Review Article

IVABRADINE - MANAGEMENT OF HEART FAILURE (SYSTEMATIC REVIEW)

ABBREVIATIONS:

AF atrial fibrillation

CVD cardiovascular disease

HF heart failure

RAAS renin-angiotensin-aldosterone system

I*f* funny current channel

LVEF left ventricular ejection fraction

RCTs Randomized Controlled Trials

NA not available

EMA European Medicines Agency

CTC Computed tomography coronary angiography

BID bis in die

ABSTRACT

Objectives: Summarize the effect of ivabradine on coronary artery disease and heart failure compared with placebo or standard care via clinical trials or meta-analysis.

Design: Systematic review and meta-analysis. Searches of electronic databases from 2003 to 2018.

Data extraction: Study results relating to benefit, risk and uses of ivabradine were extracted with individually meta-analysis or clinical trials.

Results: The primary analysis included 1413 records (key word – ivabradine), of which 53 clinical studies were separated using the PRISMA-flow diagram with the following conclusion. Ivabradine has a positive effect on heart rate reduction in heart failure and other cardiovascular diseases. The health status of patients treated by ivabradine is generally better compared to patients with placebo. Across the analysed trials, placebo, β-blockers, amlodipine or ranolazine were commonly used in the control group. Ivabradine has been generally used as a replacement of β-blockers in patients suffering from side effects. However, the effect of ivabradine is manifested only in patients with high heart rate

(≥70/min.) and left ventricular dysfunction. We showed that ivabradine treatment is associated with an increased risk of AF (atrial fibrillation), and the side effect is substantially more common than 1:10 000, presently reported in the product specification. This extent of AF incidence has not been previously reported in clinical trials.

Conclusion: Ivabradine treatment improved the cardiopulmonary function and increased the exercise capacity of patients with chronic heart failure. Ivabradine reduced the mortality and hospitalization risk and improved the quality of life. Ivabradine appears to show better efficacy in comparison with β-blockers treatment, but this finding requires further study and clinical trials.

Key words: ivabradine, meta-analysis, systematic review, PRISMA flow diagram

Introduction

Globally, cardiovascular diseases (CVD) is the leading cause of death in developed contexts and is emerging as a leading cause in developing countries. It is estimated that coronary artery disease will be responsible for a total of 11.1 million annual deaths globally in 2020 in populations over 45 years of age. The major known risk factors for CVD include smoking, hypertension, obesity, diet, and alcohol abuse, among others. Increased heart rate non-related to other cardiovascular diseases or risk factors has been linked to atherosclerosis, heart failure, coronary artery disease, hypertension, and stroke (Mengesha et al., 2017).

Heart failure (HF) is the one of the most common cardiovascular disorders. It is classified into three main forms - HF with reduced ejection fraction, HF with preserved ejection fraction and HF with a mid-range ejection fraction of either ischemic or non-ischemic origin. All these forms can present as acute/chronic or as acutely decompensated chronic HF (Müller-Werdan et al., 2016). Chronic HF negatively affects the quality of life due to the associated symptoms, such as weight gain, oedema, dyspnoea, depression (20–30%) and fatigue, all of which limit the day-to-day activities and increase the risk of hospitalization (Pereira-Barretto, 2016). Even though the treatment of CVD exists and is routinely prescribed, this medication may not be clinically applicable to all patients due to serious side effects (Mengesha et al., 2017). The treatment of HF includes angiotensin-converting enzyme inhibitors, diuretics, beta-blockers, and mineralocorticoid receptor antagonists (Thorup et al., 2017). The prolonged beta-receptor activation however results in an increase in myocardial metabolic demands, contributes to adverse ventricular remodeling, predisposes to dangerous arrhythmias, and accelerates myocyte atrophy. The continuous activation of the renin-angiotensin-aldosterone system (RAAS) leads to remodelling of the ventricle, volume overload, and increased ventricular fibrosis (Gordin and Fonarow, 2016). Recent innovations in HF treatment introduced medication for funny current channel (I*f*) modulation resulting in selective heart rate reduction. Ivabradine as an I*f* modulator was developed for coronary artery disease and heart failure treatment. Currently, various regulatory agencies recommend the use of ivabradine in patients with HR (heart rate) of ≥70 bpm (Sathyamurthy and Newale, 2018). This active substance selectively inhibits the ionic current I*f*, which modulates pacemaker activity in the sino-atrial node, providing selective heart rate reduction (Deedwania, 2013).

