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Carvedilol – is it still the *primus inter pares* among β -blockers?

Introduction

Cardiovascular diseases remain the main cause of morbidity and mortality all over the world. As a result of significant developments in the field of prevention and improvement of treatment outcomes we are observing a steady decrease in mortality due to coronary artery disease (CAD) [1]. Largely we owe it to evidence-based medicine. Results of large, randomized clinical studies constitute the rationale for using drugs with proven efficacy that reduce the occurrence of hard end points, especially mortality. In Europe 20% of deaths are attributed to CAD [2]. According to recent studies, relative incidence of ST-segment elevation myocardial infarction (STEMI) is decreasing, while that of non-ST-segment elevation myocardial infarction increases (NSTEMI) [3, 4]. Arterial hypertension remains the most important risk factor for cardiovascular diseases, including CAD, that leads to numerous premature deaths. Prevalence of arterial hypertension is steadily rising – according to the results of NATPOL 2011 study it increased from 30% to 32% in a Polish population. At this rate, by 2035 this number will have increased by half [5]. It is also a well-known fact that poor control of arterial hypertension correlates with cardiovascular risk in a linear fashion. CAD and arterial hypertension are the main etiological factors involved in development of heart failure, which affects 1-2% of adult population. In Poland, the number of patients living with heart failure is estimated at 800 000 and the number is growing. The main cause of increase in the frequency of occurrence of heart failure include ageing of the population and consequences of increasingly more effective treatment of acute conditions, e.g. acute coronary syndromes. Patients survive, but suffer from late complications, such as heart failure. The number of patients suffering from heart failure with preserved

ejection fraction steadily increases, ranging from 22% to 73% [6], which is accompanied by a decreasing trend for heart failure with reduced ejection fraction. According to the results of Heart Failure Pilot Survey registry, which included 6108 patients (1159 from Poland), Polish patients are more frequently hospitalized due to acute heart failure, develop heart failure at younger age and are more severely ill, presenting with higher New York Heart Association (NYHA) class on hospital admission [7]. The cornerstone of treatment for CAD, arterial hypertension and heart failure are β -blockers, and among them a non-selective β and α_1 receptor antagonist – carvedilol – plays an important role. Clinical potential and mechanism of action of carvedilol has been thoroughly discussed in our previous publication from 2003 [8]. However, due to the appearance of numerous new studies grounding the leading role of carvedilol among other β -blockers, we decided to prepare another article that would summarize and systematize current knowledge and highlight indications for the use of carvedilol in patients with cardiovascular disease.

Pharmacological profile and mechanism of action of carvedilol

Carvedilol is a lipophilic chemical compound, it does not dissolve in water, it is found as two optic enantiomers due to the presence of an asymmetric carbon in the molecule and the drug is a mixture of those two enantiomers (Figure 1). Carvedilol is rapidly absorbed after oral administration and reaches peak serum concentration after 1-2 hours. Its half-life amounts to 7-10 hours. It binds to serum proteins, especially albumin, is metabolized by cytochrome P450 in the liver to be excreted with bile. Carvedilol is a non-selective

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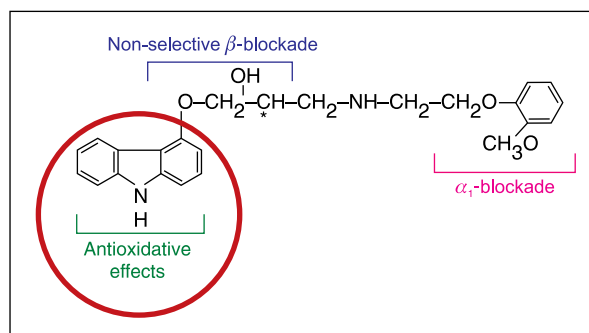


Figure 1. Chemical structure of carvedilol with marked structural elements responsible for specific actions of the compound. Source: *Choroby Serca i Naczyni* 2008, tom 5, nr 3, 150

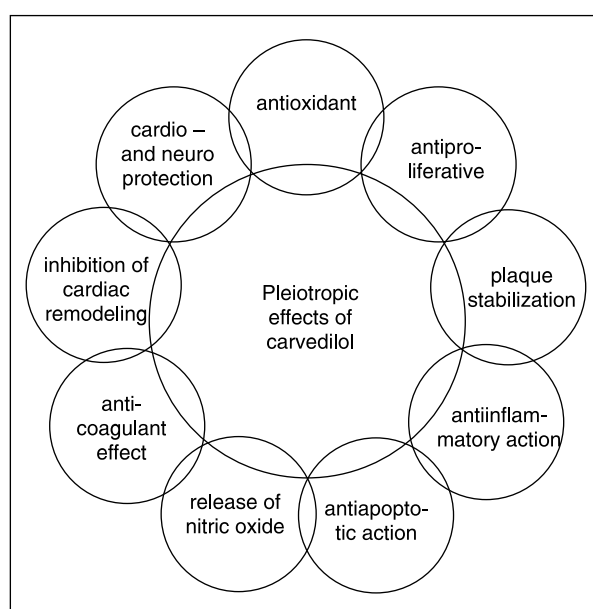


Figure 2. Pleiotropic effects of carvedilol

tive β receptor antagonist, with the greatest affinity to β_1 receptors, followed by α_1 and β_2 . Inhibition of cardiac β receptors results in reduced contractility, heart rate, minute output, atrioventricular conduction and ectopic activity, while blocking of α_1 receptor is responsible for vasodilative properties of the drug. The pleiotropic properties of carvedilol comprising particularly favorable pharmacological profile of the drug have been broadly discussed in the recent years (Figure 2) [9]. The antioxidative effect of carvedilol associated with the carbazole part of the compound has been documented most extensively (Figure 1) [10, 11]. Patients who received carvedilol during the acute phase of myocardial infarction (MI) were characterized by greater superoxide dismutase activity, while among patients with a history of myocardial infarction carvedilol was associated with

significantly greater reduction of oxidized LDL compared after 12 months of therapy to atenolol [12]. The antioxidative effect of carvedilol was also confirmed in patients with stable CAD; three months of treatment resulted in an increase in the activity of superoxide dismutase, glutathione peroxidase and catalase – enzymes responsible for protection against free radicals and oxidation reactions [13]. The effect of carvedilol on plaque stabilization postulated by Wu et al. is also attributed to its antioxidative properties, leading to reduced activity of metalloproteinases responsible for plaque instability [14]. Anti-inflammatory effect is another important action of carvedilol. In a group of 52 patients with heart failure and impaired left ventricular function (EF < 40%) treatment with carvedilol was associated with reduction of C-reactive protein concentration among patients with elevated blood levels of this marker compared to metoprolol [15]. Similar observations were made in another study that randomized 74 patients with heart failure and impaired left ventricular function (EF < 40%) into receiving carvedilol vs. placebo [16]. After 4 months of treatment authors demonstrated significant reduction in interleukin 6 (IL-6) and tumor necrosis factor α (TNF- α) concentrations among patients receiving carvedilol.

