lowering agent in the setting of ACS is not clear. We aimed to systematically review and synthesize the current evidence on the role of ivabradine use in the ACS. A systematic review was conducted for eligible randomized clinical trials and quasi-experimental studies, between 2009 and 2020, that investigated the use of ivabradine in ACS. Various clinical endpoints were evaluated such as major adverse cardiovascular events, efficacy in HR control, impact on left ventricular (LV) dimensions and function, and overall safety. Eleven publications were included encompassing a total of 1833 patients. The mean age of the examined cohort was 57 ± 11 years and 80 % were men. Seven studies were in the setting of ST-segment elevation myocardial infarction (MI) while the remaining studies also included patients with unstable angina and non-ST-segment elevation MI. Ivabradine was administered as a peroral drug with dosing from 2.5 to 7.5 mg b.i.d. Overall, the addition of ivabradine was superior to the control arm concerning HR control with a good safety profile. Beneficial effects on LV function and potential impact on infarct size reduction were observed as well. The use of ivabradine appeared to not affect short-term mortality. In conclusion, the use of ivabradine for HR control is safe, feasible, and efficacious for HR control in the ACS. Further studies are required to elucidate other potentially beneficial effects of ivabradine.

1. Introduction

Ivabradine is a heart rate (HR)-lowering agent with unique pharmacodynamic properties – it acts through selective and specific inhibition of I_f (funny) current that is chiefly responsible for spontaneous diastolic depolarization of the sinoatrial (SA) node but also other spontaneously depolarizing tissues such as atrioventricular (AV) node and Purkinje fibers [1]. By dose-dependent HR-reduction, ivabradine can decrease myocardial work thus mitigating supply/demand mismatch of oxygen and nutrient delivery to heart muscle that occurs in acute stressed conditions such as myocardial ischemia and acute coronary syndrome (ACS). The attractiveness of using ivabradine in such clinical scenarios is founded on the observation that its effects do not appear to impact intraatrial, AV, or intraventricular conduction pathways and exert no negative effects on ventricular contractility and repolarization, mean arterial pressure, and coronary vasomotion [2,3].

Abbreviations: ACS, acute coronary syndrome; HR, heart rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; UA, unstable angina; STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; MT, medical therapy; PCI, percutaneous coronary intervention.

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Such pharmacodynamic characteristics make ivabradine an attractive anti-anginal agent because it reduces the workload of the heart while preserving contractility (positive inotropy) and hemodynamic stability.

Nowadays, the rationale for clinical use of ivabradine is dominantly based on the data obtained from large randomized trials such as BEAUTIFUL [4] and SHIFT [5] thus confining its use to the treatment of selected groups of chronic heart failure (HF) [6] and chronic coronary syndrome (CCS) patients [7] Most recently, ivabradine is recommended as a second-line treatment to reduce angina frequency and improve exercise tolerance in patients with the CCS who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by conventional anti-anginal agents such as beta-blockers, calcium channel blockers (CCBs), and long-acting nitrates [8].

However, the role of ivabradine during acute ischemic events such as ACS has been poorly investigated and no large-scale trials were conducted in this setting. This is an important aspect of potential ivabradine use because its anti-ischemic effects and postulated pleiotropic effects that act beyond heart rate lowering might acutely limit the extent of myocardial injury, reduce adverse cardiac remodeling and potentially improve mortality and morbidity outcomes in the ACS setting [3].

For these reasons, we performed an extensive search and systematic review of the literature to identify primarily randomized clinical trials and quasi-experimental studies that investigated the use of ivabradine in the context of ACS. The purpose of our study was to systematically describe and evaluate the characteristics and outcomes of these studies, and to provide a narrative synthesis of obtained findings.

The protocol for this review was registered at the International prospective register of systematic reviews (PROSPERO, CRD42018103962).

2. Methods

The general methodology is described in detail in the Appendix A. Search strategies devised for this research are available in the Appendix B.

3. Results

3.1. Selection of sources of evidence

The search of bibliographical databases retrieved 427 results and search of grey literature retrieved 20 additional articles. 293 were left after deduplication (Supplementary Table S1). After the screening of titles and abstracts, 19 were selected for full-text assessment. Additional 8 articles were excluded at that step (6 articles were not available for full text and 2 were excluded for not meeting inclusion criteria). In the end, 11 articles were included in the final analysis. The flow chart of the literature review is provided in Fig. 1.