Methods

This systematic review was undertaken using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P). We planned to include all relevant clinical trials assessing the use of ivabradine in the treatment of coronary artery disease or heart failure. We searched the Science Citation Index Expanded on Web of Science, PubMed, Scopus, ScienceDirect in order to identify relevant trials. We used the following search terms, adapted for each database when appropriate: ivabradine, meta-analysis. We searched of electronic databases for studies in the reference lists of a meta-analysis and review articles published between 2003 and 2018. The primary analysis was based on 1413 records – key word "ivabradine", of which 53 were finally analysed. The total number of patients for all studies was n = 51603. All included trials assessed and classified at low risk of bias or at high risk of bias. Ethical approval was not necessary for this study.

Literature search

Study selection as described in Fig.1 shows the results of the sensitivity analyses with additional studies included. The initial database searches and identification through other sources yielded 1413 records – key word ivabradine, than 23 records were identified – key words – ivabradine, clinical trials, and meta-analysis. Of these, five were excluded, contained alone free abstract. 18 meta-analysis assessed for eligility include 171 clinical trials for analysis, but 64 clinical trials excluded (other drugs identified) and next 54 clinical trials excluded because duplicates records. This resulted in 53 full-text articles, which were individually assessed, and s were deemed suitable for qualitative and quantitative analysis. An overview of the study selection process is depicted using a PRISMA flow diagram.

