Beta-blockers for the treatment of arrhythmias: Bisoprolol – a systematic review

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Bêta-bloquants pour le traitement des arythmies: Bisoprolol - une revue systématique

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HIGHLIGHTS:

- This is the first systematic review on the role of Bisoprolol, a lipophilic beta 1 selective receptor blocker, for the treatment of arrhythmias.
- Bisoprolol is useful for the treatment of supraventricular arrhythmias, especially for rate control during atrial fibrillation.

- Evidence also exists for its efficacy in the treatment of ventricular arrhythmias, both in primary and in secondary prevention.

Abstract

Objectives: Beta blockers have long been successfully used for the treatment of both supraventricular and ventricular arrhythmias. However, differences exist between their chemical structure, pharmacokinetic and pharmacodynamic properties (absorption, bioavailability, metabolism, hydrophilic or lipophilic character, selective or non-selective nature, the presence or absence of intrinsic sympathomimetic activity), which may confer different antiarrhythmic properties to different beta blockers. The aim of this study was to analyze the current existing evidence for bisoprolol for the treatment of both supraventricular and ventricular arrhythmias.

Material and Methods: Using the keywords "bisoprolol" and "arrhythmias" or "atrial fibrillation" or "ventricular tachycardia" or "premature ventricular complexes" or "ventricular fibrillation", the Medline database was searched for articles in English or French until April 2020 assessing the role of bisoprolol in the treatment of arrhythmias. Data was then analyzed according to the type of arrhythmia treated and the quality of evidence using the GRADE approach.

Results: A total of 325 studies were identified, of which 28 were considered relevant to the current topic. Among these studies, 19 assessed the role of bisoprolol for the treatment of supraventricular arrhythmias, 8 its role in treating ventricular arrhythmias and 1 its role in supraventricular and ventricular arrhythmias. The quality of evidence varied from low (7 studies) to high (5 studies).

Conclusion: Current evidence exists supporting the use of bisoprolol for the treatment of supraventricular arrhythmias, especially for rate control during atrial fibrillation. Evidence also exists for its efficacy in the treatment of ventricular arrhythmias, both in primary and in secondary prevention.

Keywords: bisoprolol, beta blockers, arrhythmias, atrial fibrillation, ventricular arrhythmias

Abstrait

Objectifs: Les bêtabloquants sont utilisés depuis longtemps avec succès pour le traitement des arythmies supraventriculaires et ventriculaires. Cependant, des différences existent entre leur structure chimique, leurs propriétés pharmacocinétiques et pharmacodynamiques (absorption, biodisponibilité, métabolisme, caractère hydrophile ou lipophile, nature sélective ou non sélective, présence ou absence d'activité sympathomimétique intrinsèque), qui peuvent conférer des propriétés antiarythmiques différentes aux différents bêta-bloquants. Le but de cette étude était d'analyser les preuves existantes pour le bisoprolol pour le traitement des arythmies supraventriculaires et ventriculaires.

Matériel et méthodes: À l'aide des mots-clés «bisoprolol» et «arythmies» ou «fibrillation auriculaire» ou «tachycardie ventriculaire» ou «extrasystoles ventriculaires» ou «fibrillation ventriculaire», la base de données Medline a été recherchée pour des articles en anglais ou en français jusqu'en avril 2020 évaluer le rôle du bisoprolol dans le traitement des arythmies. Les données ont ensuite été analysées en fonction du type d'arythmie traitée et de la qualité des preuves en utilisant l'approche GRADE.

Résultats: Au total, 325 études ont été identifiées, dont 28 ont été jugées pertinentes pour le sujet actuel. Parmi ces études, 19 ont évalué le rôle du bisoprolol dans le traitement des arythmies supraventriculaires, 8 son rôle dans le traitement des arythmies ventriculaires et 1 son rôle dans les arythmies supraventriculaires et ventriculaires. La qualité des preuves variait de faible (7 études) à élevée (5 études).

Conclusion: Il existe des preuves actuelles soutenant l'utilisation du bisoprolol pour le traitement des arythmies supraventriculaires, en particulier pour le contrôle de la fréquence en fibrillation auriculaire. Il existe également des preuves de son efficacité dans le traitement des arythmies ventriculaires, à la fois en prévention primaire et en prévention secondaire.

Mots clés: bisoprolol, bêtabloquants, arythmies, fibrillation auriculaire, arythmies ventriculaires

Objectives

Since the first introduction in clinical practice of a beta blocker, propranolol, in 1965 (1), more than 50 different beta blockers have been used for the treatment of both cardiac and non-cardiac conditions. Current uses of beta blockers in the treatment of cardiovascular disease include arterial hypertension (2, 3), acute coronary syndromes (4-7), chronic coronary syndromes (8, 9), post myocardial revascularization (10, 11), decreased left ventricular function after myocardial infarction (12, 13), heart failure (12, 13) and cardiac arrhythmias (14-19).

Although part of the same class of drugs, important differences exist between different beta blockers regarding their chemical structure, route of administration, pharmacokinetic and pharmacodynamic properties (absorption, bioavailability, metabolism, time to effect, elimination route, hydrophilic or liphophilic character, selective or non-selective nature, the presence or absence of intrinsic sympathomimetic activity) and side effects which, at least from a theoretical perspective, may make some beta blockers more appropriate than others for the treatment of cardiac arrhythmias. Indeed, not all beta blockers have the same antiarrythmic properties in patients with long QT syndrome (LQTS), where nadolol and propranolol are to be preferred over other beta blockers (20), and metoprolol should probably be avoided (21). This observation raises the question whether all beta blockers are equally efficient in the treatment of arrhythmias, and if not, which beta blockers should be preferred? Also, if a beta blocker is inefficient in the treatment of a arrhythmia, can a different beta blocker be successfully used instead?

The European Society of Cardiology (ESC) and the American Heart Association / American College of Cardiology / Heart Rhythm Society (AHA / ACC / HRS) have published several consensus documents on the use of beta blockers for the treatment of arrhythmias (14-19). The 2004 ESC Expert consensus document on beta adrenergic receptor blockers (22) provides evidence for the use of atenolol, esmolol, metoprolol, nadolol, propranolol, sotalol, and timolol for the treatment of arrhythmias. Nevertheless, other existing beta blockers may be both safe and efficient for the treatment of both supraventricular and ventricular arrhythmias.

Bisoprolol is a lipophilic beta 1 selective receptor blocker that was patented in 1976 and introduced in clinical practice in 1986 (23-25). It has a long duration of action, with a slower drop in the action duration curve compared to propranolol (26). Its half-life is 10-11 hours (27), which allows a single daily administration (22). Common doses range from 1.25 mg to 10 mg daily (22). The maximal approved dose is 20 mg once a day (for the treatment of hypertension). It is devoid of intrinsic sympathetic activity. Its bioavailability from film-coated tablets is about 90%. In plasma, it circulates 30% protein-bound. It is moderately lipid-soluble. Fifty percent of the dose is metabolized by the liver, via CYP3A4. It is eliminated 50% by the kidney, unchanged. Both in vivo and in vitro studies have shown that it is one of the most beta 1 selective beta blockers, more selective than atenolol, betaxolol or metoprolol (28-31). It inhibits both basal and stimulated renin secretion and has antihypertensive properties that are equivalent to the ones of nebivolol (32). It is devoid of serious and unexpected side-effects, even at high doses. Glucose intolerance and sedative effects are less pronounced compared to propranolol (33). It has no significant negative effect of the lipid metabolism (33). Most common side effects are fatigue, bradycardia, hypotension and gastro-intestinal symptoms. Unlike non-selective beta blockers (nadolol, propranolol), it is not associated with a significantly increased risk of asthma exacerbations

in patients with mild or moderate forms of dieases (34). Bisoprolol will give a positive result in doping tests.