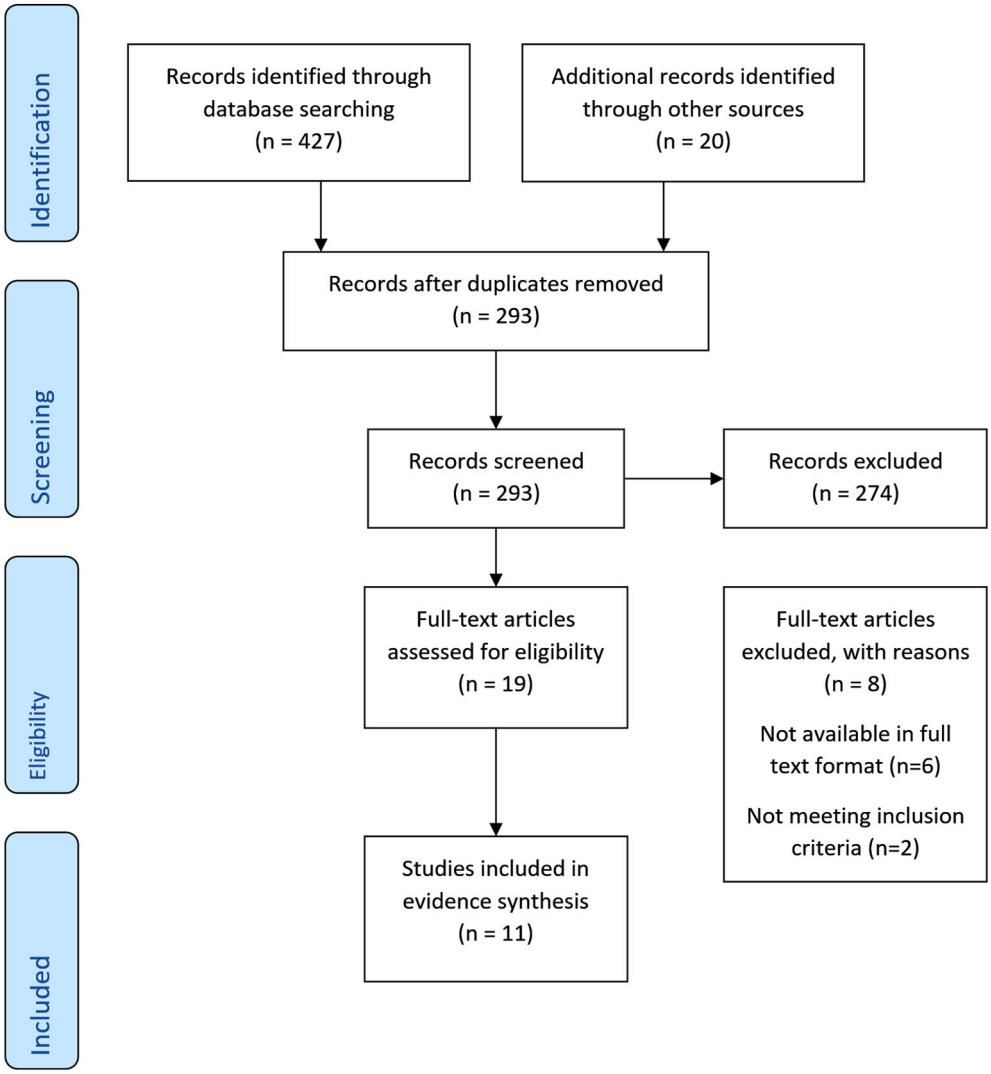

Fig. 1. A PRISMA flow diagram showing selection process of studies considered for the analysis.

3.2. Baseline study characteristics

In the present analysis, we included 10 randomized prospective studies published from 2009 to 2020 and they included 1709 patients. Half of the studies were double-blinded randomized clinical trials (defined *per protocol*) while the remaining five were randomized prospective studies with unknown blinding procedure or open-label design. Four studies were conducted in Europe of which two were from Italy (Barillà et al. [9], Fasullo et al. [10]), one from Spain (Dominguez-Rodriguez et al. [11]), and one from France (Steg et al. [12]) while three were from Egypt (Adel et al. [13], Latif et al. [14], Rezq et al. [15]), two from India (Priti et al. [16], De et al. [17]), and one from China (Xu et al. [18]). We also included one non-randomized controlled trial, conducted in France (Gerbaud et al. [19]), which was published in 2014 and included 124 patients.