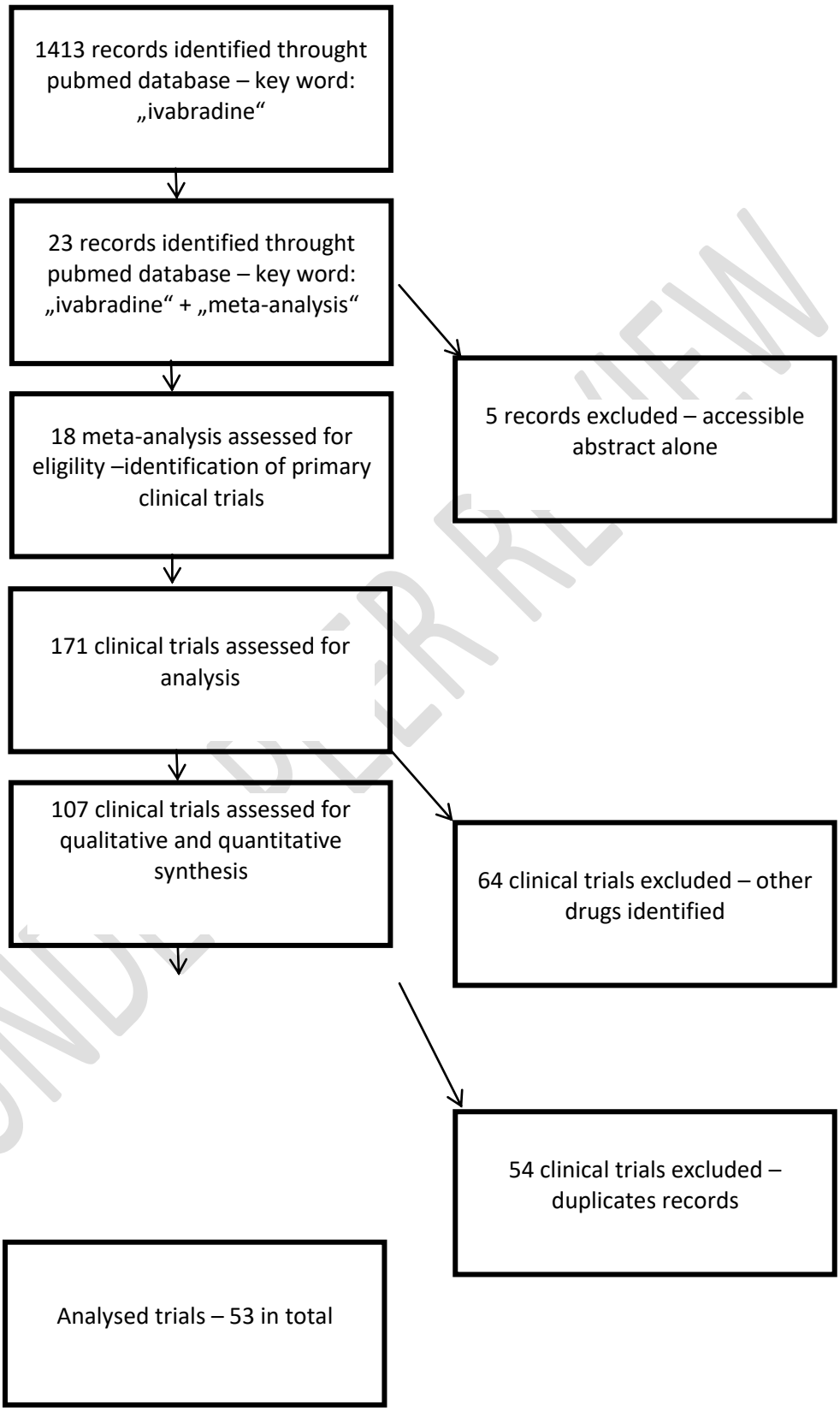

Figure 1 Flow diagram – PRISMA

Baseline characteristics analysed trials

This meta-analysis includes studies published between 2003 and 2018 (Fig.2). The greatest number of studies was published in 2012 (n=8) and 2016 (n=8) and the lowest number of studies was published in 2007 (n=1) and 2008 (n=1).

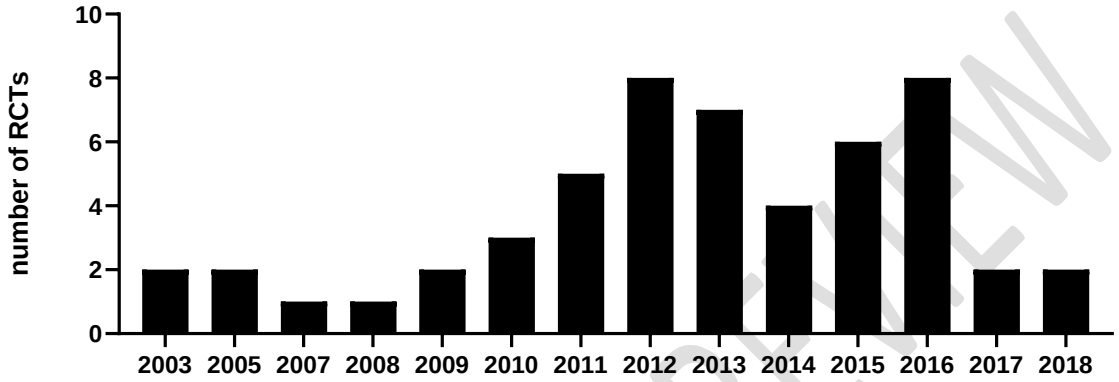

Figure 2: The Number of published studies per year (2003-2018)

Fig. 3 shows an overview of study designs between 2003 and 2018. and baseline characteristics for individual trials are detailed in Fig.4. Most of the analysed studies were blinded, followed by double-blinded trials and finally single-blinded trials. Fig.4 presents categorization of RCTs (Randomized Controlled Trials) based on different parameters – single-blinded trials, double-blinded trials and NA (not available) blinded.

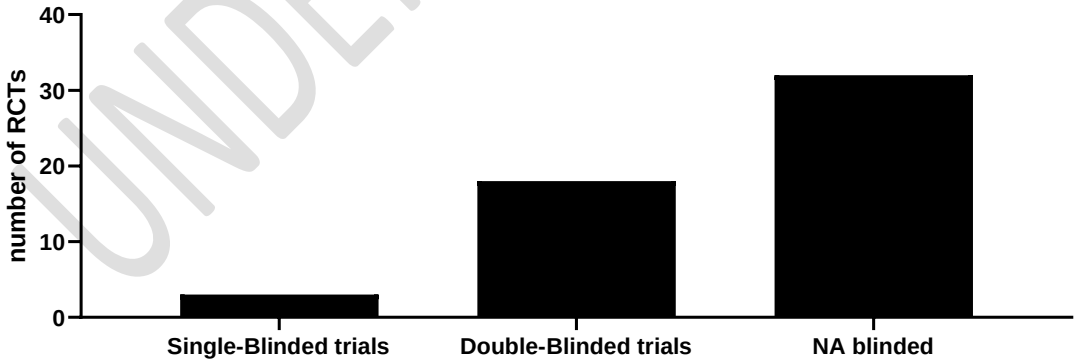

Figure 3 The categorization of RCTs studies - design.