Clinical application of carvedilol among patients with coronary artery disease

Acute coronary syndromes are of clinical presentations of CAD. According to the 2017 guidelines of the European Society of Cardiology (ESC) on management of STEMI, oral treatment with β -blockers is indicated in patients with heart failure and/or reduced ejection fraction ($\leq 40\%$). Routine use of these drugs should also be considered in all patients after STEMI, who do not have contraindications to such a treatment (Table 1) [17]. On the other hand, 2015 ESC guidelines on the management of non-ST-segment elevation acute coronary syndromes indicate early initiation of β -blocker therapy in all patients with symptoms of angina and without contraindications to such a treatment (Table 1) [18].

The CAPRICORN trial was the pivotal study that established the position of carvedilol in the treatment of patients after MI [19]. This multicenter, randomized, placebo-controlled study included 1959 patients after MI and reduced left ventricular ejection fraction $\leq 40\%$ (LVEF). Patients were randomly assigned either to carvedilol at an initial dose 2x6.25 mg, which was subsequently titrated to 2x25mg, or placebo. Primary endpoint comprised of all-cause mortality or hospitalization due to cardiovascular causes. There were no differences with regard to the frequency of primary endpoint occurrence, although there was a significant reduction in all-cause mortality in the group treated with carvedilol compared to placebo (116 [12%] vs. 151 [15%]; hazard

Table 1. Place of β -blockers in the European Society of Cardiology guidelines

Recommendation	Class	Level
Stable coronary artery disease		
First-line treatment is indicated with β -blockers and/or calcium channel blockers to control heart rate and symptoms.	I	A
Acute coronary syndromes without persistent ST-segment elevation		
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B
It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I	B
Acute coronary syndromes with persistent ST-segment elevation		
Oral treatment with beta-blockers is indicated in patients with heart failure and/or LVEF \leq 40% unless contraindicated.	I	A
Routine oral treatment with beta-blockers should be considered during hospital stay and continued thereafter in all patients without contraindications.	IIa	B
Arterial hypertension		
Diuretics (thiazides, chlorthalidone and indapamide), beta-blockers, calcium antagonists, ACE inhibitors, and angiotensin receptor blockers are all suitable and recommended for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in some combinations with each other.	I	A
Heart failure		
An ACEI is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended, in addition to an ACEI, for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A

ACEI – angiotensin converting enzyme inhibitors; HFrEF – heart failure with reduced ejection fraction

ratio [HR] 0.77; 95% confidence interval [CI] 0.60-0.98; $p=0.03$) reduction of cardiovascular mortality (104 [11%] vs. 139 [14%]; HR 0.75; 95% CI 0.58-0.96; $p=0.024$) and MI (34 [3%] vs. 57 [6%]; HR 0.59; 95% CI 0.39-0.90; $p=0.014$).

One of the first studies assessing long-term effects of β -blocker therapy in patients after MI treated with coronary angioplasty was an analysis that included 2442 patients [20]. Participants were divided into two groups – 1661 received a β antagonist and 781 patients did not. After 6 months of follow-up, the researchers noted lower mortality (2.2% vs. 6.6%; $P<0.0001$; odds ratio [OR] 0.43; 95% CI 0.26-0.73; $P=0.0016$) as well as reduced frequency of cardiovascular events (defined as death, recurrent MI or ischemia requiring revascularization) (14% vs. 17%; $P=0.036$) in the group treated with a β -blocker compared to patients who did not receive such a treatment. **The greatest benefit of β -blocker treatment was observed in patients with reduced left ventricular ejection fraction and multivessel CAD.**

Routine use of β -blockers in combination with angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB) in all patients after STEMI is a class IIa recommendation (Table 1) [17]. Konishi et al. conducted a study on 251 patients with MI treated with ACEI or ARB. Patients were divided into two groups: receiving β -blockers (171 patients, 91 received carvedilol and 80 received bisoprolol) vs. not receiving

β -blockers (80 patients) [21]. After 12 months of follow-up, the authors observed a reduction in all-cause mortality in a group of patients receiving the β receptor antagonist compared to the control group (7 [4.1%] vs. 11 [13.8%]; $P=0.006$) as well as a reduction in serious cardiovascular incidents (MI, stroke, hospitalization due to cardiovascular causes) (27 [15.8] vs. 29 [36.3]; $P<0.0001$). There were no significant differences between groups on carvedilol vs. bisoprolol with regard to all-cause mortality. However, reduction in the incidence of acute heart failure requiring hospitalization was noted in the carvedilol group compared to the bisoprolol group {6 [6%] vs. 13 [16.3%]; $P=0.04$).

Benefits of β -blocker therapy was confirmed in a multicenter registry consisting of 20 344 patients, of whom 8 510 patients with STEMI treated with primary coronary angioplasty were selected [22]. Among all recruited subjects, 6873 were treated with a β -blocker and 1637 did not receive such a treatment. After a median follow-up of 367 days all-cause mortality was significantly lower in the group of patients receiving β -blockers compared to patients not treated with β -blockers (146 [2.1%] vs. 59 [3.6%]; $P<0.001$). In a subgroup analysis, the benefits of β -blockers were also demonstrated in low-risk patients, including those with left ventricular ejection fraction $>40\%$ or single-vessel CAD.

Results of another meta-analysis consisting of 40 873 patients from 10 observational studies also cor-

roborate the effectiveness of β -blocker therapy among patients after MI treated with coronary angioplasty [23]. Patients treated with β -blockers after discharge from the hospital were characterized by lower mortality during a 12-month follow-up period (unadjusted relative risk [RR] 0.58, 95% CI 0.48-0.71; adjusted HR 0.76, 95% CI 0.62-0.94) compared to those who did not receive such a treatment. However, the benefits of β -blocker therapy were limited to patients with impaired left ventricular function or to patients with NSTEMI.

In the era of reperfusion, contrast-induced nephropathy is a frequently observed complication, especially among elderly patients with renal impairment at baseline. In a study conducted on 200 patients undergoing coronarography, of which one half received carvedilol and the other half was treated with metoprolol, contrast-induced nephropathy occurred in 7 patients (7%) treated with carvedilol and 22 (22%) patients on metoprolol ($p=0.003$) [24].

Lower incidence of contrast-induced nephropathy in the group treated with carvedilol is probably attributed to antioxidative properties of the drug.