The CIBIS trial (35) showed that bisoprolol reduces mortality in heart failure patients. However, no significant difference was observed in sudden death rate (17 patients on placebo vs 15 patients on bisoprolol) or death related to documented ventricular tachycardia or fibrillation (7 patients on placebo vs 4 patients on bisoprolol). Contrarily, in the following CIBIS-II trial (36), there were significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3·6%] vs 83 [6·3%] deaths), fact which established its use in patients with heart failure and reduced ejection fraction (HFREF) (12). Bisoprolol is currently also used for the treatment of arterial hypertension (2) and myocardial ischemia (2, 4, 36). However, its role in the treatment of arrhythmias is less well established. Unlike other beta blockers (atenolol, metoprolol, nadolol propranolol, sotalol), it is not mentioned in some of the most important international guidelines on the treatment of arrhythmias, such as the 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death (37). However, given its positive efficacy/side effects profile, bisoprolol remains one of the most largely-used beta blockers in clinical practice.

The aim of this study was to analyze the current existing evidence for bisoprolol in the treatment of arrhythmias, both supraventricular and ventricular.

Material and Methods

Using the keywords “bisoprolol” and either “arrhythmia” or “atrial fibrillation” or “ventricular tachycardia” or “premature ventricular complexes”, the Medline database was screened by 2 independent researchers for articles in the English or French language up to April 2020, assessing the role of bisoprolol in the treatment of arrhythmias. Manual additional search was then used in order to identify potential important studies on the efficacy of bisoprolol in the treatment of arrhythmias that were missed using the above-mentioned search strategy. Data was then analyzed according to the type of arrhythmia treated (supraventricular vs. ventricular), the type of results found (positive / negative / mixed) and the quality of evidence (very low, low, moderate, high) using the GRADE approach (38). Prospective randomized clinical trials were considered high quality evidence; retrospective studies on small populations of subjects were considered low quality evidence.

Studies written in languages other than English or French, case reports / case series / studies performed on less than 10 subjects, duplicate titles, studies not relevant to the current topic, abstracts of which manuscripts were not available, review articles, meta-analysis and letter to the editors were not included in the study.

Results

The search strategy identified a number of 325 studies, of which 28 met the inclusion criteria (Figure 1). Among these 28 studies, 19 assessed the role of bisoprolol in the treatment of supraventricular arrhythmias: 1 study assessed the effect of bisoprolol on respiratory sinus arrhythmia, 2 studies assessed the effect of bisoprolol on paroxysmal supraventricular tachycardia, and 1 study assessed the

role of bisoprolol on a mixed population of patients (a part with premature atrial contractions and a part with paroxysmal supraventricular tachycardia); 15 studies evaluated the role of bisoprolol for the treatment of atrial fibrillation, either as part of a rhythm control strategy (post cardioversion of atrial fibrillation or prevention of AF in a high-risk setting, post-surgery) or as a rate control strategy (negative dromotropic effect) either in patients post coronary artery bypass graft (CABG) or non-cardiac surgery, or in a non-post-surgical setting. Nine studies assessing the role of bisorpolol in the treatment of supraventricular arrhythmias compared its efficacy to other beta blockers (carvedilol, landiolol) or other antiarrhythmic drugs (amiodarone, sotalol) or to catheter ablation. Two studies did not find a beneficial effect of bisoprolol for the treatment of specific supraventricular arrhythmias; the rest of the studies identified at least some benefit. The quality of the studies varied from very low (4 studies) to high (3 studies).

There were 8 studies evaluating the role of bisoprolol in the treatment of ventricular arrhythmias. Among these studies, 2 studies evaluated its role in the treatment of premature ventricular contractions, 4 assessed its role in the treatment of patients with myocardial ischemia or heart failure, and 2 assessed the role of bisoprolol in the treatment of patients with long QT syndrome (LQTS). All but one study found positive results of bisoprolol in the treatment of ventricular arrhythmias. The quality of the studies varied from low (3 studies) to high (2 studies).

One study assessed the efficacy of bisoprolol in treating a mixed population of patients, some with supraventricular arrhythmias and some with ventricular arrhythmias (premature ventricular contractions).

A summary of these studies is presented in table 1 and table 2.

Figure 1. Flowchart describing the selection steps of the references used in this review

Table 1. The role of bisoprolol in the treatment of supraventricular arrhythmias - data from clinical studies. * - this study included a mixed population of patients, some with SVT, others with PVC. Only the effect of bisoprolol on patients with SVT is assessed here. For the discussion on this study about the efficacy of bisoprolol in patients with PVC, please see table 2. AF = Atrial Fibrillation; AT = atrial tachycardia; AV = atrio-ventricular; AVRT = atrio-ventricular reentry tachycardia; AVNRT = Atrio-ventricular node reentry tachycardia; CABG = coronary artery bypass graft; HF = heart failure; HR = heart rate; PAC = Premature atrial contractions; P-AF = Paroxysmal atrial fibrillation; PVC = premature ventricular contractions; QOL = Quality of Life; SR = sinus rhythm; SVT = Supraventricular tachycardia.

Table 2. The role of bisoprolol in the treatment of ventricular arrhythmias - data from clinical studies. * - this study included a mixed population of patients, some with SVT, others with PVC. Only the effect of bisoprolol on patients with PVC is assessed here. For the discussion on this study about the efficacy of bisoprolol in patients with SVT, please see table 1. HD = hemodynamic; HF = heart failure; HR = heart rate; LQTS = Long QT Syndrome; MACE = Major Adverse Cardiac Events; MI = myocardial infarction; NSTEMI = non ST segment elevation myocardial infarction; PVC = Premature Ventricular Contractions; ST = Sinus Tachycardia; VA = ventricular arrhythmias; VF = ventricular fibrillation; VT = ventricular arrhythmia

Figure 1. Organigramme décrivant les étapes de sélection des références utilisées dans cette revue

Tableau 1. Le rôle du bisoprolol dans le traitement des arythmies supraventriculaires - données des études cliniques. * - cette étude a inclus une population mixte de patients, certains avec SVT, d'autres avec PVC. Seul l'effet du bisoprolol sur les patients atteints de SVT est évalué ici. Pour la discussion sur cette étude sur l'efficacité du bisoprolol chez les patients atteints de PVC, veuillez consulter le tableau 2. FA = fibrillation auriculaire; AT = tachycardie atriale; AV = auriculo-ventriculaire; AVRT = tachycardie par réentrée auriculo-ventriculaire; AVNRT = tachycardie par réentrée intra-nodale; HF = insuffisance cardiaque; FC = fréquence cardiaque; PAC = extrasystoles supraventriculaires; P-AF = fibrillation auriculaire paroxystique; PVC = extrasystoles ventriculaires ; QOL = qualité de vie; SR = rythme sinusal; SVT = tachycardie supraventriculaire.

Tableau 2. Le rôle du bisoprolol dans le traitement des arythmies ventriculaires - données des études cliniques. * - cette étude a inclus une population mixte de patients, certains avec SVT, d'autres avec PVC. Seul l'effet du bisoprolol sur les patients atteints de PVC est évalué ici. Pour la discussion sur cette étude sur l'efficacité du bisoprolol chez les patients atteints de SVT, veuillez consulter le tableau 1. HD = hémodynamique; HF = insuffisance cardiaque; FC = fréquence cardiaque; LQTS = syndrome du QT long; MACE = événements cardiaques indésirables majeurs; IM = infarctus du myocarde; NSTEMI = infarctus du myocarde sans élévation du segment ST; PVC = extrasystoles ventriculaires; ST = tachycardie sinusale; VA = arythmies ventriculaires; VF = fibrillation ventriculaire; TV = tachycardie ventriculaire.