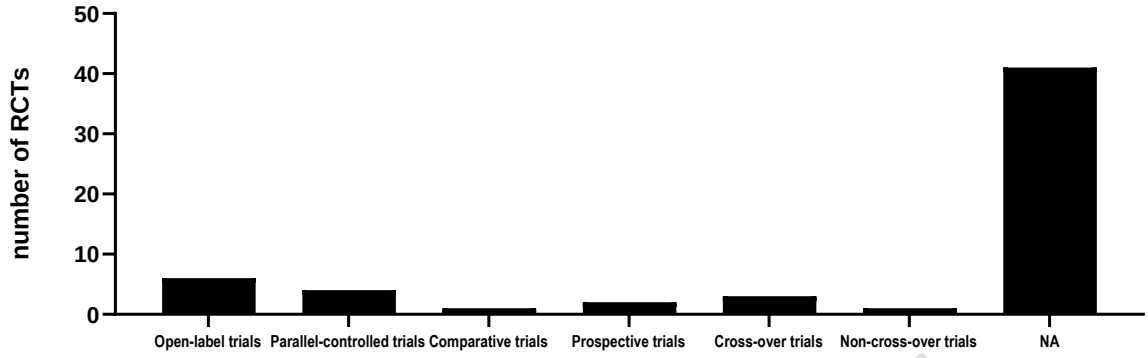

Figure 4 Elementary characteristics for individual studies

The studies varied in the size of the studied group, from less than 100 patients to more than 1000 patients. The studies included 51,603 patients in total (experimental and control groups) (Fig.5). As patients with heart failure are often elderly and have multiple morbidities the higher age average of the studied groups was expected. Based on the analysis, we identified the age range between 56 and ≥60 years with the average of 61,53±4,78 (Fig.6).

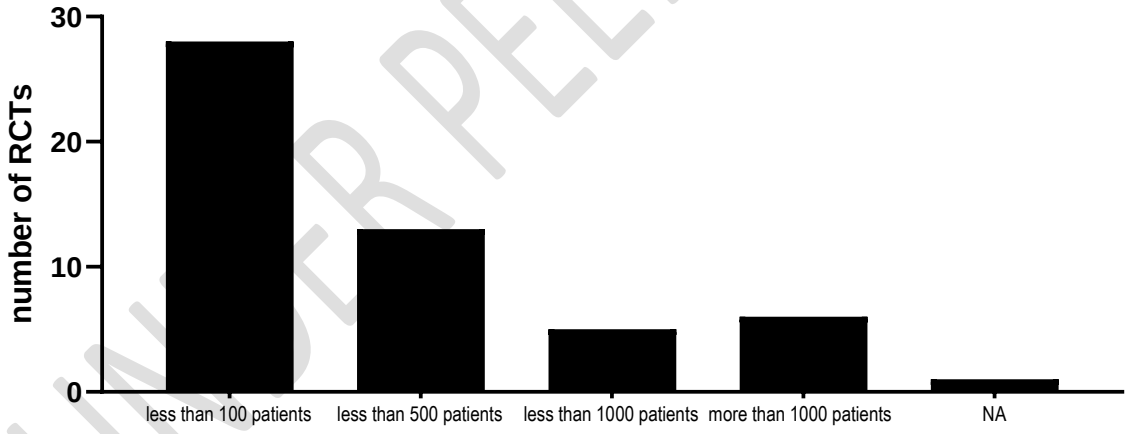

Figure 5 The number of patients who participated in each study (experimental +control groups (n=51603))