The anti-arrhythmic effect also constitutes one of the major benefits of carvedilol. A meta-analysis of four randomized studies that included a total of 601 patients with CAD undergoing coronary artery by-pass grafting compared the effects of carvedilol and metoprolol on the occurrence of atrial fibrillation during the perioperative period [25]. There was significantly lower incidence of atrial fibrillation in the group of patients treated with carvedilol compared to the group taking metoprolol (OR 0.50; 95% CI 0.32-0.80). The observed anti-arrhythmic effect is also attributed to the antioxidative properties of the drug, as well as its effect on ionic currents in cardiomyocytes [26]

According to the summary of product characteristics, the initial recommended dose of carvedilol is 12.5 mg BID for the first two days, followed by 25mg BID [27].

Carvedilol in patients with arterial hypertension

The 2013 guidelines on management of arterial hypertension elaborated by the European Society of Hypertension and the ESC consistently recommend β -blockers as one of five first-choice drug groups next to; ACEI, ARB, thiazide diuretics, and calcium antagonists (Table 1) [28]. The same position may be found in a document "Principles of management of arterial hypertension in 2015" by the Polish Society of Arterial Hypertension (PTNT) [29]. In some specific clinical situations β -blockers should be preferred over other groups of drugs, e.g. in patients with a history of MI, with angina pectoris, heart failure, aortic aneurysm, tachycardia, arrhythmia, or with hyperkinetic circulation.

Combination therapy plays an important role in the treatment of arterial hypertension. Optimal drug combinations with β -blockers include ACEI and dihydropyridine calcium antagonists. Despite numerous studies demonstrating limitations of β -blocker use in patients with arterial hypertension, a meta-analysis published by Law et al. confirmed similar efficacy of β -blockers in prevention of coronary events and very good efficacy in prevention of cardiovascular events in patients after MI or with heart failure compared to other first-line drugs [30-32]. The most important limitations of β -blockers found in the literature include: smaller effect on central blood pressure and pulse pressure compared to other classes of drugs, smaller efficacy regarding regression of left ventricular hypertrophy, as well as unfavorable metabolic profile, especially in combination with diuretics, associated with elevated risk of diabetes or weight gain [33-35]. Carvedilol undoubtedly stands out against all available β -blockers due to its vasodilative properties, making it a preferred agent for the treatment of uncomplicated arterial hypertension according to the PTNT guidelines [29]. The principal mechanism, in which β -blockers reduce blood pressure, includes decrease in cardiac output, sympathetic activity and production of renin by the cells of juxtaglomerular apparatus accompanied by an increase in peripheral resistance, which is an undesirable effect. Carvedilol, due to the blockade of α_1 receptors, lowers blood pressure by reducing peripheral vascular resistance, while cardiac output remains generally unaffected. In this manner, its hemodynamic profile is similar to ACEI or calcium antagonists [36]. Another favorable mechanism of carvedilol's vasodilative effect involves stimulation of nitric oxide production by endothelial cells [37].

Randomized GEMINI trial was designed in order to address the reports suggesting unfavorable metabolic profile of β -blockers [38]. This randomized, double-blind study included 1235 patients with type 2 diabetes and arterial hypertension. Participants were assigned to carvedilol (498 patients) or metoprolol (737 patients) BID in gradually increasing doses. Primary endpoint consisted of mean change in glycated hemoglobin (HbA1c) concentration measured at baseline and after 5 months of therapy. Secondary endpoints consisted of improvement in insulin sensitivity and microalbuminuria. Significant increase in HbA1c concentration was noted in the group of patients treated with metoprolol (mean: 0.15%, $p<0.001$) – an effect that was not seen in patients treated with carvedilol (mean: 0.02%; $p=0.65$). Moreover, improvement in insulin sensitivity was observed in the carvedilol group (-9.1%; $p=0.004$) compared to metoprolol (-2.0%; $p=0.48$). Concluding, over several months of follow-up therapy with carvedilol improved metabolic profile of patients with type 2 diabetes and arterial hypertension compared to metoprolol.

Left ventricular hypertrophy is one of the complications of arterial hypertension and a significant cardiovascular risk factor. The majority of hypotensive agents possess the ability to reverse cardiac hypertrophy, although this effect was not demonstrated for selective β -blockers [39]. In a study by Galzerano et al. carvedilol reduced cardiac hypertrophy in patients with arterial hypertension, although it was less effective than telmisartan in that regard [40].

Hypertensive nephropathy is another complication of arterial hypertension. It leads to reduction in renal blood flow and, as a result, drop in glomerular filtration. Traditional β -blockers cause an additional decrease in renal blood flow. There are several studies corroborating the nephroprotective effects of carvedilol, in which the drug increased renal blood flow and reduced microalbuminuria [41]. In the aforementioned GEMINI trial, among patients with arterial hypertension and diabetes, but without microalbuminuria at baseline, carvedilol was less likely to induce it compared to metoprolol (6.4% vs. 10.3%; OR 0.60; 95% CI 0.36-0.97; $p=0.04$) [38].

According to the summary of product characteristics, in treatment of arterial hypertension the initial recommended dose of carvedilol is 12.5 mg OD for the first two days, followed by 25mg OD. It is also allowed to increase the dose to 50 mg OD or divided into two doses [27]. Stienen et al. presented a rationale for such dosing of carvedilol in patients with arterial hypertension in his meta-analysis [42].

Clinical application of carvedilol in patients with heart failure

Beta receptor antagonists constitute the basis of treatment of heart failure, reducing mortality and morbidity in this group of patients [43,44]. According to the ESC guidelines, β -blockers in combination with ACEI are recommended for stable, symptomatic patients with heart failure and reduced left ventricular ejection fraction in order to reduce the risk of hospitalization due to heart failure or death (Table 1) [6]. In our previous publication we discussed the most important studies that made carvedilol the leading agent for treatment of patients with heart failure regardless of the severity of symptoms assessed according to the NYHA scale [44-48] (Table 2).

One of the most important randomized studies involving carvedilol was the COMET trial, which demonstrated superiority of treatment with carvedilol compared to metoprolol, expressed as 17% reduction in all-cause mortality in the group of patients with NYHA II-IV heart failure, left ventricular ejection fraction $<35\%$, who received optimal pharmacological treatment (HR 0.83; 95% CI 0.74-0.93; $p=0.0017$) [48]. In 2007 a subanalysis

of the COMET trial was published aiming to assess the mechanism, in which carvedilol reduced all-cause mortality compared to metoprolol and whether it was owed to reduction in mortality of some specific cause [49]. Over a mean follow-up period of 58 months, 1112 of 3029 patients died, including 972 deaths of cardiovascular causes (480 sudden deaths, 365 deaths due to heart failure and 51 deaths due to stroke). Multivariable Cox regression analysis demonstrated significant reduction in cardiovascular deaths (RR 0.80; 95% CI 0.7-0.91; $p=0.0009$), sudden deaths (RR 0.77; 95% CI 0.64-0.93; $p=0.0073$), and strokes (RR 0.37; 95% CI 0.19-0.71; $p=0.0027$), as well as a trend toward reduction in the rate of death secondary to heart failure (RR 0.83; 95% CI 0.66-1.04; $p=0.07$) in patients treated with carvedilol compared to metoprolol. Summarizing, in the group of patients with heart failure carvedilol was more effective in reducing the risk of death regardless of its cause.

