Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i1.3785

TREATMENT AND PREVENTION OF ANGINA PECTORIS, MYOCARDIAL INFARCTION, ARRHYTHMIAS, AND OTHER CONDITIONS WITH BETA-BLOCKERS

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ABSTRACT:

Beta-blockers are used to treat several illnesses, including arrhythmias, myocardial infarction, angina pectoris, and others, as well as to avoid these conditions. Patients who are diagnosed with ischemic heart disease usually report experiencing angina pectoris, which is a form of the condition that is fundamentally significant. The modified Delphi method was utilized in order to assess the level of consensus among specialists about the therapeutic appropriateness of utilizing beta-blockers for the treatment of angina pectoris, myocardial infarction, and cardiac arrhythmias in a variety of clinical practice settings. A first panel of fifteen claims was offered by the CE, which was based on the data that was found in the literature as well as his personal clinical experience. The CS then put these assertions to a vote. Because of their efficacy in preventing and treating recurrent angina and ischemic episodes, as well as the arrhythmias that accompany them, beta-blockers are a staple of pharmacological therapy for persons who suffer from ischemic heart disease.

Keywords: Angina pectoris, beta-blockers, ischemic, cardiovascular and heart disease.

INTRODUCTION:

Angina pectoris, which typically results from myocardial ischemia due to an imbalance between oxygen demand and blood supply, is a fundamentally important symptom in patients with ischemic heart disease. The clinical characteristics of angina are used to categorize it as stable, unstable, typical or atypical, while its staging depends on how severe the symptoms are after exertion (Figure 1). (Table 1) A vital component of treating people with ischemic heart disease is preventing and potentially treating this symptom with anti-ischaemic medications. Beta-blockers are a good treatment option in this clinical circumstance since they can lower the myocardial oxygen demand (Satyanarayana et al., 2019).

The modification of heart rhythm in response to physiological and pathological stress events depends critically on sympathetic activity. Due to these factors, beta-blockers have undergone significant research and are frequently prescribed to myocardial infarction patients. They have also shown promise in reducing cardiac remodelling and preventing ventricular arrhythmias. Even in patients receiving coronary angioplasty treatment, the early use of beta-blockers in acute myocardial infarction has been linked to reduced myocardial damage and improved clinical outcomes (Diaconu et al., 2019).

	Typical		Atypical		Not angina	
Age	Males	Females	Males	Females	Males	Females
30-39	3%	5%	4%	3%	1%	1%
40-49	22%	10%	10%	6%	3%	2%
50-59	32%	13%	17%	6%	11%	3%
60-69	44%	16%	26%	11%	22%	6%
70+	52%	27%	34%	19%	24%	10%

Figure 1 shows the pre-test probability of coronary artery disease in symptomatic patients. Stratified by age, gender, and type of symptom.

Table 1: Angina pectoris classifications.

Clinical features	**Unstable**		**Stable**
	1. Appears at rest and lasts > 20 minutes 2. New onset and moderate to severe 3. Progressive increase in severity and duration		These criteria are not present.
	Typical	**Atypical**	**Non-anginal chest pain**

	1. Tightening chest pain or in the neck, jaw, arm and 2. Worsened by physical exertion. 3. Improvement in 5 minutes with rest or nitrates	Only two features are present.	Only one feature is present.	
Degree of physical effort	**I**	**II**	**III**	**IV**
	It appears only after intense physical effort.	Appears after moderate physical effort	Appears after a slight physical effort	Also present at rest.

Statement	**Percentage of Consent 1° round**	***Statement***	**Percentage of Consent 2° round**
1. In chronic coronary syndrome, i β-blockers are drugs of first choice in the control of angina pectoris or equivalent symptoms	 100%	In cases of chronic coronary syndrome, βblockers are the primary medications recommended for managing angina pectoris or similar symptoms.	 87%
2. β-Blockers are a pillar in the treatment of acute coronary syndrome (STEMI or NSTEMI) due to their function of inhibition of the sympathetic system, which is also decisive for reducing myocardial ischemia, especially in the case of residual coronary artery disease	 88%	β-Blockers play a fundamental role in managing acute coronary syndrome (STEMI or NSTEMI) because they inhibit the sympathetic system. This inhibition is crucial for minimizing myocardial ischemia, particularly when there is underlying coronary artery disease.	 79%

		no evidence to show that the effectiveness of ß blockers in terms of reducing mortality remains after two years of treatment.	
3. In patients with electively treated coronary artery disease, in the absence of congestive heart failure, and with preserved ejection fraction, a persistence of efficacy in terms of mortality after two years of treatment with βblockers has not been demonstrated.	 88%	Among patients who have chosen elective treatment for coronary artery disease, don't have congestive heart failure, and have a preserved ejection fraction, there's	 78%