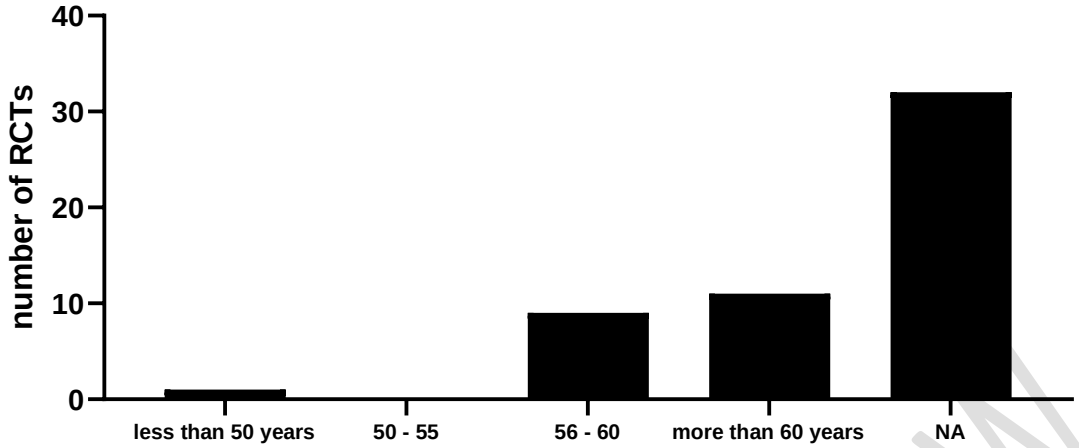

Figure 6 Categorisation of the studies according to patient's age

Hemodynamic parameters - Heart rate and ejection fraction

The effects of ivabradine in patients with heart rate ≥ 77 b.p.m. are shown in Fig.7. Systolic heart failure treatment with the *If* inhibitor ivabradine resulted in a pure heart rate reduction, a significant reduction in/of the composite endpoint of cardiovascular death and heart failure hospitalization in patients with chronic heart failure and reduced ejection fraction (left ventricular ejection fraction - LVEF ≤ 35%) who were in sinus rhythm and had resting heart rate ≥70 b.p.m. despite optimal medical therapy. The ejection fraction represents the percentage of blood volume pumped out of the left ventricle per systole. A healthy heart pumps out more than 55-60% of blood per systole. Patients with EF of <35% are at high risk of sudden cardiac death (Allison et al., 2020; Howlett, 2020) (Fig. 8).

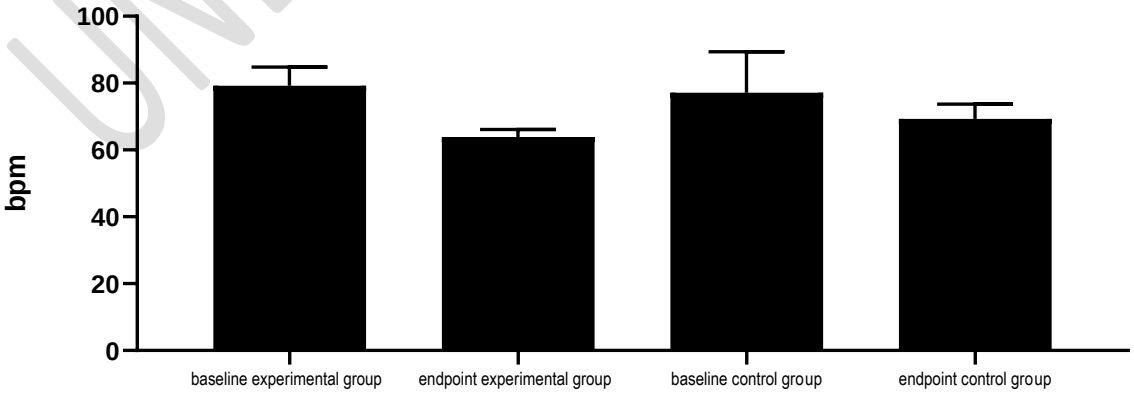

Figure 7 The Average of heart rate in the ivabradine/control group

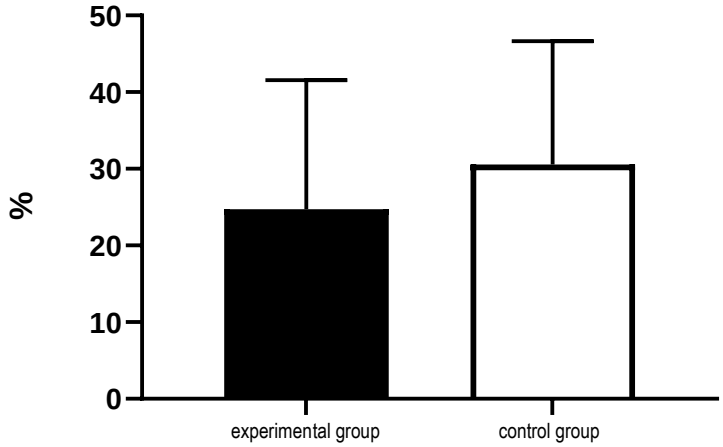

Figure 8 the average of left ventricle ejection fraction experimental/control group in each study.

Comparative therapy drugs in analysed RCTs

Figure 9 shows selected active compounds most frequently used for RCT treatment. Ivabradine, carvedilol, bisoprolol and other standard medical therapy were part of the standart care. The aim of this meta-analysis was to investigate whether ivabradine significantly reduced resting heart rate in comparison with placebo, beta-blockers or calcium channel blockers (Fig. 10).