Another interesting analysis compared the results of major randomized clinical trials that influenced current standards of care in heart failure: CIBIS-II (bisoprolol), COPERNICUS (carvedilol), SENIORS-SHF (nebivolol), and MERIT-HF (metoprolol) [Wikstrand] [50]. Since these studies differed with regard to inclusion criteria, it was necessary to select groups of patients among studied populations in order to allow reliable comparison. Reference group that other results were compared to consisted of patients from MERIT-HF trial. Similar efficacy and satisfactory tolerance of treatment was noted for carvedilol, bisoprolol and metoprolol in the population of patients with heart failure regardless of NYHA class or degree of left ventricular dysfunction, while the efficacy of treatment with nebivolol was lower with similar tolerance. Moreover, lower rate of discontinuation of the study medication was noted in the carvedilol group.

The CARMEN trial was the first study to prove that early administration of ACEI combined with carvedilol leads to reversal of pathological left ventricular remodeling in the group of patients with mild to moderate heart failure [51]. The analysis included 572 patients, who were randomly assigned to one of three arms: in one arm patients received carvedilol (190), in the second - enalapril (190), and in the third arm patients received a combination of the two (191). Over the course of the study, which lasted 18 months, medication doses were gradually increased to maximally tolerated. Primary endpoint consisted of left ventricular remodeling defined as change in end-diastolic volume assessed in transthoracic echocardiography. Treatment with both drugs resulted in significant reduction in the left ventricular end-diastolic volume index compared to treatment with enalapril alone ($p=0.0015$), proving that it is possible to reverse unfavorable left ventricular remodeling.

Another study that corroborated the beneficial effects of carvedilol on left ventricular systolic func-

Table 2. A compilation of most important randomized clinical trials with carvedilol

	MOCHA (1996) [Bristow]	PRECISE (1996) [Packer]	US Carvedilol Trial (1996) [Packer]	CAPRICORN (2001) [Dargie]	COPERNICUS (2001) [Krum]	COMET (2003) [Poole-Wilson]
Population characteristics						
Number of patients	345	278	1094	1959	2289	3029
Heart failure	100%	100%	100%	n/a	100%	100%
NYHA class >II	62.6%	60.1%	46.8%	n/a	n/a	51.6%
Coronary artery disease	60.3%	51.8%	47.6%	100% MI	67.2%	52.5%
Ejection fraction	<35%	<35%	<35%	<40%	<25%	<35%
Intervention						
Carvedilol dose	2x6.25mg/ 2x12.5mg/ 2x25mg	2x25-50 mg	2x6.25 → 2x50 mg	2x6.25 → 2x25 mg	2x3.125 → 2x25 mg	2x3.125 → 2x25 mg
vs. placebo	Yes	Yes	Yes	Yes	Yes	No
vs. other drug	No	No	No	No	No	Metoprolol 2x5mg → 2x50 mg
Results						
Primary endpoint	Assessment of exercise capacity in a 6-minute walking test and 9-minute treadmill exercise test	Assessment of exercise capacity in a 6-minute walking test and 9-minute treadmill exercise test	All-cause mortality	Composite endpoint: all-cause mortality and hospitalization due to cardiovascular causes	All-cause mortality	All-cause mortality
Follow-up	6 months	6 months	6.5 months*	1.3 year	10.4 months*	58 months
Results – primary endpoint	No difference between groups: 6-minute walking test, p=0.50; exercise test, p=0.27	Longer distance in a 6-minute walking test in the carvedilol group, p=0.048; no difference in exercise test, p=0.324	Carvedilol 3.2% vs. placebo 7.8%; (RR 0.65; 95% CI 0.39-0.80; p<0.001)	Carvedilol 35% vs. placebo 37%; p=0.296	Carvedilol 11.2% vs. placebo 16.8% (RR 0.35; 95% CI 0.19-0.48; p=0.00013)	Carvedilol 34% vs. metoprolol 40%; p=0.002
Reduction of all-cause mortality	Yes, effect enhanced with increasing dose of carvedilol (RR 0.27; 95% CI 0.12-0.60; p<0.001)	No, carvedilol 4.5% vs. placebo 7.6%; p=0.26	Yes, v.s.	Yes, carvedilol 12% vs. placebo 15%; p=0.031	Yes, v.s.	Yes, v.s.
Reduction of cardiovascular mortality	n/a	n/a	Yes, as a combined endpoint consisting of death or hospitalization due to cardiovascular causes: carvedilol 15.8% vs. placebo 24.6%; (RR 0.38; 95% CI 0.18-0.53; p<0.001)	Yes, carvedilol 11% vs. placebo 14%; p=0.024	n/a	Yes, carvedilol 29% vs. metoprolol 35%; p=0.0004



Table 2 cont. A compilation of most important randomized clinical trials with carvedilol

	MOCHA (1996) [Bristow]	PRECISE (1996) [Packer]	US Carvedilol Trial (1996) [Packer]	CAPRICORN (2001) [Dargie]	COPERNICUS (2001) [Krum]	COMET (2003) [Poole-Wilson]
Reduction of hospitalizations	Yes, effect enhanced with increasing dose of carvedilol (p=0.01)	Yes, carvedilol 25.5% vs. placebo 16.5%; p=0.060	Yes, carvedilol 14.1% vs. placebo 19.6%; (RR 0.27; 95% CI 0.03-0.45; p=0.036)	No (due to heart failure) carvedilol 12% vs. placebo 14%; p=0.215	Yes (as a combined endpoint: all-cause mortality + hospitalizations) carvedilol 36.8% vs. placebo 44.7% (RR 0.24; 95% CI 0.13-0.33; p<0.001)	No (as a combined endpoint: all-cause mortality + hospitalizations) carvedilol 74% vs. metoprolol 76%; p=0.122
Improved left ventricular function	Yes, effect enhanced with increasing dose of carvedilol (p<0.001)	Yes, carvedilol +8% vs. placebo +3%; p<0.001	n/a	n/a	n/a	n/a

*. trial was stopped early due to an effect exceeding expectations: reduction of all-cause mortality in the group treated with carvedilol compared to placebo; CI – confidence interval; MI – myocardial infarction; NYHA – New York Heart Association; RR – risk reduction

tion was the CHRISTMAS trial [52]. Analysis included 305 patients with chronic heart failure of atherosclerotic etiology. Patients were randomized to carvedilol or placebo and followed-up lasted for 6 months. Significant increase in left ventricular ejection fraction was observed in patients treated with carvedilol compared to placebo (p<0.0001). Also, greater improvement in left ventricular systolic function was shown in the group of patients with larger area of stunned or stunned and ischemic myocardium.