3.2.1. Randomized controlled studies

When randomized studies were analyzed together, these studies recruited predominantly men (N = 1353, 79.2 %) while women comprised less than one-quarter of the cohort (N = 356, 20.8 %). The mean age of participants at admission was 56.6 ± 10.8 years. The most prevalent comorbidity in this cohort was arterial hypertension with an average prevalence of 52.2 %, followed by dyslipidemia (45.1 %) and diabetes mellitus (38.6 %). Nearly half of the cohort were smokers (48.1 %) while more than one-third of participants had a positive family history of coronary artery disease (37.6 %). The average systolic function at baseline, determined by the left ventricular ejection fraction (LVEF) was 47.9 ± 7.3 %. Four studies (Fasullo et al., Dominguez-Rodriguez et al., Priti et al., Xu et al.) excluded patients with previous myocardial infarction (MI) or revascularization as per original study protocol, two studies allowed recruitment of patients with previous MI or revascularization procedure (Steg et al. and Adel et al.) while in the remaining four studies this was not explicitly declared or unknown (Latif et al., Barillà et al., De et al., and Rezq et al.) (Table 1).

3.2.2. Non-randomized study

In one non-randomized study, which included predominantly men (90.3 % in intervention and 88.7 % in the control group), the mean age in the ivabradine group was 56.7 ± 11.7 and 58.2 ± 10.5 years. The most common comorbidity was dyslipidemia (67.7 % in the ivabradine and 64.5 % in the control group), followed by arterial hypertension (37.1 % vs. 41.9 %). More than half of patients were smokers (69.3 % vs. 67.7 %) with a positive family history of heart disease (40.3 % vs. 45.2 %). The LVEF at baseline was 57.9 ± 9.8 % in the ivabradine 56.4 ± 9.1 % for the control group. There was no information on whether previous MI or revascularization were excluded from the study.

3.3. Characteristics of studies with respect to acs type, reperfusion strategy and pharmacologic comparators

3.3.1. Randomized controlled studies

Six studies (Fasullo et al., Steg et al., Barillà et al., Priti et al., Rezq et al., and Xu et al.) recruited patients with ST-elevation myocardial infarction (STEMI) exclusively, a study by De et al. recruited a majority (82.5 %) of patients with STEMI, while other three studies (Dominguez-Rodriguez et al., Latif et al., and Adel et al.) recruited patients with non-ST-segment elevation acute coronary syndromes (NSTE-ACS) consisting of unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI).

Concerning reperfusion strategy, all patients from five studies (Fasullo et al., Steg et al., Barilla et al., Rezq et al., and Xu et al.) and the majority from the total pool of patients (N = 1073, 62.8 %) received the percutaneous coronary intervention (PCI) and had ivabradine administered after the procedure or periprocedurally during the index hospitalization. In three studies, no PCI was performed in any patient: Latif et al. reported that 100 % of patients received conservative medical treatment (MT), Priti et al. reported that 100 % of their patients received thrombolysis for inferior STEMI while in a study by De et al., 57.5 % of patients received thrombolysis and the rest were treated conservatively. Finally, in two remaining studies (Dominguez-Rodriguez et al. and Adel et al.), PCI was performed in nearly half of the patients while most of the

Table 1
Baseline population characteristics of studies included in the synthesis and analysis.