Due to their capacity to control the structural and functional changes brought on by cardiac injury, beta-blockers are also regarded as effective antiarrhythmics. They may be employed in specific therapeutic situations. These medications are currently given to about 80% of patients who suffer from these illnesses. This document's primary goal is to provide clinicians with clinical practice guidelines from a panel of experts who can help them manage patients who have angina pectoris, myocardial infarction, and cardiac arrhythmias (Mancia et al., 2022).

This pharmacological class has been shown to improve the Rate of clinical events and serve as a crucial pillar in the management of patients with these pathologies. According to a wealth of scientific evidence published in the literature, most of which comes from randomized controlled trials (Yarmukhamedova, Alisherovna, Tashtemirovna, & Nizamitdinovich, 2023).

METHODOLOGY:

The level of agreement among experts on the therapeutic appropriateness of using beta-blockers to treat angina pectoris, myocardial infarction, and cardiac arrhythmias in various clinical practice contexts was evaluated using the modified Delphi technique. Editorial Committee (CE) and Scientific Committee (SC) Boards of Experts have been established to ensure the indications' reliability. Based on the existing scientific data, the authors of this publication and the CE's five members produced several statements, which the SC's nine members then reviewed. The latter submitted suggestions for integration or modification where it was deemed acceptable (Martinez-Milla, Raposeiras-Roubin, PascualFigal, & Ibanez, 2019).

The CS anonymously conducted two rounds of voting. The SC also decided on any suggested alterations/integrations about a particular statement, once more in an anonymous fashion. A predetermined % consensus level of 75% was agreed upon among the CS members as the threshold for each statement's ratification. The CE had the final say on whether or not to approve the accounts as defined. The Designated Methodologist supported the CS and CE's cooperation and adherence to the Delphi process (Chakraborty, 2023; Habib, Alam, Mustafa, & Verma).

RESULTS:

The CE offered a first panel of 15 statements, which was put to a vote by the CS based on the information in the literature and his own clinical experience. Without any requested adjustment or integration, all statements suggested by the CE were adopted by the CS in the first round with a consensus rate > 75%. During the first round, the SC advanced the anonymous submission of three new statements, which after the voting in the second round received a

percentage of consensus greater than 75%. As a result, 18 assertions in total were authorized (Table 2) (Sabah et al., 2023).

Table 2 shows the outcomes of the two iterations of the modified Delphi approach.

Statement	Percentage of Consent 1° round	*Statement*	Percentage of Consent 2° round
4. The type of beta-blocker used as an antiarrhythmic is determined by its tolerance and effectiveness in individuals with heart failure. Propranolol and nadolol are the most effective -blockers as antiarrhythmics, used to treat catecholaminergic polymorphic VT, but they are not genuinely recommended in the case of heart failure. Metoprolol* appears to have a more antiarrhythmic solid action than atenolol, carvedilol, bisoprolol, and nebivolol. However, there is a shortage of information in this area.	88%		
5. Due to its unfavourable inotropic action and proarrhythmic impact, it should not be used as an antiarrhythmic in patients with reduced or partially reduced ejection fraction. These patients frequently have extended QTc and electrolyte abnormalities that might lead to ventricular arrhythmias. Sotalol may make these conditions worse and may even favour polymorphic VT.	88%		
6. The target heart rate for patients with acute myocardial ischemia and sinus rhythm is 70 bpm.	 77%		
7. Metoprolol* is well tolerated even during titration in patients with recent myocardial ischemia due to its short half-life, twofold dose, and quick beginning of action.	 88%		
8. Combining or substituting ivabradine may be necessary for individuals with chronic coronary syndrome, left ventricular dysfunction, and sinus rhythm who cannot tolerate beta-blocker titration.	 88%		