There is an ongoing debate regarding selection of an optimal β -blocker for patients with heart failure and results of new studies are constantly emerging. Based on the data from a national Danish registry Pasternak et al. led a cohort study on patients with heart failure and impaired systolic function of the left ventricle ($\leq 40\%$), which included 6026 patients treated with carvedilol and 5638 patients receiving metoprolol succinate [53]. Follow-up lasted for a median of 2.4 years, during which there were 875 deaths in the carvedilol group and 754 in the metoprolol group (18.3% vs. 18.8%; corrected HR 0.99; 95% CI 0.88-1.11). The risk of death due to cardiovascular causes did not differ significantly between the two groups (corrected HR 1.05; 95% CI 0.88-1.26). Results of this study suggest similar efficacy of treatment with carvedilol compared to metoprolol with regard to both all-cause and cardiovascular mortality.

Another study aiming to explain whether the reduction in mortality associated with β -blockers can be attributed to a class effect or does it differ for specific compounds encompassed 6010 stable patients with heart failure and reduced ejection fraction from 3 national registries: Norwegian, British, and German [54]. The study analyzed mortality among patients receiving bisoprolol – 302 (29.5%), carvedilol – 637 (37.0%), or metoprolol succinate – 1232 patients (37.7%). Univariate analysis showed that all-cause mortality was lower in the group treated with bisoprolol compared to metoprolol (HR 0.80, 95% CI 0.71-0.91, p < 0.01) and in the carvedilol arm compared to metoprolol group (HR 0.86, 95% CI 0.78-0.94, p < 0.01), while bisoprolol seemed to be equally effective as carvedilol (HR 0.94, 95% CI 0.82-1.08, p = 0.37). However, in propensity score analysis, where patients were matched with regard to the type of β -blocker used and its dose, it appeared that the type of β -blocker did not significantly impact mortality (bisoprolol vs. carvedilol: HR 0.90; 95% CI 0.76-1.06; p = 0.20; bisoprolol vs. metoprolol HR 1.10, 95% CI 0.93-1.31, p = 0.24; and carvedilol vs. metoprolol HR 1.08, 95% CI 0.95-1.22, p = 0.26).

The above observations are not in line with an article recently published in American Heart Journal, which reported superiority of carvedilol compared to metoprolol succinate in the largest to date group of patients with heart failure and impaired left ventricular systolic func-

tion [55]. Primary analysis included 114 745 patients with heart failure treated with carvedilol or metoprolol and, after propensity score analysis, patients were matched with regard to age, sex, comorbidities, other medication and their doses, resulting in homogeneous groups of 43 941 patients in each arm of the study. Higher mortality was noted among patients treated with metoprolol compared to carvedilol (corrected HR 1.069; 95% CI 1.046-1.092; $p < 0.001$) over a 3.5-year observation period, while in a 6-year prognosis the probability of survival was higher in patients on carvedilol compared to the metoprolol group (55.6% vs. 49.2%; $p < 0.001$).

Nebivolol is another, beside carvedilol, third-generation β -blocker with vasodilative properties. The aim of a study conducted by Patrianakos et al. was to compare the effects of carvedilol vs nebivolol on function of the left ventricle and exercise capacity in 72 patients with heart failure due to dilated cardiomyopathy [56]. Carvedilol arm consisted of 38 patients, while 34 subjects received nebivolol. Echocardiographic examination and exercise tests were conducted before the commencement of treatment, after 3 and 12 months of therapy. Improvement in left ventricular function in relation to baseline values was observed during treatment with both compounds, although greater improvement was noted in the group treated with carvedilol compared to nebivolol, both after three months ($p = 0.004$) and after a year ($p = 0.02$). Moreover, among patients in the carvedilol arm, improvement in diastolic function was observed after only 3 months of therapy ($p = 0.02$), while in the nebivolol group gradual improvement was observed after as long as a year ($p = 0.02$). Exercise capacity was enhanced over a 1-year follow-up period in both study groups ($p = 0.01$ for both groups), although in the nebivolol group researchers observed transient worsening after 3 months of treatment ($p = 0.07$).

Conclusions

Possible indications for carvedilol are very broad and, due to its unique properties that go far beyond the traditional β receptor blockade, the drug may be used as a hypotensive, anti-anginal, or anti-arrhythmic agent, however, it is definitely the number one choice for the treatment of patients with heart failure. Despite being a non-selective β -blocker, due to concomitant α_1 receptor blockade it exhibits vasodilative action and avoids the disadvantages associated with this generation of β -blockers. Patients, who gain the greatest benefit from carvedilol therapy are those with heart failure, after MI, with impaired left ventricular function, at risk of developing life-threatening arrhythmias or atrial fibrillation. Among numerous patients with arterial hypertension, carvedilol will be a particularly good choice for young

patients, with hyperkinetic circulation, or arrhythmias, women of child-bearing age, or patients with coexisting metabolic syndrome, hyperlipidemia or diabetes and indications for β -blockade. It should be also emphasized that in randomized, double-blind clinical trials carvedilol reduced hard endpoints, such as mortality, compared to placebo. The evidence from numerous studies comparing carvedilol to other drugs of the same class also corroborates the uniqueness of this compound. Typical blockade of β receptors, favorable metabolic profile, and beneficial hemodynamic profile due to α_1 receptor antagonism combined with vastness of pleiotropic effects make carvedilol a leader among β -blockers across all of its indications.