Study	Study design	N	M/F (Male %)	Age (years)	Baseline LVEF (%)	DM (%)	AH (%)	DL (%)	Positive CAD FH (%)	Current smoker (%)	Previous MI or revasc. (%)
Fasullo et al. 2009 [10]	Double-blinded prospective RCT[a]	155	105/50 (67.7)	61.9 ± 7.9	41.9 ± 5.1	34.8	45.2	48.4	46.5	35.5	Excluded (per protocol)
Dominguez-Rodriguez et al. 2012 [11]	Double-blinded prospective RCT[a]	27	25/2 (92.6)	61.5 ± 19.5	65.5 ± 21.5	40.7	63.0	74.1	N/A	48.1	Excluded (per protocol)
Steg et al. 2013 [12]	Double-blinded prospective RCT[a]	124	97/27 (78.2)	59.1 ± 11.2	47.5 (39.5–58.5)	18.5	47.6	41.9	N/A	38.7	14.5
Latif et al. 2015 [14]	Randomized prospective study	60	24/36 (40.0)	53.5 ± 7.8	58.0 ± 4.9	43.3	60.0	50.0	41.7	53.3	N/A
Adel et al. 2016 [13]	Randomized prospective study	45	29/16 (64.4)	57.3 (51.4–61.7)	53.5 (40.3–64.3)	62.2	57.8	31.1	N/A	35.6	31.1
Barillà et al. 2016 [9]	Randomized prospective study	58	39/19 (67.2)	55.4 ± 10.0	33.8 ± 3.5	41.4	53.4	58.6	27.6	63.8	N/A
Priti et al. 2017 [16]	Double-blinded prospective RCT[a]	464	355/109 (76.5)	54.6 ± 9.8	47.1 ± 4.2	32.1	39.4	27.2	N/A	26.1	Excluded (per protocol)
De et al. 2019 [17]	Randomized prospective study	40	24/16 (60.0)	54.9	39.0 ± 3.01	47.5	77.5	62.5	62.5	N/A	N/A
Rezq et al. 2020 [15]	Double-blinded prospective RCT[a]	670	591/79 (88.2)	56.0 ± 10.4	44.0 ± 7.3	36.6	36.7	9.9	9.9	71.6	N/A
Xu et al. 2020 [18]	Randomized prospective study	66	64/2 (97.0 %)	51.4 ± 9.5	48.9 ± 8.8	28.8	40.9	46.9	N/A	60.6	Excluded (per protocol)
Total or average	–	1709	1353/356 79.2 %	56.6 ± 10.8 years	47.9 ± 7.3 %	38.6 %	52.2 %	45.1 %	37.6 %	48.1 %	–

Abbreviations: AH – arterial hypertension; CAD – coronary artery disease; DL – dyslipidemia or hypercholesterolemia; DM – diabetes mellitus; FH - family history; M/F – denotes absolute number of males and females enrolled in the study;MI – myocardial infarction; NSTEMI-Non-ST-segment elevation myocardial infarction; PCI-percutaneous coronary intervention; RCT – randomized controlled trial; STEMI – ST-elevation myocardial infarction; UA – unstable angina.

[a] A double-blinded prospective randomized controlled trial as defined per available study protocol.

patients received conservative MT (Fig. 2).

Fll studies included only patients that were in sinus rhythm at the time of admission and all reported the heart rate cut-off value for inclusion, except Rezq et al. in which this was not defined. The inclusion sinus rhythm heart rate ranged from ≥60 to >90 beats per minute (bpm) in available studies (Table 2).

In 9 out of 10 studies (with Steg et al. as an exception), ivabradine as a treatment arm was administered perorally in at least a total of 5 mg per day while it was added to guideline-directed optimal medical treatment (OMT) established for ACS in all studies. Furthermore, ivabradine was added to the prespecified beta-adrenergic blocking (BB) drug in two studies (bisoprolol 2.5 QD in Rezq et al. and metoprolol tartarate 12.5–25 mg BID in Xu et al.). Regarding the comparator arm, ivabradine was compared to OMT in most of the studies while it was compared to prespecified BB drug in 6 studies (metoprolol succinate 25–100 mg BID in Fasullo et al., bisoprolol 2.5–10 mg daily in Adel et al., metoprolol tartarate 25–100 mg BID in Priti et al., metoprolol in De et al., bisoprolol 2.5 mg QD in Rezq et al., and metoprolol tartarate 12.5–25 mg BID in Xu et al.).

3.3.2. Non-randomized study

The study conducted by Gerbaud et al. included patients with a diagnosis of STEMI, after the successful reperfusion (as defined by the TIMI flow grade 3 in the infarct-related artery). Patients with atrial arrhythmia or those with HR < 70 bpm were excluded. Patients in the intervention group were given ivabradine orally, 10 mg per day (5 mg BID), with the concomitant beta-blocker (bisoprolol), titrated up to 10 mg. Other drugs were given if indicated. The Control group received treatment according to standard guidelines (bisoprolol).