Discussion

This review focused on assessing the current existing evidence regarding bisoprolol for the treatment of arrhythmias, both supraventricular and ventricular. The main findings can be summarized as follows: regarding supraventricular arrhythmias, 1. bisoprolol is less effective than catheter ablation in preventing recurrences in patients with AVNRT; 2. It is useful as part of a rate control strategy by efficiently lowering heart rate in patients with atrial fibrillation; 3. It is efficient as part of a rhythm control strategy by preventing the onset of atrial fibrillation in patients who have undergone surgery (both cardiac and non-cardiac); 4. Less robust evidence exists concerning its role in pharmacological cardioversion of atrial fibrillation, in preventing AF recurrence after electrical cardioversion and in improving symptoms and quality of life in patients with paroxysmal atrial fibrillation. Regarding ventricular arrhythmias: 1. bisoprolol reduces mortality and is efficient in reducing the number of hospitalizations due to severe arrhythmias (sustained VT or VF) in patients with stable heart failure; 2. Administered early (<4 hours) after myocardial infarction, it lowers mortality, it reduces the number of episodes of ventricular arrhythmias and major adverse cardiac events (MACE) in patients with NSTEMI; 3. It efficiently reduces the ventricular arrhythmia burden in patients with PVC; 4. Its role in treating patients with LQTS is less well established.

Bisoprolol for the treatment of supraventricular arrhythmias

Most of the studies assessing the role of bisoprolol in the treatment of supraventricular arrhythmias focused on its role in the treatment of atrial fibrillation, either in a post-surgical setting or not related to surgery. In a surgical setting, either post CABG or after non-cardiac surgery, all of the evaluated

studies addressing this topic (39-44) identified at least some benefit of bisoprolol, with low rates of adverse events, with one study finding a higher efficacy compared to carvedilol (39) and another an efficacy equal to that of amiodarone (40). Bisoprolol was also efficient in decreasing heart rate in patients who developed atrial fibrillation (44). A recent Cochrane systematic review confirms these findings, concluding that beta blockers reduce the burden of both supraventricular and ventricular arrhythmias after cardiac surgery, and substantially reduce the burden of supraventricular arrhythmias after non-cardiac surgery (45). Concerning bisoprolol, it states that if beta-blockers are started before surgery, bisoprolol may be considered as first choice (class IIb, level of evidence B).
In a non-surgical setting, there is weak evidence that bisoprolol prevents recurrence post electrical cardioversion of AF, with bisoprolol being as efficient as sotalol (weak evidence) (46). Data regarding its efficacy compared to carvedilol in this setting is mixed (47, 48). In combination with propafenone, it was shown to be efficient in converting AF to sinus rhythm more rapidly compared to propafenone alone (weak evidence), but in this study, the percentage of patients who converted to sinus rhythm after 24 hours was equal in both groups (49). Bisoprolol is also efficient in lowering heart rate in patients with atrial fibrillation (50-53), with its transdermal administration being as efficient as iv landiolol (54) or oral bisoprolol (53). There is also some evidence that bisoprolol improves symptoms and quality of life in patients with paroxysmal AF, being well tolerated (55). Even though the authors of this study state that elimination of AF episodes on ECGs was observed in 84 patients (62%), the efficacy of bisoprolol in the prevention on AF recurrence cannot be assessed based on this study, since there was no control group.

A meta-analysis performed by Nasr et al showed that taken together, carvedilol, bucindolol, metoprolol, nebivolol and bisoprolol prevent the onset of atrial fibrillation in patients with heart failure (56). The evidence for the efficacy of bisoprolol in this setting comes from the CIBIS I and II trials (35, 36). Taking together the evidence on bisoprolol and metoprolol, the authors found a relative risk (RR) reduction of 41% ($p = 0.006$) for the onset of new atrial fibrillation.

During the past years, catheter ablation has become an established technique for the treatment of atrial fibrillation. Initially, this was considered an alternative technique for patients who presented atrial fibrillation recurrence under antiarrhythmic drugs, which usually included a beta blocker (17). Lately, catheter ablation has become the better choice for rhythm control strategy (vs. antiarrhythmic drugs), given the results of latest trials (57, 58). Several studies have demonstrated its superiority to antiarrhythmic drugs for the maintenance of sinus rhythm, regardless of the type of energy used: radiofrequency (59-66) or cryoenergy (57, 58). Beta blockers were largely used in these trials, along with class I (flecainide, propafenone) or class III antiarrhythmic drugs (mostly amiodarone). Explicit references to specific beta blockers were usually not made in these trials. Up to the present date, there is no specific trial focusing on the efficacy of bisoprolol compared to catheter ablation in patients with atrial fibrillation.

Concerning the role of bisoprolol in the treatment of paroxysmal SVT, there is little but solid evidence showing that it is less efficient in preventing AVNRT recurrence compared to catheter ablation (64). In their study, Katritsis et al demonstrated significantly more AVNRT recurrences in the medical treatment group (bisoprolol 5 mg od or diltiazem 120 – 300 mg od) vs catheter ablation ($p<0.001$). Evidence assessing its role in patients atrio-ventricular reentry tachycardia (AVRT) and in patients with atrial tachycardia (24) is limited, since no randomized control trial evaluating the role of bisoprolol was

conducted in these patients. Therefore, firm conclusions about its efficacy in this setting cannot be drawn.

Overall, in patients with supraventricular arrhythmias, bisoprolol is efficient in patients with atrial fibrillation both as part of a rhythm control and a rate control strategy in patients undergoing cardiac or non-cardiac surgery. In non-surgical patients, it is efficient as a rate control agent and it likely improves symptoms and quality of life. In patients with AVNRT, it is less efficient than catheter ablation in preventing recurrences.

Bisoprolol for the treatment of ventricular arrhythmias

Our search strategy found evidence supporting the use of bisoprolol for the treatment of ventricular arrhythmias, both in patients without structural heart disease (either in otherwise healthy subjects or in patients with channelopathies) and in patients with heart disease, namely myocardial ischemia and heart failure.

The positive impact of ventricular arrhythmia reduction of bisoprolol in patients with heart failure relies on the CIBIS (35) and the CIBIS-II trials (36). A comprehensive discussion of these studies is outside the purpose of this review and can be found elsewhere (67). The CIBIS trial (35) showed that, bisoprolol reduces mortality in heart failure patients, but not sudden cardiac death (17 patients on placebo vs 15 patients on bisoprolol) nor death related to documented ventricular tachycardia or fibrillation (7 patients on placebo vs 4 patients on bisoprolol, p=ns). However, the following CIBIS-II trial (36), performed on a larger population of patients, found significantly fewer sudden deaths among patients on bisoprolol than in those on placebo (48 [3·6%] vs 83 [6·3%] deaths), demonstrating the efficient antiarrhythmic properties of bisoprolol in a clinical setting.

In patients with acute myocardial ischemia, namely NSTEMI, after adjusting for confounders, Maclean et al (68) found that early (less than 4 hours) bisoprolol administration was protective for ventricular arrhythmia (p=0.038, OR 0.114, CI 0.015 to 0.885) and MACE (p=0.011, OR 0.064, CI 0.008 to 0.527), with few adverse effects of Bisoprolol (one episode of symptomatic bradycardia).