9. To control heart rate during exercise in patients with chronic ischemia illness, ivabradine and beta-blockers may be used.	 88%		
10. Treatment with beta-blockers is still recommended for elderly patients over 75 with chronic coronary syndrome, although it should be initiated and titrated cautiously due to comorbidities.	 88%		
		11. The presumptive result of erectile dysfunction in male patients is one of the potential causes of arbitrary termination or non-compliance with beta-blocker treatment.	 100%
		12. In patients with erectile dysfunction, vasodilator beta-blockers are preferred to nonvasodilators.	 100%

Table 2 shows the outcomes of the two iterations of the modified Delphi approach.

Statement	**Percentage of Consent 1° round**	***Statement***	**Percentage of Consent 2° round**
13. The use of beta-blockers with amiodarone in patients with congestive heart failure and ventricular arrhythmias is a possibility. There is no data on mortality reduction, although this link has been proven to synergize in lowering complicated ventricular arrhythmias (polymorphic and recurrent).	 88%		
		14. The combination of flecainide and metoprolol reduces atrial fibrillation	

15. Although the findings point to a potential benefit of their connection, there are few investigations on the relationship between beta-blockers and ranolazine.	 88%		
16. Selective therapy with beta-blockers may be employed in patients with COPD and ischemic heart disease.	 100%		
17. Highly selective beta-blockers are favoured in patients with ischemic heart disease and mild to moderate asthma, either with or without ivabradine.	 77%		
18. However, patients with ischemic heart disease, chronic peripheral artery disease, or noncritical peripheral ischemia should take beta-blockers as treatment.	 88%		
		symptomatic recurrences*.	100%

BASIC ELEMENTS:

Statement

1. Beta-blockers are the first line of treatment for angina pectoris or comparable symptoms in patients with chronic coronary syndrome.

2. Because beta-blockers inhibit the sympathetic nervous system, which is essential for minimizing myocardial ischemia, especially in cases with residual coronary artery disease, they are a cornerstone in treating acute coronary syndrome (STEMI or NSTEMI).

3. It has not been shown that beta-blockers continue to be effective in reducing mortality in patients with electively treated coronary artery disease who have retained ejection fraction, are not experiencing congestive heart failure, and have been taking them for two years.

4. The tolerability and efficacy of a beta-blocker in patients with heart failure influence the choice of beta-blocker type as an antiarrhythmic. Propranolol and nadolol, used to treat catecholaminergic polymorphic VT, are the most effective beta-blockers as antiarrhythmics, but they are not particularly recommended in cases of heart failure. Comparing metoprolol to atenolol, carvedilol, bisoprolol, and nebivolol, it appears that metoprolol* has a more pronounced antiarrhythmic action. However, there isn't much data available in this area.

5. Due to its unfavourable inotropic action and proarrhythmic impact, sotalol should not be used as an antiarrhythmic in patients with reduced or partially reduced ejection fraction. These patients frequently have extended QTc and electrolyte abnormalities that might lead to ventricular arrhythmias. Sotalol may make these conditions worse and may even favour polymorphic VT.

Beta-blockers are a mainstay of anti-ischaemic therapy in patients with chronic stable coronary artery disease, especially in those who have experienced a recent or previous myocardial infarction. Blockers reduce heart rate, afterload, and contractility as part of their antianginal function, ultimately decreasing myocardial oxygen demand. They also improve myocardial oxygenation support, diastolic filling, and coronary perfusion. Because of these pharmacological mechanisms, beta-blockers can reduce the frequency of angina attacks and raise the threshold for the start of the condition. For instance, in the TIBBS research, it was found that giving patients with stable chronic angina bisoprolol (10 mg/d) was more successful than providing them nifedipine (20 mg/d) at reducing the number and length of transient ischemic episodes (Baldaçara et al., 2022).

Similar to this, the IMAGE trial showed that metoprolol, 200 mg daily, was more effective than nifedipine, 20 mg twice daily, in enhancing physical effort tolerance in patients with stable angina (measured as the amount of exercise time needed to achieve 1 mm STsegment depression). Before systematic primary angioplasty, multiple randomized trials showed that beta-blockers effectively lowered both myocardial infarction patients' short-term and long-term mortality. This efficacy has been supported by more recent investigations in individuals who have had percutaneous revascularization (Sahai et al., 2022).