3.4. Mortality and/or MACE endpoints

3.4.1. Randomized controlled studies

Five of the studies (Dominguez-Rodriguez et al., Steg et al., Latif et al., Adel et al., and De et al.) were not designed to assess all-cause or cardiovascular (CV) mortality and/or major adverse cardiovascular event (MACE) rates as principal study endpoints between compared groups. Half of the studies reported on mortality outcome during the follow-up period and this was reported as all-cause mortality in 4 studies (Fasullo et al., Barillà et al., Priti et al., Rezq et al.) while Xu et al. reported cardiovascular mortality. In all studies that reported these outcomes, there was no significant difference in mortality rates between groups that were treated with ivabradine added to OMT versus groups that were treated with OMT or BB added to OMT. Similarly, concerning MACE endpoint, these events were registered in 4 studies (Latif et al., Adel et al., Priti et al., De et al.) and no significant differences were observed between compared treatment arms in all these studies.

3.4.2. Non-randomized study

The included non-randomized study did not measure all-cause or CV mortality or MACE rates.

3.5. Other outcome measures

Other outcome measures are shown in detail within the Supplementary Table S2.

3.5.1. Randomized controlled studies

Studies measured several different outcomes. LVEF as an indicator of systolic cardiac function was measured in five studies (Barilla et al., De et al., Fasullo et al., Steg et al., and Xu et al.). In these studies, ivabradine was either superior (Fasullo et al., Barilla et al., Xu et al) or equivalent to control treatment (De et al.). There was no observed difference in LVEF in one study (Steg et al.).

Heart rate was measured in nine studies. Ivabradine was superior to control in achieving heart rate reduction in six studies (Adel et al., Barilla et al., De et al., Rezq et al., Steg et al., and Xu et al.). There was no difference between two treatment groups in the three studies (Fasullo et al., Latif et al., Priti et al.).

Left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) were measured in five studies (Fasullo et al., Latif et al., Priti et al., Steg et al., and Xu et al.). LVESV was significantly lower in the ivabradine group when compared to control (Fasullo et al., Steg et al., Xu et al.). There was no difference in LVESV in one study (Latif et al.), and the metoprolol group had a significantly larger reduction of LVEDV in one study when compared to ivabradine (Priti et al.).

Seven studies measured laboratory biomarkers of cardiac injury or systemic inflammation. High-sensitivity C-reactive protein (hs-CRP) was measured in four studies (Adel et al., Dominguez-Rodriguez et al., Lafit et al., and Xu et al). Ivabradine was superior to control in achieving a reduction of hs-CRP levels in two studies (Dominguez-Rodriguez et al. and Latif et al.), while no difference was observed between groups in two other studies (Adel et al. and Xu et al.).

Biomarkers of cardiac injury and/or stretch were measured in four studies (Barilla et al., Fasullo et al., Steg et al., and Xu et al.). There was a significant reduction of circulating natriuretic peptide levels in three studies (Barilla et al., Fasullo et al., and Xu et al.) in the ivabradine group when compared to control at least in one measuring time point. In the studies conducted by Steg et al. and Xu et al., there was no difference in creatine kinase, troponin T, and troponin I when comparing ivabradine to control.

3.5.2. Non-randomized study

Several outcomes were measured in the study conducted by Gerbaud

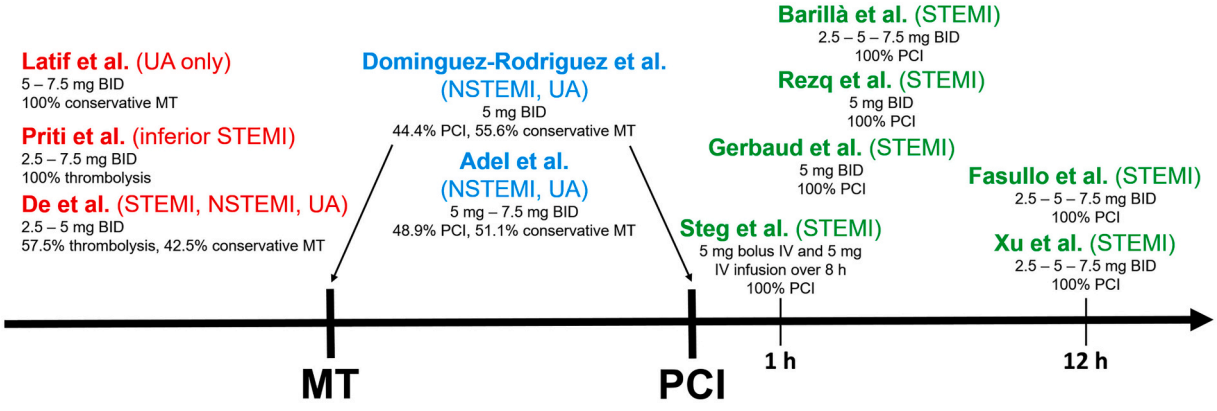

Fig. 2. A scheme depicting included studies with respect if medical therapy (MT) alone, MT and percutaneous coronary intervention (PCI), or PCI alone were used. Studies are also stratified by the type of the acute coronary syndrome.