References:

- Hartley A, Marshall DC, Saliccioli JD, et al. Trends in Mortality From Ischemic Heart Disease and Cerebrovascular Disease in Europe: 1980 to 2009. *Circulation*. 2016; 133(20): 1916–1926, doi: [10.1161/CIRCULATIONAHA.115.018931](https://doi.org/10.1161/CIRCULATIONAHA.115.018931), indexed in Pubmed: [27006480](https://pubmed.ncbi.nlm.nih.gov/27006480/).
- Townsend N, Wilson L, Bhatnagar P, et al. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J*. 2016; 37(42): 3232–3245, doi: [10.1093/eurheartj/ehw334](https://doi.org/10.1093/eurheartj/ehw334), indexed in Pubmed: [27523477](https://pubmed.ncbi.nlm.nih.gov/27523477/).
- Sugiyama T, Hasegawa K, Kobayashi Y, et al. Differential time trends of outcomes and costs of care for acute myocardial infarction hospitalizations by ST elevation and type of intervention in the United States, 2001–2011. *J Am Heart Assoc*. 2015; 4(3): e001445, doi: [10.1161/JAHA.114.001445](https://doi.org/10.1161/JAHA.114.001445), indexed in Pubmed: [25801759](https://pubmed.ncbi.nlm.nih.gov/25801759/).
- McManus DD, Gore J, Yarzebski J, et al. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med*. 2011; 124(1): 40–47, doi: [10.1016/j.amjmed.2010.07.023](https://doi.org/10.1016/j.amjmed.2010.07.023), indexed in Pubmed: [21187184](https://pubmed.ncbi.nlm.nih.gov/21187184/).
- Zdrojewski T. Rozpowszechnienie i kontrola nadciśnienia tętniczego w Polsce – porównanie z wybranymi krajami w Europie i na świecie. Rozdział książki pod redakcją: Więcek A, Januszewicz A, Szczepańska-Sadowska E, Prejbisz A. Hipertensjologia: patogeneza, diagnostyka i leczenie nadciśnienia tętniczego. Kraków, Medycyna Praktyczna. 2011; 1: 1–6.
- Ponikowski P, Voors AA, Anker SD, et al. ESC Scientific Document Group. 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. *Eur Heart J*. 2016; 37(27): 2129–2200, doi: [10.1093/eurheartj/ehw128](https://doi.org/10.1093/eurheartj/ehw128), indexed in Pubmed: [27206819](https://pubmed.ncbi.nlm.nih.gov/27206819/).
- Sosnowska-Pasiarska B, Bartkowiak R, Wozakowska-Kaplon B, et al. Population of Polish patients participating in the Heart Failure Pilot Survey (ESC-HF Pilot). *Kardiol Pol*. 2013; 71(3): 234–240, doi: [10.5603/KP.2013.0034](https://doi.org/10.5603/KP.2013.0034), indexed in Pubmed: [23575777](https://pubmed.ncbi.nlm.nih.gov/23575777/).
- Kubica J, Grzešek G, Bogdan M, et al. Karwedilol — primus inter pares w leczeniu chorych z niewydolnością serca. *Folia Cardiol*. 2003; 10: 407–414.
- Górska D. Karwedilol – więcej niż b-bloker. *Farm Pol* 2009; 65: 780–787. Yue TL, Cheng HY, Lysko PG, McKenna PJ, Feuerstein R, Gu JL, Lysko KA, Davis LL, Feuerstein G. Carvedilol, a new vasodilator and beta adrenoceptor antagonist, is an antioxidant and free radical scavenger. *J Pharmacol Exp Ther*. 1992; 263: 92–8.
- Yue TL, McKenna PJ, Gu JL, et al. Carvedilol, a new antihypertensive agent, prevents lipid peroxidation and oxidative injury to endothelial cells. *Hypertension*. 1993; 22(6): 922–928, indexed in Pubmed: [7902335](https://pubmed.ncbi.nlm.nih.gov/7902335/).
- Kastratović DA, Vasiljević ZM, Spasić MB, et al. Carvedilol increases copper-zinc superoxide dismutase activity in patients with acute myocardial infarction. *Basic Clin Pharmacol Toxicol*. 2007; 101(2): 138–142, doi: [10.1111/j.1742-7843.2007.00094.x](https://doi.org/10.1111/j.1742-7843.2007.00094.x), indexed in Pubmed: [17651317](https://pubmed.ncbi.nlm.nih.gov/17651317/).
- Jonsson G, Abdelnoor M, Seljeflot I, et al. The antioxidative effects of long-term treatment are more pronounced for carvedilol than for atenolol in post-myocardial infarction patients. *J Cardiovasc Pharmacol*. 2007; 49(1): 27–32, doi: [10.1097/FJC.0b013e31802bdd8c](https://doi.org/10.1097/FJC.0b013e31802bdd8c), indexed in Pubmed: [17261960](https://pubmed.ncbi.nlm.nih.gov/17261960/).