Metoprolol was shown to be particularly effective in ST-segment elevation myocardial infarction (STEMI) patients in reducing the extent of the ischemic area (25.6 15.3 g versus 32.0 22.2 g) and increasing left ventricular ejection fraction (+2.7%) without an increased risk of complications in the 24 hours after drug administration (composite event including death, malignant ventricle). In the therapy group, no patients passed away. A recent investigation on mice models of myocardial infarction similarly supported the effectiveness of metoprolol in lowering the size of the ischemic region. Regarding the length of -blocker therapy in this clinical situation, data from a recent meta-analysis showed how their use can lower the risk of subsequent heart attacks and angina in the short term (30 days after the acute event) in patients who have already received the most effective treatment currently available (including primary angioplasty) (Hiraoka et al., 2023).

However, long-term use of this pharmacological family requires careful consideration due to the elevated risk of heart failure, cardiogenic shock, and drug stoppage. The effectiveness on all-cause mortality would seem to remain significant during the first (Hazard Ratio 0.81; 95% confidence intervals, 0.72-0.91) and second (Hazard Ratio 0.86; 95% confidence intervals, 0.75 - 0.99) years after acute myocardial infarction and initiation of beta-blocker therapy, but not after the third year (Hazard Ratio 0.87; 95% confidence intervals, 0.73 - 1. Because of their antiarrhythmic qualities, beta-blockers may also be employed in specific therapeutic situations (Barton, McGowan, Smyth, Wright, & Gardner, 2020; Martinez-Milla et al., 2019).

In reality, -adrenergic activity also substantially impacts cardiac electrophysiology. It helps patients with structural abnormalities of the myocardium, such as dilatation, fibrosis, hypertrophy, or ischemia, develop potentially lethal arrhythmias. For this reason, depending on the kind of arrhythmia created, beta-blockers have been linked to reducing the proarrhythmic effect resulting from an altered adrenergic activity. Particularly in patients with myocardial infarction and heart failure, the addition of metoprolol to standard therapy has been linked to a decrease in malignant arrhythmias and sudden cardiac death. Similarly, nadolol was demonstrated to help lower the incidence and severity of ventricular arrhythmias in a small trial, including individuals with catecholaminergic polymorphic ventricular tachycardia (Gupta, Gupta, & Gupta, 2023).

The effectiveness of bisoprolol in lowering the risk of ventricular arrhythmias has also been shown in studies using pig models of myocardial infarction. Last but not least, sotalol is a medication that exhibits extraordinary antiarrhythmic properties that, in a sense, are comparable to those of class I antiarrhythmics. This medication has been proven to lessen ventricular ectopia and stop ventricular tachycardia and fibrillation from returning. On the other hand, Sotalol use should not be considered in patients with ischemic heart disease and left ventricular dysfunction because it has been linked to a higher risk of death, most likely from arrhythmic causes, compared to placebo (5% vs. 3%). Bradyarrhythmias and polymorphic ventricular tachycardias are the arrhythmias most frequently linked to the administration of sotalol (Watson, Bennett, Hamilton, Hill, & McNally, 2022).

DRUG TITRATION, THERAPEUTIC TARGET ACCOMPLISHMENT, AND ADHERENCE

Statement

6. The target goal of beta-blocker therapy in individuals with acute myocardial ischemia and sinus rhythm is 70 bpm.
7. Metoprolol* is well tolerated even during titration in patients with recent myocardial ischemia due to its short half-life, dual delivery, and quick commencement of action.
8. A combination or substitution with ivabradine may be warranted in patients with chronic coronary syndrome, left ventricular dysfunction, and sinus rhythm who do not tolerate -blocker titration adequately.
9. To reduce heart rate under stress in patients with chronic ischemia pathology, ivabradine and beta-blockers may be helpful.
10. Treatment with beta-blockers is always recommended for people older than 75 with chronic coronary syndrome, even though it should be introduced and titrated carefully due to comorbidities.
11. In male patients, the alleged effect of erectile dysfunction is one of the potential reasons for willful discontinuation or non-adherence to -blocker therapy.
12. In patients with erectile dysfunction, vasodilator beta-blockers are preferred to nonvasodilators.