Three trials on small populations of patients examined the role of bisoprolol, in patients with PVC (25, 69, 70). These trials found a significant reduction in the ventricular arrhythmia burden, at doses of 2.5 – 5 mg po or 4 mg transdermal. Sugimoto et al (25) found more than 50% reduction of the PVC burden in 7 out of 16 patients on bisoprolol. Kobayashi et al (69) found that bisoprolol effectively inhibited PVC in 5 of 12 dipyridamole-respondent patients (reduction of 88 ± 16% of PVC) and in 3 of 6 dipyridamole-non-respondent patients. In their study, Shinohara et al (70) found that transdermal bisoprolol significantly reduced the PVC burden in the positive heart rate-PVC group, while the PVC burden did not change significantly in the non-positive heart rate-PVC group. In the positive heart rate dependent-PVC group, the patients with mean HRs > 80 bpm had a significantly higher percent improvement in the PVC count than those with mean HRs <80 bpm (p = 0.0080). However, all these 3 studies were performed on small populations of patients and therefore the results should be interpreted with caution.

Concerning patients with LQTS, there is weak evidence that bisoprolol might be both safe and efficient in the treatment of patients with this type of channelopathy. In their study on 34 patients with LQTS, Fazio et al found no major adverse cardiac event in patients treated with bisoprolol. Of the 12 minor

cardiovascular events, 3 occurred in absence of treatment, 7 during treatment with nadolol or propranolol, and 2 during treatment with bisoprolol. The authors conclude that bisoprolol at doses of 0.1 – 0.2 mg/kg might be less harmful and easier to manage than propranolol and nadolol (71).
In their study of 114 patients with LQTS, Steinberg et al (72) observed QTc shortening in 59 subjects treated with bisoprolol (ΔQTc -5 ± 31 ms; p = 0.049). Bisoprolol was well tolerated during long-term administration (1 cardiac event = 1.7% during a 3-year follow-up). However, the authors conclude that the equivalence of bisoprolol for protection from ventricular arrhythmia in LQT patients compared to established beta-blockers remains unknown.
Despite these promising results, due to the reduced number of studies on Bisoprolol in patients with LQTS, these data should be confirmed in larger clinical trials, before recommending bisoprolol as a safe and efficient beta blocker in this population of patients.

Overall, in patients with ventricular arrhythmias, bisoprolol reduces mortality and is efficient in reducing the number of hospitalizations due to severe arrhythmias in patients with stable heart failure. It lowers mortality and reduces the number of episodes of ventricular arrhythmias and MACE in patients with NSTEMI. It efficiently reduces the ventricular arrhythmia burden in patients with PVC. Its role in treating patients with LQTS is less well established.

Limitations of the study
The main limitation of this study is the heterogeneity of the studies included. The quality of the evidence is mixed, ranging from low quality to a few high quality studies, with the majority of the studies having a moderate quality. Few randomized clinical trials were found on this topic. With these heterogeneous data, a meta-analysis was impossible to conduct.

Conclusion
Current evidence exists supporting the use of Bisoprolol for the treatment of supraventricular arrhythmias, especially for rate control during atrial fibrillation. Evidence also exists for its efficacy in the treatment of ventricular arrhythmias, both in primary and in secondary prevention. Head to head clinical trials on large populations of patients comparing the safety and efficacy of Bisoprolol and other beta blockers are needed in order to better understand its rank among beta blockers for the treatment of arrhythmias.

References

1. Quirke V. Putting theory into practice: James Black, receptor theory and the development of the beta-blockers at ICI, 1958-1978. Medical history. 2006;50(1):69-92.
2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 Practice Guidelines for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Blood pressure. 2018;27(6):314-40.
3. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2018;138(17):e426-e83.
4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment

elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2018;39(2):119-77.
5. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). European heart journal. 2016;37(3):267-315.
6. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., Chung MK, de Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;61(4):e78-e140.
7. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2014;64(24):e139-e228.
8. Knuuti J WW, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ; ESC Scientific Document Group . <2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.pdf>. European heart journal. 2019;14(41):407-47.
9. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Journal of the American College of Cardiology. 2014;64(18):1929-49.
10. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. European heart journal. 2019;40(2):87-165.
11. Patel MR, Calhoon JH, Dehmer GJ, Grantham JA, Maddox TM, Maron DJ, et al. ACC/AATS/AHA/ASE/ASNC/SCAI/SCCT/STS 2017 Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease : A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society of Thoracic Surgeons. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology. 2017;24(5):1759-92.
12. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016;37(27):2129-200.
13. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Journal of cardiac failure. 2017;23(8):628-51.
14. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace : European pacing,

arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015;17(11):1601-87.
15. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140(2):e125-e51.
16. Page RL, Joglar JA, Caldwell MA, Calkins H, Conti JB, Deal BJ, et al. 2015 ACC/AHA/HRS Guideline for the Management of Adult Patients With Supraventricular Tachycardia: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology. 2016;67(13):1575-623.
17. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European heart journal. 2016;37(38):2893-962.
18. Brugada J, Katritsis DG, Arbelo E, Arribas F, Bax JJ, Blomstrom-Lundqvist C, et al. 2019 ESC Guidelines for the management of patients with supraventricular tachycardiaThe Task Force for the management of patients with supraventricular tachycardia of the European Society of Cardiology (ESC). European heart journal. 2020;41(5):655-720.
19. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart rhythm. 2018;15(10):e190-e252.
20. Ackerman MJ, Priori SG, Dubin AM, Kowey P, Linker NJ, Slotwiner D, et al. Beta-blocker therapy for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia: Are all beta-blockers equivalent? Heart rhythm. 2017;14(1):e41-e4.
21. Chockalingam P, Crotti L, Girardengo G, Johnson JN, Harris KM, van der Heijden JF, et al. Not all beta-blockers are equal in the management of long QT syndrome types 1 and 2: higher recurrence of events under metoprolol. Journal of the American College of Cardiology. 2012;60(20):2092-9.
22. Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, et al. Expert consensus document on beta-adrenergic receptor blockers. European heart journal. 2004;25(15):1341-62.
23. Dorow P, Bethge H, Tonnesmann U. Effects of single oral doses of bisoprolol and atenolol on airway function in nonasthmatic chronic obstructive lung disease and angina pectoris. European journal of clinical pharmacology. 1986;31(2):143-7.
24. Neuss H, Conrad A, Mitrovic V, Schlepper M. Electrophysiologic effects of an acute beta-blockade induced by bisoprolol in patients with supraventricular tachycardia as assessed by His-bundle electrograms. Journal of cardiovascular pharmacology. 1986;8 Suppl 11:S167-70.
25. Sugimoto T, Hayakawa H, Osada H, Yamazaki N, Mori H, Yasuda H, et al. Clinical evaluation of bisoprolol in the treatment of extrasystoles and sinus tachycardia: an interim report. Journal of cardiovascular pharmacology. 1986;8 Suppl 11:S171-4.
26. Kramer B, Balser J, Stubbig K, Kramer G, Kubler W. Comparison of bisoprolol with other beta-adrenoceptor blocking drugs. Journal of cardiovascular pharmacology. 1986;8 Suppl 11:S46-57.
27. Leopold G. Balanced pharmacokinetics and metabolism of bisoprolol. Journal of cardiovascular pharmacology. 1986;8 Suppl 11:S16-20.
28. Harting J, Becker KH, Bergmann R, Bourgois R, Enenkel HJ, Fuchs A, et al. Pharmacodynamic profile of the selective beta 1-adrenoceptor antagonist bisoprolol. Arzneimittel-Forschung. 1986;36(2):200-8.
29. Wellstein A, Palm D, Belz GG. Affinity and selectivity of beta-adrenoceptor antagonists in vitro. Journal of cardiovascular pharmacology. 1986;8 Suppl 11:S36-40.