13. Kowalski J, Banach M, Barylski M, et al. Carvedilol modifies antioxidant status of patients with stable angina. *Cell Mol Biol Lett*. 2008; 13(2): 230–239, doi: [10.2478/s11658-007-0049-3](https://doi.org/10.2478/s11658-007-0049-3), indexed in Pubmed: [18026857](https://pubmed.ncbi.nlm.nih.gov/18026857/).
14. Wu TC, Chen YH, Leu HB, et al. Carvedilol, a pharmacological antioxidant, inhibits neointimal matrix metalloproteinase-2 and -9 in experimental atherosclerosis. *Free Radic Biol Med*. 2007; 43(11): 1508–1522, doi: [10.1016/j.freeradbiomed.2007.08.010](https://doi.org/10.1016/j.freeradbiomed.2007.08.010), indexed in Pubmed: [17964422](https://pubmed.ncbi.nlm.nih.gov/17964422/).
15. Nagatomo Y, Yoshikawa T, Kohno T, et al. Effects of beta-blocker therapy on high sensitivity c-reactive protein, oxidative stress, and cardiac function in patients with congestive heart failure. *J Card Fail*. 2007; 13(5): 365–371, doi: [10.1016/j.cardfail.2007.02.004](https://doi.org/10.1016/j.cardfail.2007.02.004), indexed in Pubmed: [17602983](https://pubmed.ncbi.nlm.nih.gov/17602983/).
16. Tatli E, Kurum T, Aktöz M, et al. Effects of carvedilol on right ventricular ejection fraction and cytokines levels in patients with systolic heart failure. *Int J Cardiol*. 2008; 125(2): 273–276, doi: [10.1016/j.ijcard.2007.07.166](https://doi.org/10.1016/j.ijcard.2007.07.166), indexed in Pubmed: [18053592](https://pubmed.ncbi.nlm.nih.gov/18053592/).
17. Ibanez B, James S, Agewall S, et al. Widimský P; ESC Scientific Document Group. 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). *Eur Heart J*. 2018; 39: 119–177.
18. Roffi M, Patrono C, Collet JP, et al. ESC Scientific Document Group . 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). *Eur Heart J*. 2016; 37(3): 267–315, doi: [10.1093/eurheartj/ehv320](https://doi.org/10.1093/eurheartj/ehv320), indexed in Pubmed: [26320110](https://pubmed.ncbi.nlm.nih.gov/26320110/).
19. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001; 357(9266): 1385–1390, indexed in Pubmed: [11356434](https://pubmed.ncbi.nlm.nih.gov/11356434/).
20. Kernis SJ, Harjai KJ, Stone GW, et al. Does beta-blocker therapy improve clinical outcomes of acute myocardial infarction after successful primary angioplasty? *J Am Coll Cardiol*. 2004; 43(10): 1773–1779, doi: [10.1016/j.jacc.2003.09.071](https://doi.org/10.1016/j.jacc.2003.09.071), indexed in Pubmed: [15145098](https://pubmed.ncbi.nlm.nih.gov/15145098/).
21. Konishi M, Haraguchi Go, Yoshikawa S, et al. Additive effects of β -blockers on renin-angiotensin system inhibitors for patients after acute myocardial infarction treated with primary coronary revascularization. *Circ J*. 2011; 75(8): 1982–1991, indexed in Pubmed: [21697605](https://pubmed.ncbi.nlm.nih.gov/21697605/).
22. Yang JH, Hahn JY, Song YB, et al. Association of beta-blocker therapy at discharge with clinical outcomes in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *JACC Cardiovasc Interv*. 2014; 7(6): 592–601, doi: [10.1016/j.jcin.2013.12.206](https://doi.org/10.1016/j.jcin.2013.12.206), indexed in Pubmed: [24947717](https://pubmed.ncbi.nlm.nih.gov/24947717/).
23. Huang BT, Huang FY, Zuo ZL, et al. Meta-Analysis of Relation Between Oral β -Blocker Therapy and Outcomes in Patients With Acute Myocardial Infarction Who Underwent Percutaneous Coronary Intervention. *Am J Cardiol*. 2015; 115(11): 1529–1538, doi: [10.1016/j.amjcard.2015.02.057](https://doi.org/10.1016/j.amjcard.2015.02.057), indexed in Pubmed: [25862157](https://pubmed.ncbi.nlm.nih.gov/25862157/).
24. Yılmaz M, Aydınlı A, Okyay K, et al. Comparison of Carvedilol and Metoprolol for Preventing Contrast-Induced Nephropathy after Coronary Angiography. *Cardiorenal Med*. 2015; 5(3): 199–207, doi: [10.1159/000381964](https://doi.org/10.1159/000381964), indexed in Pubmed: [26195972](https://pubmed.ncbi.nlm.nih.gov/26195972/).
25. DiNicolantonio JJ, Beavers CJ, Menezes AR, et al. Meta-analysis comparing carvedilol versus metoprolol for the prevention of postoperative atrial fibrillation following coronary artery bypass grafting. *Am J Cardiol*. 2014; 113(3): 565–569, doi: [10.1016/j.amjcard.2013.10.020](https://doi.org/10.1016/j.amjcard.2013.10.020), indexed in Pubmed: [24332247](https://pubmed.ncbi.nlm.nih.gov/24332247/).
26. Acikel S, Bozbas H, Gultekin B, et al. Comparison of the efficacy of metoprolol and carvedilol for preventing atrial fibrillation after coronary bypass surgery. *Int J Cardiol*. 2008; 126(1): 108–113, doi: [10.1016/j.ijcard.2007.03.123](https://doi.org/10.1016/j.ijcard.2007.03.123), indexed in Pubmed: [17499863](https://pubmed.ncbi.nlm.nih.gov/17499863/).
27. Charakterystyka produktu leczniczego. : Vivacor.
28. Mancia G, Fagard R, Narkiewicz K, et al. Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology, ESH/ESC Task Force for the Management of Arterial Hypertension, Task Force Members, Task Force for the management of arterial hypertension of the European Society of Hypertension, Task Force for the management of arterial hypertension of the European Society of Cardiology. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013; 34(28): 2159–2219, doi: [10.1093/eurheartj/ehi151](https://doi.org/10.1093/eurheartj/ehi151), indexed in Pubmed: [23771844](https://pubmed.ncbi.nlm.nih.gov/23771844/).
29. Tykarski A, Narkiewicz K, Gaciong Z, et al. Zasady postępowania w nadciśnieniu tętniczym — 2015 rok. Wytyczne Polskiego Towarzystwa Nadciśnienia Tętniczego — wersja skrócona. *Kardiologia Polska*. 2015; 73(8): 676–700, doi: [10.5603/kp.2015.0157](https://doi.org/10.5603/kp.2015.0157).
30. Wiysonge CS, Bradley HA, Volmink J, et al. Beta-blockers for hypertension. *Cochrane Database Syst Rev*. 2017; 1: CD002003, doi: [10.1002/14651858](https://doi.org/10.1002/14651858).
31. Bradley HA, Wiysonge CS, Volmink JA, et al. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. *J Hypertens*. 2006; 24(11): 2131–2141, doi: [10.1097/01.hjh.0000249685.58370.28](https://doi.org/10.1097/01.hjh.0000249685.58370.28), indexed in Pubmed: [17053529](https://pubmed.ncbi.nlm.nih.gov/17053529/).
32. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009; 338: b1665, indexed in Pubmed: [19454737](https://pubmed.ncbi.nlm.nih.gov/19454737/).
33. Williams B, Lacy PS, Thom SM, et al. CAFE Investigators, Anglo-Scandinavian Cardiac Outcomes Trial Investigators, CAFE Steering Committee and Writing Committee. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. *Circulation*. 2006; 113(9): 1213–1225, doi: [10.1161/CIRCULATIONAHA.105.595496](https://doi.org/10.1161/CIRCULATIONAHA.105.595496), indexed in Pubmed: [16476843](https://pubmed.ncbi.nlm.nih.gov/16476843/).
34. Sharma AM, Pischon T, Hardt S, et al. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. *Hypertension*. 2001; 37(2): 250–254, indexed in Pubmed: [11230280](https://pubmed.ncbi.nlm.nih.gov/11230280/).
35. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet*. 2007; 369(9557): 201–207, doi: [10.1016/S0140-6736\(07\)60108-1](https://doi.org/10.1016/S0140-6736(07)60108-1), indexed in Pubmed: [17240286](https://pubmed.ncbi.nlm.nih.gov/17240286/).
36. Messerli FH, Grossman E. beta-Blockers in hypertension: is carvedilol different? *Am J Cardiol*. 2004; 93(9A): 7B–712B, doi: [10.1016/j.amjcard.2004.01.020](https://doi.org/10.1016/j.amjcard.2004.01.020), indexed in Pubmed: [15144930](https://pubmed.ncbi.nlm.nih.gov/15144930/).
37. Kalinowski L, Dobrucki LW, Szczepanska-Konkel M, et al. Third-generation beta-blockers stimulate nitric oxide release from endothelial cells through ATP efflux: a novel mechanism for antihypertensive action. *Circulation*. 2003; 107(21): 2747–2752, doi: [10.1161/01.CIR.0000066912.58385.DE](https://doi.org/10.1161/01.CIR.0000066912.58385.DE), indexed in Pubmed: [12742996](https://pubmed.ncbi.nlm.nih.gov/12742996/).
38. Bakris GL, Fonseca V, Katholi RE, et al. GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004; 292(18): 2227–2236, doi: [10.1001/jama.292.18.2227](https://doi.org/10.1001/jama.292.18.2227), indexed in Pubmed: [15536109](https://pubmed.ncbi.nlm.nih.gov/15536109/).
39. Schulman SP, Weiss JL, Becker LC, et al. The effects of antihypertensive therapy on left ventricular mass in elderly patients. *N Engl J Med*. 1990; 322(19): 1350–1356, doi: [10.1056/NEJM199005103221904](https://doi.org/10.1056/NEJM199005103221904), indexed in Pubmed: [2139175](https://pubmed.ncbi.nlm.nih.gov/2139175/).
40. Galzerano D, Tammaro P, del Viscovo L, et al. Three-dimensional echocardiographic and magnetic resonance assessment of the effect of telmisartan compared with carvedilol on left ventricular mass: a multicenter, randomized, longitudinal study. *Am J Hypertens*. 2005; 18(12 Pt 1): 1563–1569, doi: [10.1016/j.amjhyper.2005.06.011](https://doi.org/10.1016/j.amjhyper.2005.06.011), indexed in Pubmed: [16364826](https://pubmed.ncbi.nlm.nih.gov/16364826/).
41. Stafylas PC, Sarafidis PA. Carvedilol in hypertension treatment. *Vasc Health Risk Manag*. 2008; 4(1): 23–30, indexed in Pubmed: [18629377](https://pubmed.ncbi.nlm.nih.gov/18629377/).
42. Stienen U. The once-daily dose regimen of carvedilol: a meta-analysis approach. *J Cardiovasc Pharmacol*. 1992; 19 Suppl 1: S128–S133, indexed in Pubmed: [1378140](https://pubmed.ncbi.nlm.nih.gov/1378140/).
43. Ghali JK, Wikstrand J, Van Veldhuisen DJ, et al. MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). *MERIT-HF Study Group. JAMA*. 2000; 283(10): 1295–1302, indexed in Pubmed: [10714728](https://pubmed.ncbi.nlm.nih.gov/10714728/).
44. Packer M, Coats AJ, Fowler MB, et al. Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. 2001; 344(22): 1651–1658, doi: [10.1056/NEJM200105313442201](https://doi.org/10.1056/NEJM200105313442201), indexed in Pubmed: [11386263](https://pubmed.ncbi.nlm.nih.gov/11386263/).
45. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *MOCHA Investigators. Circulation*. 1996; 94(11): 2807–2816, indexed in Pubmed: [8941106](https://pubmed.ncbi.nlm.nih.gov/8941106/).
46. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. *U.S. Carvedilol Heart Failure Study Group. N Engl J Med*. 1996; 334(21): 1349–1355, doi: [10.1056/NEJM199605233342101](https://doi.org/10.1056/NEJM199605233342101), indexed in Pubmed: [8614419](https://pubmed.ncbi.nlm.nih.gov/8614419/).
47. Colucci WS, Packer M, Bristow MR, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. *The PRECISE Trial. Prospective Randomized*