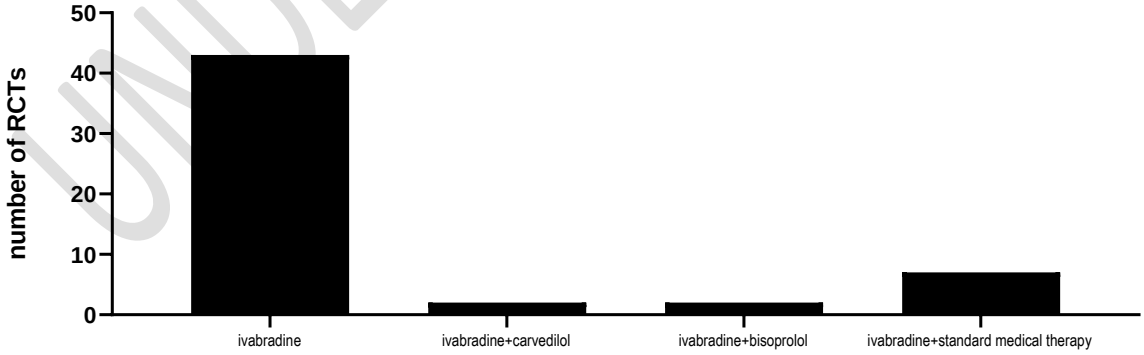

Figure 9 An overview of ivabradine clinical studies – categorised by the control group treatment

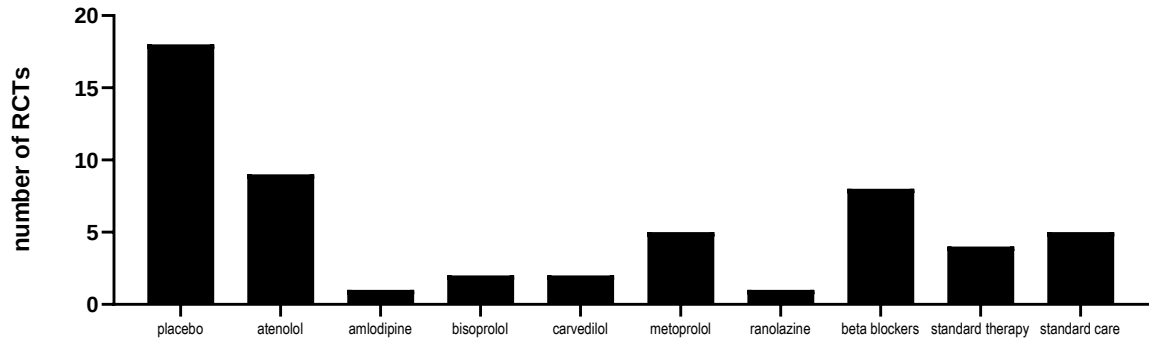

Figure 10 The number of studies by types of control group, comparative drugs in RCTs

Summary of results for all outcomes and comparisons:

1) *Ivabradine vs. placebo:* Ivabradine reduced HR compared with placebo or standard care. The effect on major adverse cardiovascular events or mortality in acute care remains unclear.
2) *Ivabradine vs. placebo/beta-blockers:* Compared with beta-blockers and placebo, ivabradine improved exercise duration and time to angina onset in patients with stable angina. However, the ability to improve exercise duration became significant after at least 3 months of treatment.
3) *Results ivabradine vs. beta-blockers:* Compared with β-blockers for heart rate reduction, ivabradine is a potentially attractive alternative for patients undergoing CTC (Computed tomography coronary angiography). It appears that the efficacy of ivabradine is good in comparison with betablockers, but more clinical trials are required to confirm this effect. Future will show whether ivabrandine will be a preferred treatment compared to β-blockers.

In three trials ivabradine was administered intravenously, per oral doses ranging from 2,5 to 7,5 mg with most studies allowing dose titration up to 7,5 mg according to the individual's HR (Fig.11). Other criticisms of the trial include the unusual dosing regimen that allowed for higher than usual daily doses of 10 mg twice daily (clinically recommended maximum doses being 7,5 mg twice daily).