30. Schliep HJ, Harting J. Beta 1-selectivity of bisoprolol, a new beta-adrenoceptor antagonist, in anesthetized dogs and guinea pigs. Journal of cardiovascular pharmacology. 1984;6(6):1156-60.
31. Klockow M, Greiner HE, Haase A, Schmitges CJ, Seyfried C. Studies on the receptor profile of bisoprolol. Arzneimittel-Forschung. 1986;36(2):197-200.
32. Czuriga I, Riecansky I, Bodnar J, Fulop T, Kruzsicz V, Kristof E, et al. Comparison of the new cardioselective beta-blocker nebivolol with bisoprolol in hypertension: the Nebivolol, Bisoprolol Multicenter Study (NEBIS). Cardiovascular drugs and therapy. 2003;17(3):257-63.
33. Buhring KU, Sailer H, Faro HP, Leopold G, Pabst J, Garbe A. Pharmacokinetics and metabolism of bisoprolol-14C in three animal species and in humans. Journal of cardiovascular pharmacology. 1986;8 Suppl 11:S21-8.
34. Morales DR, Lipworth BJ, Donnan PT, Jackson C, Guthrie B. Respiratory effect of beta-blockers in people with asthma and cardiovascular disease: population-based nested case control study. BMC medicine. 2017;15(1):18.
35. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. Circulation. 1994;90(4):1765-73.
36. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.
37. Priori SG, Blomstrom-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). European heart journal. 2015;36(41):2793-867.
38. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.
39. Marazzi G, Iellamo F, Volterrani M, Caminiti G, Madonna M, Arisi G, et al. Comparison of effectiveness of carvedilol versus bisoprolol for prevention of postdischarge atrial fibrillation after coronary artery bypass grafting in patients with heart failure. The American journal of cardiology. 2011;107(2):215-9.
40. Sleilaty G, Madi-Jebara S, Yazigi A, Haddad F, Hayeck G, El Rassi I, et al. Postoperative oral amiodarone versus oral bisoprolol as prophylaxis against atrial fibrillation after coronary artery bypass graft surgery: a prospective randomized trial. International journal of cardiology. 2009;137(2):116-22.
41. Behmanesh S, Tossios P, Homedan H, Hekmat K, Hellmich M, Muller-Ehmsen J, et al. Effect of prophylactic bisoprolol plus magnesium on the incidence of atrial fibrillation after coronary bypass surgery: results of a randomized controlled trial. Current medical research and opinion. 2006;22(8):1443-50.
42. Sezai A, Nakai T, Hata M, Yoshitake I, Shiono M, Kunimoto S, et al. Feasibility of landiolol and bisoprolol for prevention of atrial fibrillation after coronary artery bypass grafting: a pilot study. The Journal of thoracic and cardiovascular surgery. 2012;144(5):1241-8.
43. Okamura H, Arakawa M, Miyagawa A, Adachi H. Incidence of postoperative atrial fibrillation in transdermal beta-blocker patch users is lower than that in oral beta-blocker users after cardiac and/or thoracic aortic surgery. General thoracic and cardiovascular surgery. 2019;67(12):1007-13.
44. Yasui T, Oka T, Shioyama W, Oboshi M, Fujita M. Bisoprolol transdermal patch treatment for patients with atrial fibrillation after noncardiac surgery: A single-center retrospective study of 61 patients. SAGE open medicine. 2020;8:2050312120907817.
45. Blessberger H, Kammler J, Domanovits H, Schlager O, Wildner B, Azar D, et al. Perioperative beta-blockers for preventing surgery-related mortality and morbidity. The Cochrane database of systematic reviews. 2018;3:CD004476.
46. Plewan A, Lehmann G, Ndrepepa G, Schreieck J, Alt EU, Schomig A, et al. Maintenance of sinus rhythm after electrical cardioversion of persistent atrial fibrillation; sotalol vs bisoprolol. European heart journal. 2001;22(16):1504-10.

47. Katritsis DG, Panagiotakos DB, Karvouni E, Giazitzoglou E, Korovesis S, Paxinos G, et al. Comparison of effectiveness of carvedilol versus bisoprolol for maintenance of sinus rhythm after cardioversion of persistent atrial fibrillation. The American journal of cardiology. 2003;92(9):1116-9.
48. Konishi M, Haraguchi G, Kimura S, Inagaki H, Kawabata M, Hachiya H, et al. Comparative effects of carvedilol vs bisoprolol for severe congestive heart failure. Circulation journal : official journal of the Japanese Circulation Society. 2010;74(6):1127-34.
49. Negreva MN, Penev AP. Effect of selective beta-blockade with bisoprolol in the treatment of recent-onset atrial fibrillation. Folia medica. 2012;54(2):27-31.
50. Lechat PP. Beta-blocker efficacy according to heart rate and rhythm in patients with heart failure. Commentary on the Cardiac Insufficiency Bisoprolol Study II analysis. Cardiac electrophysiology review. 2003;7(3):233-5.
51. Yamashita T, Inoue H. Heart rate-reducing effects of bisoprolol in Japanese patients with chronic atrial fibrillation: results of the MAIN-AF study. Journal of cardiology. 2013;62(1):50-7.
52. Stankovic I, Neskovic AN, Putnikovic B, Apostolovic S, Lainscak M, Edelmann F, et al. Sinus rhythm versus atrial fibrillation in elderly patients with chronic heart failure--insight from the Cardiac Insufficiency Bisoprolol Study in Elderly. International journal of cardiology. 2012;161(3):160-5.
53. Yamashita T, Ikeda T, Akita Y. Comparison of heart rate reduction effect and safety between bisoprolol transdermal patch and bisoprolol fumarate oral formulation in Japanese patients with persistent/permanent atrial fibrillation (BISONO-AF study). Journal of cardiology. 2019;73(5):386-93.
54. Nakamura K, Inokuchi R, Hiruma T, Tokunaga K, Doi K, Nakajima S. Switching therapy from intravenous beta blocker to bisoprolol transdermal patch for atrial fibrillation tachycardia. Journal of anesthesia. 2016;30(5):891-4.
55. Ishiguro H, Ikeda T, Abe A, Tsukada T, Mera H, Nakamura K, et al. Antiarrhythmic effect of bisoprolol, a highly selective beta1-blocker, in patients with paroxysmal atrial fibrillation. International heart journal. 2008;49(3):281-93.
56. Nasr IA, Bouzamondo A, Hulot JS, Dubourg O, Le Heuzey JY, Lechat P. Prevention of atrial fibrillation onset by beta-blocker treatment in heart failure: a meta-analysis. European heart journal. 2007;28(4):457-62.
57. Andrade JG, Wazni OM, Kuniss M, Hawkins NM, Deyell MW, Chierchia GB, et al. Cryoballoon Ablation as Initial Treatment for Atrial Fibrillation: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2021;78(9):914-30.
58. Wazni OM, Dandamudi G, Sood N, Hoyt R, Tyler J, Durrani S, et al. Cryoballoon Ablation as Initial Therapy for Atrial Fibrillation. The New England journal of medicine. 2021;384(4):316-24.
59. Marrouche NF, Brachmann J, Committee C-AS. Catheter ablation versus standard conventional treatment in patients with left ventricular dysfunction and atrial fibrillation (CASTLE-AF) - study design. Pacing and clinical electrophysiology : PACE. 2009;32(8):987-94.
60. Packer DL, Piccini JP, Monahan KH, Al-Khalidi HR, Silverstein AP, Noseworthy PA, et al. Ablation Versus Drug Therapy for Atrial Fibrillation in Heart Failure: Results From the CABANA Trial. Circulation. 2021;143(14):1377-90.
61. Kuck KH, Merkely B, Zahn R, Arentz T, Seidl K, Schluter M, et al. Catheter Ablation Versus Best Medical Therapy in Patients With Persistent Atrial Fibrillation and Congestive Heart Failure: The Randomized AMICA Trial. Circulation Arrhythmia and electrophysiology. 2019;12(12):e007731.
62. Virk SA, Bennett RG, Chow C, Sanders P, Kalman JM, Thomas S, et al. Catheter Ablation Versus Medical Therapy for Atrial Fibrillation in Patients With Heart Failure: A Meta-Analysis of Randomised Controlled Trials. Heart, lung & circulation. 2019;28(5):707-18.
63. Chen C, Zhou X, Zhu M, Chen S, Chen J, Cai H, et al. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing. 2018;52(1):9-18.
64. Katritsis DG, Zografos T, Katritsis GD, Giazitzoglou E, Vachliotis V, Paxinos G, et al. Catheter ablation vs. antiarrhythmic drug therapy in patients with symptomatic atrioventricular nodal re-entrant tachycardia: a randomized, controlled trial. Europace : European pacing, arrhythmias, and

cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2017;19(4):602-6.
65. Elgendy AY, Mahmoud AN, Khan MS, Sheikh MR, Mojadidi MK, Omer M, et al. Meta-Analysis Comparing Catheter-Guided Ablation Versus Conventional Medical Therapy for Patients With Atrial Fibrillation and Heart Failure With Reduced Ejection Fraction. The American journal of cardiology. 2018;122(5):806-13.
66. Muhammad ZK, Safi UK, Adeel A, Muhammad SZ, Muhammad UK, Muhammad SK, et al. Meta-Analysis of Catheter Ablation versus Medical Therapy in Patients with Atrial Fibrillation Without Heart Failure. Journal of atrial fibrillation. 2020;12(6):2266.
67. Leizorovicz A, Lechat P, Cucherat M, Bugnard F. Bisoprolol for the treatment of chronic heart failure: a meta-analysis on individual data of two placebo-controlled studies--CIBIS and CIBIS II. Cardiac Insufficiency Bisoprolol Study. American heart journal. 2002;143(2):301-7.
68. Maclean E, Zheng S, Nabeebaccus A, O'Gallagher K, Stewart A, Webb I. Effect of early bisoprolol administration on ventricular arrhythmia and cardiac death in patients with non-ST elevation myocardial infarction. Heart Asia. 2015;7(2):46-51.
69. Kobayashi Y, Miyata A, Chiyoda K, Nakagawa H, Jinbo Y, Tanno K, et al. Dipyridamole suppresses catecholamine- and Ca++ influx-sensitive ventricular arrhythmias. Japanese circulation journal. 1996;60(9):629-40.
70. Shinohara M, Fujino T, Koike H, Kitahara K, Kinoshita T, Yuzawa H, et al. Assessment of a novel transdermal selective beta1-blocker, the bisoprolol patch, for treating frequent premature ventricular contractions in patients without structural heart disease. Journal of cardiology. 2017;70(3):212-9.
71. Fazio G, Vernuccio F, Lo Re G, Grutta G, Mongiovi M. Role of bisoprolol in patients with long QT syndrome. Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc. 2013;18(5):467-70.
72. Steinberg C, Padfield GJ, Al-Sabeq B, Adler A, Yeung-Lai-Wah JA, Kerr CR, et al. Experience with bisoprolol in long-QT1 and long-QT2 syndrome. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing. 2016;47(2):163-70.
73. Medigue C, Girard A, Laude D, Monti A, Wargon M, Elghozi JL. Relationship between pulse interval and respiratory sinus arrhythmia: a time- and frequency-domain analysis of the effects of atropine. Pflugers Archiv : European journal of physiology. 2001;441(5):650-5.
74. Lechat P, Hulot JS, Escolano S, Mallet A, Leizorovicz A, Werhlen-Grandjean M, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. Circulation. 2001;103(10):1428-33.
75. Verrostte JM, van Hemel NM, Kingma JH. Interaction of bisoprolol and procainamide in human cardiac impulse generation and conduction. Journal of cardiovascular pharmacology. 1990;16 Suppl 5:S193-5.