Heart rate stands out as the most important clinical factor to be assessed during the titration of therapy with beta-blockers because it is directly linked to a higher prevalence and severity of angina, a higher prevalence of myocardial ischemia, and a worse state of health in patients with ischemic heart disease. The research on patient management of heart failure patients provides the majority of the available data regarding the therapeutic aim to be attained during the titration of therapy with beta-blockers. The limit of 70 beats per minute would appear to be the most helpful in this clinical circumstance regarding therapeutic efficacy (Heriansyah, Nur Chomsy, Febrianda, Farahiya Hadi, & Andri Wihastuti, 2020).

During beta-blocker medication, patients with heart rates 70 beats per minute seem to have a reduced risk of dying than those with heart rates > 70 beats per minute. Additionally, the reduction in mortality would appear to be directly proportional to heart rate rather than the total dose of -blocker delivered. Ivabradine addition may be a viable therapeutic option, particularly in patients with trouble achieving therapeutic heart rate objectives. In fact, in ischemic heart disease patients, the addition of this medication to the beta-blocker was found to be much more effective than the placebo in lowering heart rate at rest (-6.9 vs. -1.1 beats per minute) and during exercise (-8.9 vs. -0.1 beats per minute) (LAJOIE & DC).

Additionally, this therapeutic relationship helps extend the time spent exercising overall, delaying the start of angina and preventing the formation of 1 mm of ST-segment depression while exerting oneself. The individual characteristics of the patient (such as the presence of comorbidities) and the pharmacological characteristics of the molecule used (such as half-life, rapidity of action, number of daily doses required, and cardio-selectivity) should be taken into consideration during the selection and titration of beta-blockers as these factors could alter the efficacy of the therapy administered or reduce adherence to the proposed pharmacological treatment (Joshi, Tepper, Lucas, Rasmussen, & Nelson, 2021).

The patient's age must also be taken into account. Compared to younger individuals (between 42 and 87%), only 31% of senior patients were able to meet the treatment aim. Last but not least, the alleged impact of beta-blockers on erectile function may be another reason for decreased medication adherence. This clinical circumstance is prevalent in the general population, especially older individuals with cardiovascular problems, and can harm their quality of life. However, a recent meta-analysis showed that neither the use of vasodilating (Odds Ratio, 2.07; 95% confidence intervals, 0.6 - 7.1) nor non-vasodilating (Odds Ratio, 0.96; confidence intervals, 0.33 - 2.82) ß -blockers is linked to a higher risk of erectile dysfunction (Farmakis et al., 2022).

Nebivolol would appear to have the most negligible impact on the likelihood of developing erectile dysfunction, followed by the other vasodilating -blockers, notwithstanding the inherent limitations of the study design. Therefore, in patients who are complaining of erectile dysfunction, the usage of vasodilator ß -blockers should be taken into consideration (Viigimaa et al., 2020).

COMBINING ß-BLOCKERS WITH OTHER MEDICATIONS

Statement

13. Combining beta-blockers and amiodarone may be an option for patients with congestive heart failure and ventricular arrhythmias. No information is available about reducing mortality, although this link has been found to have a synergistic effect in removing complicated ventricular arrhythmias (polymorphic and recurrent).

14. The combination of flecainide and metoprolol decreases atrial fibrillation symptomatic recurrences*.

15. There aren't many studies on the relationship between beta-blockers and ranolazine, but the findings point to a potential benefit of that relationship.

In the management of patients with specific clinical circumstances, such as, for example, cases of complex ventricular arrhythmias or atrial fibrillation and persistence of angina despite established medical treatment, the combination of beta-blockers with other antiarrhythmic or antianginal medications may be helpful. Amiodarone is a notable example of an antiarrhythmic drug with complicated characteristics and potential antiadrenergic effects. The available data have shown that this connection effectively reduces death from arrhythmic causes in patients with ischemic heart disease (Relative Risk, 0.68; 95% confidence intervals, 0.48 - 0.95), although it should be reviewed and utilized cautiously (Gillessen, Randerath, Mockel, Noetel, & Seiler, 2019).