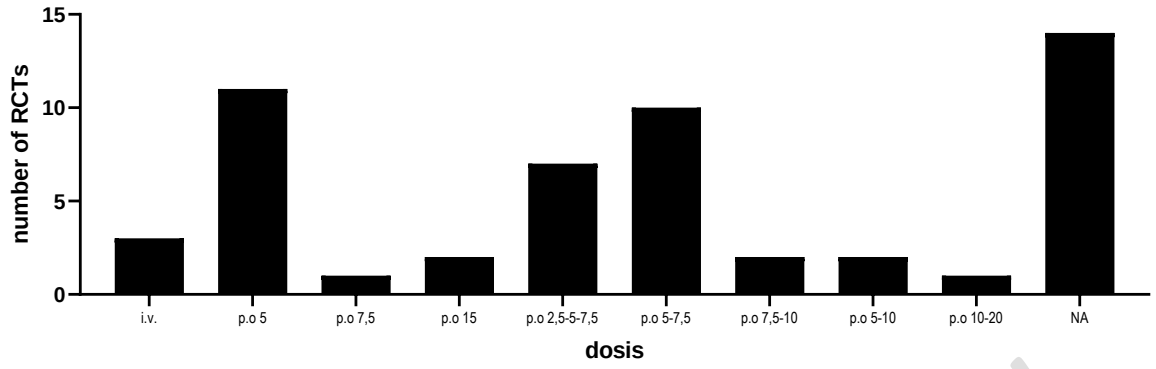

Figure 11 Ivabradine treatment doses in analysed studies.

To this trial attempted to further define the role of ivabradine in patients with stable angina, but with faster heart rates or heart failure (Fig. 12). We find that the most common indication was angina pectoris (n=10).

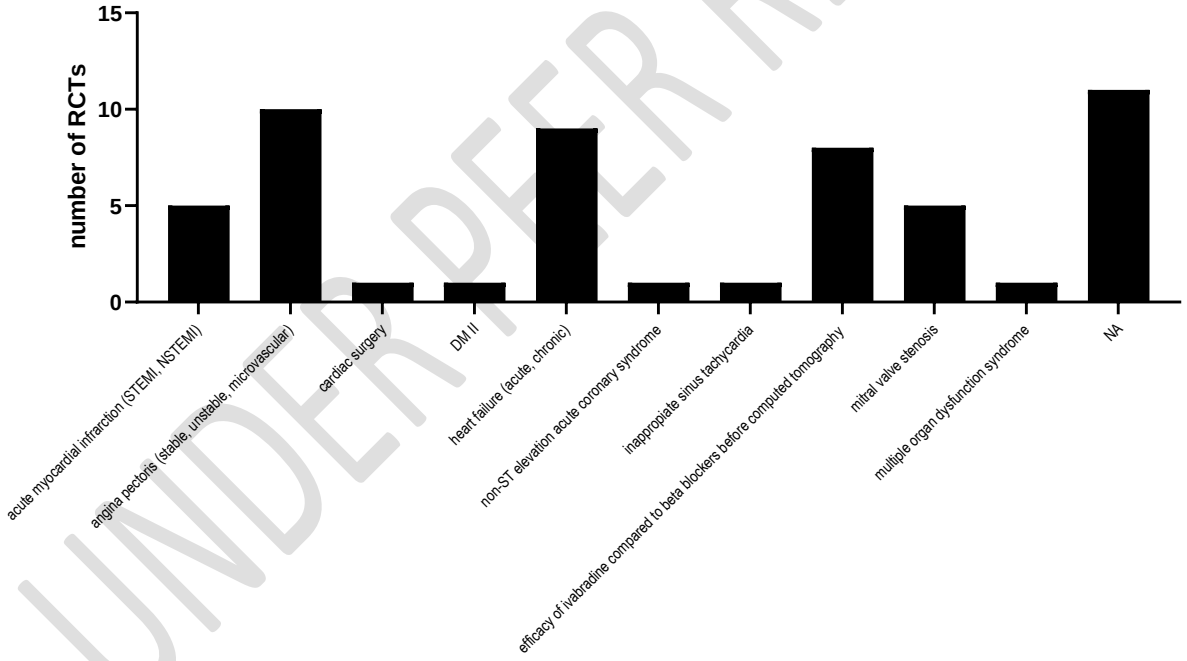

Figure 12 Frequency of specific indications for ivabrandine treatment in clinical trials

Treatment effects of ivabradine

In the primary analysis based on RCTs listed in guidelines, it was found that ivabradine did not show significant effects on both mortality and heart failure hospitalization (neutral effect on mortality). In contrast, the existing evidence showed that adding standard

treatment with ivabradine significantly improved the cardiopulmonary function and increased the exercise capacity of patients with chronic heart failure.

The common adverse effects were phosphenes and flashing light in the visual field and they were characteristic of ivabradine and were observed in analysed trials (Tab 1). These effects are related to partial antagonism of I*f* -channels, which are found in retinal tissue. Other adverse effects are bradycardia and atrial fibrillation. Less common adverse effect, include headache, rash, diplopia, angioedema, pruritus, urticaria, visual impairment, erythema, and vertigo. Therefore, ivabradine should not be used in patients with an HR lower than 70 bpm and in those with a second-degree atrioventricular block. Ivabradine should be avoided during pregnancy because it exhibited foetal toxicity in animal trials (Cammarano et al., 2016; Martin et al., 2014; Tanboğa et al., 2016; Badu-Boateng et al., 2018; Thorup et al., 2017; Sathyamurthy and Newale, 2018) (Tab 1).