Figure 1

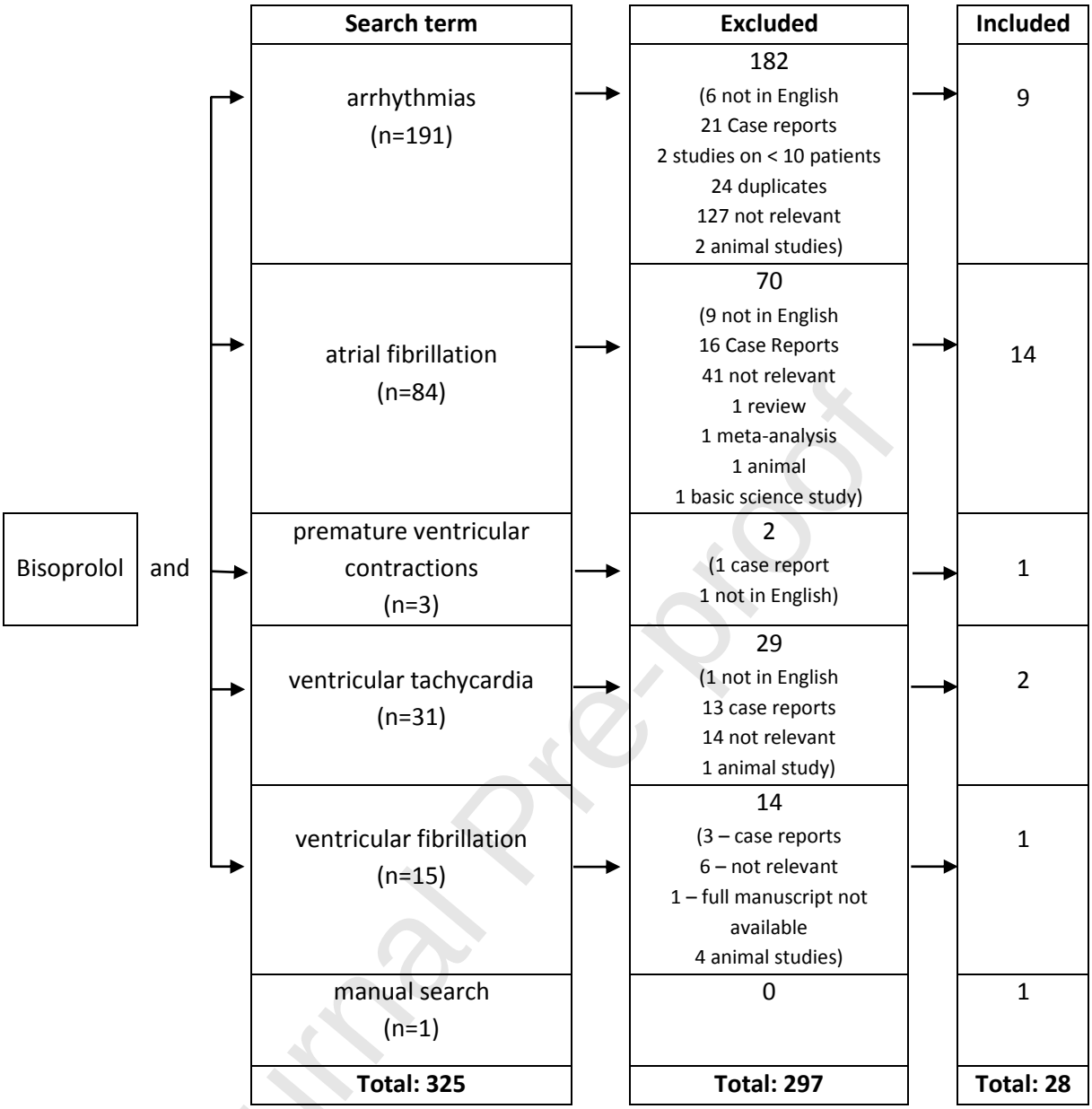

Table 1

Reference	Type of study	Drug / intervention compared to	Patients (number)	Type of arrhythmia	Dose of Bisoprolol	Findings	Conclusion on efficacy (positive / negative / mixed)	Quality of evidence
Neuss H et al [24], 1986	Open label cohort	-	n=10	Paroxysmal SVT (of which 6 AVRT 2 AT 1 PAF)	10 mg iv	In 5 of 6 patients with accessory AV-pathways, circus movement tachycardia could be elicited prior to as well as after bisoprolol administration. In 1 of 2 patients with ectopic atrial tachycardia, bisoprolol prevented the induction of paroxysms. In one patient with paroxysmal atrial fibrillation, the ventricular response decreased from 128/min to 94/min.	Mixed	Low
Sugimoto T et al [25], 1986	Open label cohort	-	n=32 (of 15 with SVT and 17 with PVC)	8 patients with PAC 7 patients with SVT	2.5 mg/day	The PAC frequency was decreased in 50% of the patients, and sinus tachycardia was improved in all 7 patients. Adverse reactions were observed in 8 of 32 patients.	Positive	Low
Wargon M et al [73], 2001	Double-blind, placebo-controlled, cross-over	placebo	n=15 (healthy subjects)	Respiratory Sinus Arrhythmia	10 mg	Bisoprolol administration resulted in a significant reduction in HR reaching 60.3 +/- 1.4 bpm at a tidal volume of 500 mL (compared to 70.5 +/- 1.8 bpm with placebo, $p < 0.001$). Similar changes were observed at a tidal volume of 700 mL.	Positive	Low
Katritsis DG et al [64]*, 2017	Randomized clinical trial	catheter ablation	n=61	AVNRT	5 mg/day	Bisoprolol is less effective than catheter ablation in patients with symptomatic AVNRT (log-rank test, $p < 0.001$). 68% of patients could not tolerate either bisoprolol or diltiazem.	Negative	High
Plewan A et al [46], 2001	Open label randomized controlled trial	Sotalol	n=128	Atrial Fibrillation (recurrence post electrical cardioversion)	5 mg / day	After a follow-up of 12 months, 58% of patients on bisoprolol were still in sinus rhythm. This study demonstrates that sotalol (160 mg / day) and bisoprolol (5 mg / day) are equally effective in maintaining sinus rhythm. Symptomatic bradycardias occurred in two patients on sotalol and three on bisoprolol.	Positive	Moderate
Lechat P et al (the CIBIS II Investigato	Retrospective analysis of the CIBIS II study	Placebo	n=2184 (of which 1271 received	Atrial Fibrillation (plus a second group in SR)	1.25 to 10 mg	Two months after inclusion, heart rate decrease (baseline to 2 months) was 0.2 ± 13.7 bpm (placebo) and 9.8 ± 14.7 bpm (bisoprolol), $p<0.0001$. However, a benefit of bisoprolol on survival was obtained only in patients with sinus rhythm and was questionable in patients with atrial fibrillation.	Positive	High

rs) [74], 2001			Bisoprolol)					
Katritsis D et al [47], 2003	Open label cohort	Carvedilol	n=90	Atrial Fibrillation	5 – 10 mg / day	Bisoprolol is not superior to carvedilol in preventing AF recurrence: 23 patients (46%) in the bisoprolol group and 17 patients (32%) in the carvedilol group relapsed into AF during the 1 year of total follow-up (p = 0.486).	Negative	Moderate
Ishiguro H et al [55], 2008	Open label cohort	-	n=136	Paroxysmal Atrial Fibrillation	2.5 – 5 mg/day	On bisoprolol, 109 patients (80%) experienced subjective symptom improvement, 103 patients (76%) experienced QOL improvement, and elimination of P-AF episodes on ECGs was observed in 84 patients (62%), a higher percentage in the diurnal P-AF group than in the diurnal & nocturnal P-AF group (p =0.042). Five patients (3.7%) discontinued bisoprolol due to side effects.		
Konishi M et al [48], 2010	Open label cohort	Carvedilol	n=217 (of which 107 received Bisoprolol)	Atrial Fibrillation	SR:2.22± 0.67 mg to 3.37±1.41 mg / day AF:2.29± 0.81 mg / day to 2.76± 1.26 mg / day	More patients with AF in the bisoprolol group converted to sinus rhythm than those in the carvedilol group (48% vs 16%; P=0.03) and maintained sinus rhythm on 24h Holter ECG after a follow-up period of 18 months.	Positive	Moderate
Negreva MN et al [49], 2012	Open label cohort	Propafenone + Bisoprolol vs Propafenone	n=164	Atrial Fibrillation (of recent onset < 48h)	5 or 10 mg od	Treatment with iv propafenone + oral bisoprolol restored sinus rhythm in a greater number of patients in comparison with propafenone monotherapy (at the 6th hour 67.07% versus 48.78%, p < 0.05; at the 12th hour it was 87.80% versus 75.60%, respectively, P < 0.05). However, 24 hours after the initiation of pharmacological cardioversion, the percentage of patients in sinus rhythm was the same in both groups (82%).	Positive	Low
Stankovic I et al [52], 2012	multicenter, double-blind trial (predefined analysis of the CIBIS-ELD trial)	Carvedilol	n=876	Atrial Fibrillation or Sinus Rhythm	up to 10 mg / day	Patients with higher baseline heart rates had larger reductions in heart rate, regardless of rhythm. This study comparing carvedilol and bisoprolol in patients with chronic HF complicated by AF did not demonstrate drug-related differences in achieving beneficial clinical effects of the beta-blocker titration.	Positive	High
Yamashita T (the MAIN-AF study	Double blind cohort	-	n=78	Atrial Fibrillation (Persistent or Permanent)	2.5 mg (open label, all patients) and 5 mg (24 patients,	After 2 weeks of bisoprolol 2.5 mg/day, mean HR was significantly lower than that before treatment (12.2±9.1 beats/min, p < 0.001). Mean HRs in the 5-mg and 2.5-mg continuation groups were also significantly decreased compared with those before treatment (17.3 ± 12.9 and 11.4 ± 7.4	Positive	Moderate