Table 2
Baseline population characteristics of studies considered for the analysis.

Study	ACS type	PCI performed	Inclusion rhythm	Intervention arm	Comparator arm	Follow-up period	Mortality reported
Fasullo et al. 2009 [9]	STEMI only (LVEF <50 %)	YES (100 %)	Sinus rhythm >80 bpm	Ivabradine, PO 2.5–5–7.5 mg bid (12 h after PCI)	Metoprolol succinate, PO 25–50–100 mg bid (12 h after PCI)	12 h after PCI 10–30-60 days	YES (at 60 days) IVA – 1/78 (1.28 %) METO- 1/75 (1.33 %) p = NS
Dominguez-Rodriguez et al. 2012 [11]	NSTEMI and UA	YES (44.4 %) NO (55.6 %)	Sinus rhythm ≥60 bpm	Ivabradine, PO 5 mg bid + OMT	Placebo, PO + OMT	24 h 48 h 30 days	NO
Steg et al. 2013 [12]	STEMI only	YES (100 %)	Sinus rhythm >80 bpm	Ivabradine, IV bolus 5 mg + infusion/8 h 5 mg	Placebo, IV bolus 5 mg + infusion/8 h 5 mg	Multiple endpoints	NO
Latif et al. 2015 [14]	UA only	NO	Sinus rhythm > 60 bpm	Ivabradine, PO 5 mg bid ↓ 7.5 mg bid (uptitrated after 1 week) + OMT	OMT only	Day 0 Day 4 Day 30	NO NO DIFFERENCE IN MACE AT 30 DAYS
Adel et al. 2016 [13]	NSTEMI and UA	YES (48.9 %) NO (51.1 %)	Sinus rhythm ≥70 bpm	Ivabradine, PO 5 mg bid (1 week) 7.5 mg bid (until 30 days) + OMT	Bisoprolol, PO 2.5, 5, 10 mg + OMT	30 days	NO MACE endpoint IVA – 4/23 (17.4 %) BISO – 9/22 (40.9 %)
Barillà et al. 2016 [9]	STEMI only (with cardiogenic shock)	YES (100 %)	Sinus rhythm ≥75 bpm	Ivabradine 2.5–7.5 mg bid + OMT	OMT only (beta-blockers not administered)	Total of 6 months 4 points of FU – 1 week, 1 month, 3 months and 6 months	YES (In-hospital mortality) IVA – 2/30 (6.7 %) OMT – 4/28 (14.3 %) $p = 0.416$
Priti et al. 2017 [16]	STEMI only (inferior wall)	NO Thrombolysis in all patients	Sinus rhythm > 70 bpm	Ivabradine, PO 2.5–7.5 mg bid + OMT	Metoprolol tartarate, PO 25–50-100 bid ↓ Metoprolol succinate, PO (switch-over) + OMT	30 days	YES (at 30 days) IVA - 4/232 (1.72 %) METO – 4/232 (1.72 %) p = NS No difference in MACE-free survival at 9 months
De et al. 2019 [17]	STEMI – 82.5 % NSTEMI - 12.5 % UA – 5 %	NO Thrombolysis 57.5 % Conservative treatment 42.5 %	Sinus rhythm >60 bpm	Ivabradine, PO 2.5 mg bid (48 h) 5 mg bid (up to 30 days) + OMT	Metoprolol, PO	Day 0 Day 30	NO No difference in MACE at 30 day
Rezq et al. 2020 [15]	STEMI only (anterior wall)	YES (100 %)	Sinus rhythm	Ivabradine, PO 5 mg bid + Bisoprolol 2.5 mg qd	Bisoprolol, PO 2.5 mg qd + Placebo	In-hospital 2–4-6 weeks 6–12 months (secondary outcomes)	YES (In-hospital/6 months 12 months) IVA – 0/335 (0 %) BISO – 0/335 (0 %)
Xu et al. 2020 [18]	STEMI only	YES (100 %)	Sinus rhythm ≥ 80 bpm	Ivabradine, PO 2.5 mg bid + Metoprolol tartarate, PO 12.5–25 mg bid + OMT	Metoprolol tartarate, PO 12.5–25 mg bid + OMT	Multiple endpoints 1, 7, 30, 90, and 180 days after PCI	YES (Cardiovascular death) 0.0 % during FU
Gerbaud et al. 2013 [19]	STEMI only	YES (100 %)	Sinus rhythm ≥ 70 bpm	Ivabradine, PO 5 mg bid (2.5 mg bid if HR during hospitalization is <50 bpm or symptomatic bradycardia developed) + Bisoprolol, PO 10 mg daily + OMT	Bisoprolol, PO 10 mg daily + OMT	Day 0 Day 6 Day 90	NO