Table 1 The common adverse effects (Sathyamurthy and Newale, 2018)

The most frequent adverse effects	phosphenes and flashing light bradycardia atrial fibrillation
Less common adverse effects	headache rash diplopia angioedema pruritus urticaria erythema vertigo

This systematic review shows that ivabradine treatment is associated with high risk of atrial fibrillation, 1 : 10 000, significantly higher than reported in product specifications. In contrast, the incidence of AF has not routinely been reported in clinical trials of ivabradine.

Discussion

There has been significant improvement in the treatment of cardiac diseases in the past few decades, however heart failure still remains a serious public health issue because of its

rising prevalence and poor prognosis. Elevated heart rate (HR) is an independent risk factor for cardiovascular morbidity and mortality (Koroma et al., 2020).

This systematic review includes 53 studies with a total of 51,603 patients, with stable angina pectoris in majority of subjects, treated by ivabradine, or placebo or comparative drugs defined as beta-blockers, calcium channel blockers and other anti-anginal drugs (ranolazine). Ivabradine was administered IV or per oral, at dosage 2,5- 5 mg, 7,5 mg or 10 mg bis in die (BID), with 10 mg BID noticeably above the manufacturer's recommended maximum daily dose.

Ivabradine is the sole available HCN (hyperpolarization-activated cyclic nucleotide-gated) inhibitor. It slows HR by reduction of the I*f* current-regulated diastolic depolarization in the sinoatrial node, increasing diastolic time without altering the action potential duration or causing negative inotropy (Sathyamurthy and Newale, 2018).

Positive effects of ivabradine were observed in several studies. A comparison between ivabradine and placebo showed significant benefits of ivabradine in terms of individual quality of life. In contrast the largest manufacturer-sponsored multi-centre study in more than 12,000 CAD patients, SIGNIFY, did not show any significant effect of ivabradine on cardiovascular mortality (Kalvelage et al., 2020). Beta-blockers in particular represent a rational intervention for HR modulation. Their data indicated a higher risk of bradycardia with ivabradine compared with placebo as well as an increase in the absolute incidence of atrial fibrillation. One reason for these negative outcomes of SIGNIFY might be the higher dosage of 10 mg BID in some patients, however, an audit of the data by the European Medicines Agency (EMA) did not agree with these findings. To reduce this risk of atrial fibrilation the EMA gives the following recommendations: dosage of 5 to 7,5 mg BID, no combination with verapamil or diltiazem and sole use in angina patients in sinus rhythm with a heart rate ≥70 bpm who remain symptomatic despite anti-anginal therapy (Kalvelage et al., 2020). This data is in line with the recommendations by the EMA to use ivabradine only if the patient cannot be treated with beta-blockers, or in combination if beta-blockers alone are not sufficient.

Ivabradine takes several hours to elicit a stable reduction in the spontaneous action potential firing rate of isolated SAN (sinoatrial node) because it binds to intercellular sites of the HCN4 channel with an open channel configuration (Ide et al., 2019).

Foetal toxicity of ivabrandine was studied only in experimentaly on animal models. Foetuses of pregnant rats showed embryo-foetal toxicity and cardiac teratogenic effects when treated at 1 to 3 times the maximum recommended human dose. No adequate studies of

ivabradine in pregnant women were conducted and therefore it is not possible to assess the drug's possible risk to the mother or the foetus. Contraception is therefore recommended in female patients taking ivabradine (Reed et al., 2020).

In terms of pharmacokinetics, after oral administration, ivabradine reaches the maximum concentration in about 1 hour and has an elimination half-life of about 2 hours. The absolute bioavailability of oral film-coated tablets is 40%. Cytochrome P4503A4 is involved in the metabolism of ivabradine and metabolites of ivabradine are eliminated through urine and faeces. Caution is required in patients with creatinine clearance below 15 ml/min. Ivabradine is contraindicated in patients with severe liver damage (Sathyamurthy and Newale, 2018).

Conclusion

In conclusion, this systematic review make an important contribution to optimal patient care in heart failure and decisively complements the current EMA. We conlcude the usage ivabradine only if In cases where the standard beta-blocker treatment is not recommended, In combination with beta-blockers, where beta-blockers alone are not sufficient

This systematic review including 53 clinical trials did not find any convicing evidence of significant advantages of ivabrandine tretment compared to other currently used medication.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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