- Evaluation of Carvedilol on Symptoms and Exercise. *Circulation*. 1996; 94(11): 2793–2799, indexed in Pubmed: [8941104](#).
48. Boman K, Jansson JH, Nilsson T, et al. COMET Investigators, COMET investigators, COMET Investigators, COMET investors, COMET Investigators, Carvedilol or Metoprolol European Trial Investigators, Carvedilol Or Metoprolol European Trial Investigators. Rationale and design of the carvedilol or metoprolol European trial in patients with chronic heart failure: COMET. *Eur J Heart Fail*. 2002; 4(3): 321–329, indexed in Pubmed: [12034158](#).
 49. Remme WJ, Cleland JG, Erhardt L, et al. Effect of carvedilol and metoprolol on the mode of death in patients with heart failure. *Eur J Heart Fail*. 2007; 9(11): 1128–1135, doi: [10.1016/j.ejheart.2007.07.014](#), indexed in Pubmed: [17716943](#).
 50. Wikstrand J, Wedel H, Castagno D, et al. The large-scale placebo-controlled beta-blocker studies in systolic heart failure revisited: results from CIBIS-II, COPERNICUS and SENIORS-SHF compared with stratified subsets from MERIT-HF. *J Intern Med*. 2014; 275(2): 134–143, doi: [10.1111/joim.12141](#), indexed in Pubmed: [24118421](#).
 51. Remme WJ, Riegger G, Hildebrandt P, et al. The benefits of early combination treatment of carvedilol and an ACE-inhibitor in mild heart failure and left ventricular systolic dysfunction. The carvedilol and ACE-inhibitor remodelling mild heart failure evaluation trial (CARMEN). *Cardiovasc Drugs Ther*. 2004; 18(1): 57–66, doi: [10.1023/B:CARD.000025756.32499.6f](#), indexed in Pubmed: [15115904](#).
 52. Cleland JGF, Pennell DJ, Ray SG, et al. Carvedilol hibernating reversible ischaemia trial: marker of success investigators. Myocardial viability as a determinant of the ejection fraction response to carvedilol in patients with heart failure (CHRISTMAS trial): randomised controlled trial. *Lancet*. 2003; 362(9377): 14–21, indexed in Pubmed: [12853194](#).
 53. Pasternak B, Svanström H, Melbye M, et al. Association of treatment with carvedilol vs metoprolol succinate and mortality in patients with heart failure. *JAMA Intern Med*. 2014; 174(10): 1597–1604, doi: [10.1001/jamainternmed.2014.3258](#), indexed in Pubmed: [25173681](#).
 54. Fröhlich H, Torres L, Täger T, et al. Bisoprolol compared with carvedilol and metoprolol succinate in the treatment of patients with chronic heart failure. *Clin Res Cardiol*. 2017; 106(9): 711–721, doi: [10.1007/s00392-017-1115-0](#), indexed in Pubmed: [28434020](#).
 55. Ajam T, Ajam S, Devaraj S, et al. Effect of carvedilol vs metoprolol succinate on mortality in heart failure with reduced ejection fraction. *Am Heart J*. 2018; 199: 1–6, doi: [10.1016/j.ahj.2018.01.005](#), indexed in Pubmed: [29754646](#).
 56. Patrianakos AP, Parthenakis FI, Mavrakas HE, et al. Comparative efficacy of nebivolol versus carvedilol on left ventricular function and exercise capacity in patients with nonischemic dilated cardiomyopathy. A 12-month study. *Am Heart J*. 2005; 150(5): 985, doi: [10.1016/j.ahj.2005.07.024](#), indexed in Pubmed: [16290981](#).