Another randomized controlled trial's results supported the effectiveness of this combination in preventing implantable cardiac defibrillator discharges in patients receiving secondary prophylaxis for malignant ventricular arrhythmias (Hazard ratio, 0.27; intervals 95% confidence) (Swapna, Maheswaramma, & Reddy).

Particularly in patients with atrial fibrillation

If the given monotherapy doesn't work, adding flecainide to the beta-blocker can be tested. Combining this medication with metoprolol enhances rhythm regulation and minimizes symptom recurrences more than monotherapy. Thanks to decreased side effects and improved quality of life, atrial fibrillation can be treated more effectively and with better tolerance and treatment adherence. Finally, individuals with ischemic heart disease who continue to experience symptoms despite receiving established maximal anti-ischemic therapy can test the co-administration of ranolazine (Steffel et al., 2021).

The use of ranolazine in a population in which almost all patients were already taking a β-blocker was associated with a reduction in ischemic recurrences (Hazard Ratio, 0.78; 95% confidence intervals, 0.67 - 0.91) or angina (Hazard Ratio, 0.77; 95% confidence intervals, 0.59 - 1.00) and longer exercise duration (514 s vs 482 s), in the absence of an effect beneficial on cardiovascular mortality (Hazard Ratio, 0.97; 95% confidence intervals, 0.80 - 1.16) (Santos, António, Rocha, & Fortuna, 2020).

TAKING BETA-BLOCKERS WHILE A PATIENT HAS ADDITIONAL COMORBID CONDITIONS

Statement

16. Selective therapy with beta-blockers may be employed in patients with COPD and ischemic heart disease.
17. Prefer highly selective -blockers, whether or not they are used with ivabradine, for patients with ischemic heart disease and mild to moderate asthma.
18. Patients with ischemic heart disease, chronic peripheral arterial obliterans, or noncritical peripheral ischemia are candidates for blocker therapy.

Chronic obstructive pulmonary disease (COPD), asthma, and other pulmonary and cardiovascular conditions frequently co-occur in the general population, making clinical care challenging due to potential drug interactions. However, the distribution of the various adrenergic receptors within organs varies, with a higher concentration of 1 receptor in the heart and receptors in the lungs. Because of this, cardioselective beta-blockers might be considered when treating individuals with COPD and ischemic heart disease (Kong et al., 2014).

The limited evidence that is currently available supports this idea because, when compared to a placebo, using cardioselective beta-blockers does not appear to worsen symptoms, respiratory function, or response to treatment with beta2-agonists but instead appears to reduce mortality (28%) and risk of exacerbation (37%). In the latter scenario, it is possible to surmise that the beta-blocker is efficient because some of the events that constitute exacerbations are cardiac events. A subsequent observational study also validated the data on mortality decrease in COPD patients taking beta-blockers, especially with bisoprolol. Even less information is now available regarding beta-blocker usage in asthma patients (Kotalczyk, Mazurek, Kalarus, Potpara, & Lip, 2021).

However, it does not seem that using cardioselective beta-blockers in this clinical situation increases the frequency of asthma flare-ups. Pulmonary function tests should be assessed to confirm response and likely tolerance in light of the hazards associated with betablocker medication in patients with COPD and asthma, especially those with more severe lung illness. Patients with chronic peripheral artery disease are more likely to develop ischemic heart disease than other types of cardiovascular disease. Additionally, 5% of these individuals pass away after an acute myocardial infarction (Seiffge et al., 2020).

Although very little data supports this, using beta-blockers seems to lower the incidence of myocardial infarction recurrence (53%) without changing arterial flow or vascular resistance distal to the walking distance. However, utmost caution should be

exercised when evaluating the usage of these medications in patients with critical limb ischemia (Ponikowski et al., 2021).

CONCLUSION:

Due to their effectiveness in preventing and treating recurrent anginal and ischemic episodes and related arrhythmias, beta-blockers are a mainstay of the pharmaceutical therapy of patients with ischemic heart disease. Clinical management of these individuals is challenging due to their comorbidities, and it is occasionally necessary to combine other treatments that can improve their efficacy and safety. The clinical indications described in this paper can be a beneficial tool for the daily care of patients who need beta-blocker therapy to prevent and treat angina, myocardial infarction, and arrhythmias because they have cardiovascular disease.

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