Abbreviations: bid-twice daily; FU-follow-up; MACE-major adverse cardiovascular events; NSTEMI-non-ST-elevation myocardial infarction; OMT-optimal medical treatment; PCI-percutaneous coronary intervention; PO-peroral; STEMI-ST-elevation myocardial infarction; UA-unstable angina.

et al. LVEF improved significantly in the intervention group, and LVEDV increase was smaller in the intervention group while LVESV increased more in the control group. HR was reduced in both groups when compared to a baseline measurement, but the decrease of HR was significantly higher in the ivabradine group. LV mass index was reduced in the control group.

3.6. Critical appraisal of evidence

See Figs. S1 and S2 for the illustration of the risk of bias (RoB) rating for each randomized study and across studies for each risk of bias domains. Detailed results with respect to critical evaluation of the quality of evidence are provided in Appendix C.

4. Discussion

To our knowledge, this is the first study that systematically analyzed and synthesized available evidence regarding the use of ivabradine in the ACS. Our analysis showed that ivabradine is a feasible, safe, and effective treatment option to be used in the ACS for heart rate control, either alone or on top of the concomitant beta-blocker use. Treatment with ivabradine might beneficially impact the left ventricular function as its use was associated with higher LVEF and smaller LV volumes in studies that reported on these endpoints. Ivabradine use might also be associated with reduced infarct size, however, such relationship in human studies remains ambiguous, as well as concerning the reduction in circulating biomarkers reflecting systemic inflammation and myocardial injury or pressure-volume overload. Furthermore, the use of ivabradine appears to have no impact on the reduction of short-term mortality and MACE events compared to control treatment.

Across included studies, ivabradine showed superiority in acute HR reduction, compared to control treatment and this effect might translate to better clinical outcomes in the ACS. From the perspective of pathophysiology, reducing HR should improve the supply-to-demand oxygen ratio by increasing subendocardial perfusion and contraction during acute ischemia, even when maximal coronary vasomotion is achieved [20]. Of note, under physiological conditions and normal metabolic regulation in the myocardium, tachycardia will increase blood flow through coronary arteries [21]. In contrast to this, regions of the myocardium that are supplied by obstructed coronary arteries with an exhausted dilatory reserve and shortened diastolic filling time will exhibit reduced blood flow proportionally to the degree of tachycardia. The contemporary use of beta-blockade in ACS is often able to efficiently decrease HR, however, this is counterbalanced with unmasked alpha-adrenergic coronary vasoconstriction, negative cardiac inotropism and bronchal vasoconstriction [22,23]. The importance of HR control in the setting of ACS and its impact on both short- and long-terms has been well-substantiated in clinical practice. For example, data from the European Hospital Benchmarking by Outcomes in ACS Processes (EURHOBOP) study showed that admission HR was an independent predictor of in-hospital mortality in both STEMI and NSTE-ACS patients while HR >80 bpm was associated with the highest risk of in-hospital mortality, irrespective of diabetes, initial rhythm and age [24]. A relative risk of death during the 3-year follow-up increased by 35 % for every 10 bpm increase in discharge HR among patients admitted for AMI [25]. A recent meta-analysis encompassing 156,374 patients from 11 studies showed that elevated HR was independently associated with increased mortality of ACS patients in the modern PCI era [26]. Equally important, HR is the integral component of the GRACE score, a widely used and validated risk prediction tool in ACS [27]. Therefore, a selective and efficacious HR lowering in ACS by the pharmacological agent such as ivabradine, devoid of hemodynamic side-effects seems like an attractive therapeutic concept that has been largely supported by preclinical data [3,28].