) [51], 2013					double blind)	beats/min, respectively, both p < 0.001), with a significant between-group difference (p = 0.033).		
Nakamura K et al [54], 2016	Open label retrospective cohort	Landiolol	n=16	Atrial Fibrillation	4 mg	Compared to landiolol 3 µg/kg/min, the introduction of the bisoprolol patch did not induce any significant changes in heart rate. There were no adverse events.	Positive	Moderate
Yamashita T et al [53], 2019	Multicenter double-blind comparative study	transdermal vs oral administration	n=220	Atrial Fibrillation (persistent / permanent)	oral: 2.5 and 5 mg patch: 4 mg and 8 mg	In Japanese patients with persistent or permanent AF, transdermal 4 mg and 8 mg had heart rate reducing effects similar to those of oral bisoprolol 2.5 mg and 5 mg, respectively.	Positive	Moderate
Behmanesh S et al [41], 2006	Open label prospective cohort	usual care	n=100 (of which 50 received bisoprolol + Magnesium)	Atrial Fibrillation (prophylaxis after CABG)	5 mg / day	The combination of bisoprolol plus Mg effectively reduces the incidence of postoperative AF following on-pump CABG, particularly in elderly patients, and is associated with a shorter hospital length of stay. In the prophylaxis group, the incidence of postoperative AF was significantly lower, with 20% (10 / 50) compared to 42% (21 / 50) among controls (p = 0.030, 95% CI for absolute risk reduction = 2-42%).	Positive	Moderate
Sleilaty G et al [40], 2009	Open label cohort	Amiodarone	n=200 (of which 102 received Bisoprolol)	Atrial Fibrillation (prophylaxis after CABG)	2.5 mg bid	Postoperative oral bisoprolol and amiodarone are equally effective for prophylaxis of AF after CABG (prevalence of AF of 12.7% vs 15.3%, p=0.60). Treatment with bisoprolol resulted in a trend to lower ventricular response rate in AF cases (125±6 beats/min vs 144±7 beats/min, p=.06). Both regimens are well tolerated. There was no difference between the 2 groups for the onset time of AF episodes, total AF duration, AF recurrence and postoperative length of hospital stay. Two reversible low cardiac output cases occurred with bisoprolol.	Positive	Moderate
Marazzi G et al [39], 2011	Open label prospective cohort	Carvedilol	n=320 (of which 160 received du Bisoprolol)	Atrial Fibrillation (prophylaxis after CABG)	2.5 ± 0.2 mg	Bisoprolol is more effective than carvedilol in decreasing the incidence of post-discharge AF after CABG in patients with decreased left ventricular function. During follow-up, 23 patients (14.6%) in the bisoprolol group and 37 patients (23%) in the carvedilol group developed AF (relative risk 0.6, confidence interval 0.4 to 0.9, p < 0.032). After 4 weeks of treatment, patients in the bisoprolol group showed a significantly greater decrease in heart rate, being in sinus rhythm or AF (-15.6 ± 3 vs -9.4 ± 3 beats/min, p < 0.021).	Positive	Moderate
Sezai A et al [42], 2012	Open label cohort	vs no therapy vs Landiolol	n=105 (of which 33 received Bisoprolol)	Atrial Fibrillation (prophylaxis after CABG)	2.5 mg / day	Oral bisoprolol in combination with iv Landiolol is superior to iv landiolol and to no beta blocker therapy in the prevention of post CABG AF. Postoperative AF occurred in 14.5% of group landiolol, 9.1% of group landiolol + bisoprolol, and 35.3% of group without beta blockers.	Positive	Moderate

Okamura H et al [43], 2019	Retrospective cohort	transdermal vs oral administration	n=108	Atrial Fibrillation (Post-operative)	2.5 mg oral vs 4 mg transdermal	AF occurred in 24% of patients in the transdermal and in 46% of patients in the oral bisoprolol groups (p = 0.027). The use of transdermal bisoprolol was independently associated with a lower rate of AF (OR 0.21, 95% CI 0.05-0.84, p = 0.027). The incidence of post-operative AF in this group was lower than that in users of oral bisoprolol.	Positive	Moderate
Yasui T et al [44], 2020	Open label retrospective cohort	-	n=61	Atrial Fibrillation (post non-cardiac surgery)	not mentioned	Sinus rhythm was restored within 24 h in 47 patients (77.0%). The heart rate significantly decreased from 124.8 ± 26.3 bpm at the baseline to 78.9 ± 16.6 bpm at 24 h after treatment (p < 0.001). The bisoprolol transdermal patch was discontinued due to bradycardia in two patients (3.3%).	Positive	Moderate

Table 2

Reference	Type of study	Patients (number)	Type of arrhythmia	Dose of Bisoprolol	Findings	Positive / Negative results	Quality of evidence
Sugimoto T et al [25], 1986	Open label prospective	n=37 (of which 17 received Bisoprolol)	PVC	2.5 mg/day	More than 50% reduction of the PVC frequency was observed in 7 out of 16 patients on bisoprolol. The number of PVC was reduced in 2 out of 5 patients at a daily dose of 2.5 mg. Adverse reactions were observed in 8 of 32 patients.	Positive	Low
Kobayashi Y et al [69], 1996	Open label prospective	n=12	PVC	5 mg/day	Bisoprolol effectively inhibited PVC in 5 of 12 dipyridamole-respondent patients (reduction of 88 ± 16% of PVC) and in 3 of 6 dipyridamole-non-respondent patients.	Positive	Low
Shinohara M et al [70], 2017	Open label prospective	n=44	PVC (in patients without structural heart disease)	4 mg transdermal patch	The bisoprolol patch reduced the PVC count significantly in the positive HR-PVC group (P-PVC), while the PVC count did not change significantly in the non-positive HR-PVC group. In the P-PVC group, the patients with mean HRs > 80 bpm had a significantly higher percent improvement in the PVC count than those with mean HRs <80 bpm (p = 0.0080).	Positive	Moderate
Verrostte JM [75], 1990	Open label prospective	n=10	VA (post MI)	5 mg of oral bisoprolol daily + 10mg/kg of procainamide iv	Ventricular effective refractory periods were increased significantly after several days of oral bisoprolol treatment. Combined use of bisoprolol and a class I antiarrhythmic drug appears to be safe in patients with ventricular tachyarrhythmias late after MI.	Positive	Low
CIBIS Investigators [35], 1994	Prospective, double blind, placebo-controlled	n=641	VT / VF (in HF patients)	1.25 mg – 5 mg	No significant difference was observed in death related to documented ventricular tachycardia or fibrillation (7 on placebo, 4 on bisoprolol).	Negative	High
CIBIS-II Investigators [36], 1999	Prospective, double blind, placebo-controlled	n = 2647 (of which 1327 received Bisoprolol)	VT / VF (in HF patients)	1.25 mg – 10 mg	Hospital admissions were significantly fewer in the bisoprolol group than in the placebo group for ventricular tachycardia and ventricular fibrillation (six *vs* 20, p=0·006). This finding supports the drug's potential antiarrhythmic effect.	Positive	High
Maclean E et al [68], 2015	Retrospective cohort	n=399	VA (monomorphic/ polymorphic VT ± HD compromise, or VF) in patients	1.25 – 2.5 mg/kg	After adjusting for the confounders of pulse, blood pressure, smoking and creatinine, logistic regression analysis identified early bisoprolol administration as protective for VA (p=0.038, OR 0.114, CI 0.015 to 0.885) and MACE (p=0.011, OR 0.064, CI 0.008 to 0.527). There was one episode of symptomatic bradycardia in the late group.	Positive	Moderate

			with NSTEMI				
Fazio G et al [71], 2013	Open label prospective cohort	n=34	LQTS	0.1 – 0.2 mg/kg	Of the 12 minor cardiovascular events 3 occurred in absence of treatment, 7 during treatment with nadolol or propranolol, and 2 during treatment with bisoprolol. Bisoprolol proved to be less harmful and easier to manage than propranolol and nadolol in patients with LQTS, with the same effectiveness in preventing major cardiovascular events after a follow-up period of 3 x 31 months (31 months without treatment, 31 months on nadolol or propranolol and 31 months on bisoprolol).	Positive	Moderate
Steinberg C et al [72], 2016	Retrospective cohort	n=114 (of which 59 treated with Bisoprolol)	LQTS type 1 and type 2	5 ± 1.8 mg	QTc shortening was observed in individuals on bisoprolol (ΔQTc -5 ± 31 ms; p = 0.049). The antiadrenergic effect of bisoprolol correlated with the reduction of peak HR at exercise testing. However, the equivalence of bisoprolol for protection from ventricular arrhythmia in LQT patients compared to established beta-blockers remains unknown. Bisoprolol is well tolerated during long-term administration (1 cardiac event = 1.7% during a 3-year follow-up).	Positive	Moderate