Among included studies that investigated the impact of ivabradine on echocardiographic parameters in patients with ACS, it was demonstrated that ivabradine might act favorably on systolic function by improving LVEF and also decreasing end-systolic LV volumes, compared to control treatment. This notion has a biological plausibility as Heusch and colleagues demonstrated that ivabradine use in a pig model of myocardial ischemia/reperfusion improved myocardial blood flow and function and reduced infarct size while some of these effects were not entirely dependent on the HR-lowering action [28]. Later on, Covreur et al. demonstrated the beneficial effect of ivabradine administration on ameliorating ischemia-reperfusion injury in the animal model of coronary occlusion [29]. In this experiment, ivabradine significantly improved systolic function compared to placebo by dual mechanism encompassing direct mechanical action and long-term adaptation in calcium handling by myocytes. The neutral hemodynamic effects of ivabradine on left ventricular contractility were demonstrated in the clinical experiment by Manz and colleagues showing that 0.25 mg/kg intravenous infusion of ivabradine in patients with coronary disease or LV dysfunction decreased HR by nearly 18 % while fully preserving fractional shortening and stroke volume [30]. Similar observations were attained in the large echocardiographic subanalysis of the SHIFT trial showing that, among patients with heart failure, ivabradine significantly reduced LV end-systolic volume index (LVESVI) compared to placebo [31]. Taken together, beneficial effects of ivabradine on left ventricular function in ACS are worthy of further exploration in the large randomized controlled trials since there is a signal of benefit, however, currently available data are derived from studies that were too small and too few to unequivocally demonstrate such beneficial impact.

Similarly, the anti-inflammatory effects of ivabradine remain to be investigated to a larger extent since some small-sized and pilot studies demonstrated benefit in this regard whereas others reported no difference. It is well-known that the ACS event is characterized by adaptive immunity dysregulation [32] and potent acute activation of inflammatory pathways [33], therefore, mitigating the extent of damage inflicted by these systems is of great clinical relevance. Mechanisms for anti-inflammatory effects of ivabradine are not fully elucidated, however, it was demonstrated in a preclinical model of viral myocarditis and dilated cardiomyopathy that ivabradine reduced myocardial fibrosis by inhibiting proinflammatory cytokines such as TNF-α, IL-1ß, and IL-6 [34]. Likewise, ivabradine prevents low shear stress-induced endothelial inflammation and oxidative stress by acting through mTOR/eNOS pathway [35].

Overall, the effect of ivabradine on hard endpoints such as all-cause mortality or MACE in ACS has not been demonstrated but such observation is largely determined by the small size of most studies that were significantly underpowered or not at all designed to measure these outcomes. It is reasonable to expect that enrollment of a large number of patients in randomized trials that could generate the adequate number of adverse events over a longer follow-up period would be required to detect the possible impact of ivabradine on these outcomes.

Finally, it is important to mention some notable limitations of this analysis. Most of the studies were small-sized, methodologically heterogeneous, and statistically underpowered to detect differences in major clinical outcomes while a majority of studies displayed an unclear risk regarding selection, performance, and detection bias. The majority of participants in the included studies were male, therefore, results on the use of ivabradine in female patients with ACS are especially lacking and this sex discrepancy should be carefully addressed in future prospective randomized studies on the use of ivabradine in the ACS. Also, ACS was not defined equally across the studies, and its severity (e.g., initial flow analyzed using diagnostic coronary angiography, maximal circulating high-sensitivity cardiac troponin levels) was not reported

and not available for the majority of studies. Additionally, there was heterogeneity across the studies regarding the reperfusion strategies employed. Such study characteristics, therefore, may have limited the interpretation and conclusions of our present work. We firmly hold that future studies investigating the role of ivabradine in the ACS should consider substantially larger patient enrollment and be designed in a prospective randomized fashion in order to elucidate its potential beneficial impact on clinical outcomes.

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CRediT authorship contribution statement

Josip A. Borovac: Conceptualization, Methodology, Data curation, Writing – original draft, Visualization, Writing – review & editing, Supervision. **Martin Kowalski:** Methodology, Data curation, Writing – review & editing. **Tina Poklepovic Pericic:** Methodology, Data curation, Writing – review & editing, Validation. **Marin Vidak:** Data curation, Methodology, Writing – review & editing, Validation. **Konstantin Schwarz:** Writing – review & editing. **Domenico D'Amario:** Writing – review & editing. **Dino Miric:** Writing – review & editing. **Duska Glavas:** Writing – review & editing. **Josko Bozic:** Writing – review & editing, Supervision, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendices. Supplementary data

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