

# A meta-analysis of the effects of $\beta$ -adrenergic blockers in chronic heart failure

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**Abstract.** Adrenergic  $\beta$ -blockers are drugs that bind to, but do not activate  $\beta$ -adrenergic receptors. Instead they block the actions of  $\beta$ -adrenergic agonists and are used for the treatment of various diseases such as cardiac arrhythmias, angina pectoris, myocardial infarction, hypertension, headache, migraines, stress, anxiety, prostate cancer, and heart failure. Several meta-analysis studies have shown that  $\beta$ -blockers improve the heart function and reduce the risks of cardiovascular events, rate of mortality, and sudden death through chronic heart failure (CHF) of patients. The present study identified results from recent meta-analyses of  $\beta$ -adrenergic blockers and their usefulness in CHF. Databases including Medline/Embase/Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed were searched for the periods May, 1985 to March, 2011 and June, 2013 to August, 2015, and a number of studies identified. Results of those studies showed that use of  $\beta$ -blockers was associated with decreased sudden cardiac death in patients with heart failure. However, contradictory results have also been reported. The present meta-analysis aimed to determine the efficacy of  $\beta$ -blockers on mortality and morbidity in patients with heart failure. The results showed that mortality was significantly reduced by  $\beta$ -blocker treatment prior to the surgery of heart failure patients. The results from the meta-analysis studies showed that  $\beta$ -blocker treatment in heart failure patients correlated with a significant decrease in long-term mortality, even in patients that meet one or more exclusion criteria of the MERIT-HF study. In summary, the findings of the current meta-analysis revealed beneficial effects different  $\beta$ -blockers have on patients with heart failure or related heart disease.

## Introduction

$\beta$ -blockers generally improve the symptoms and reduce the risk of cardiovascular events. However, there is no conclusive definition regarding the most sensitive endpoint for the efficacy of  $\beta$ -blockers in the treatment of chronic heart failure (CHF). A meta-analysis published in 1998 included 18 published double-blind, placebo-controlled, parallel-group trials of  $\beta$ -blockers in 3,023 patients with heart failure, which supported the therapeutic benefits of  $\beta$ -blockers treatment on left ventricular ejection fraction, New York Heart Association (NYHA) functional class, hospital stays and mortality rate (1). The  $\beta$ -blockers showed the most significant effects on ejection fraction and on the combined risk of mortality and hospital stays in patients with heart failure. The ejection fraction was increased by  $\beta$ -blockers by 29% ( $P<10^{-9}$ ). Additionally,  $\beta$ -blockers significantly reduced the combined risk of mortality and hospital stays in patients with heart failure by 37% ( $P<0.001$ ). The two effects remained statistically significant when  $<90\%$  trials were excluded from the analysis, or when a number of trials with a neutral result were added to the analysis (1). By contrast, improvement on the NYHA functional class by  $\beta$ -blockers was of borderline significance ( $P=0.04$ ), which became of no statistical significance when even one moderate-size study was added or removed from the analysis. In addition,  $\beta$ -blockade significantly reduced mortality by 32% ( $P=0.003$ ), although this effect was only moderately strong and varied depending on the type of  $\beta$ -blocker used, i.e., non-selective  $\beta$ -blockers were significantly more effective in reducing mortality risk than  $\beta_1$ -selective agents (49 vs. 18%,  $P=0.049$ ) (1). By contrast, selective and non-selective  $\beta$ -blockers were not significantly different when their clinical efficacy was evaluated using other measures. Therapeutic benefits of  $\beta$ -blockers on ejection fraction and the combined risk of mortality and hospital stays in patients with heart failure were thus identified.

Due to their ability to prevent against adverse effects resulting from sympathetic stimulation on the failing heart (2),  $\beta$ -adrenergic blocking agents have been widely used for the treatment of heart failure, and provided therapeutic benefits to patients in a large number of clinical trials (3,4). These clinical trials varied markedly in sample size and duration, baseline characteristics, and study objectives. In addition, the  $\beta$ -blockers used in these trials varied in selectivity for

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adrenergic receptors and effects on the peripheral blood circulation. The results from the meta-analysis studies on the  $\beta$ -blockers treatment for CHF were assessed.

## Materials and methods

The literature regarding meta-analysis studies was searched from May, 1985 to March, 2011 and June, 2013 to August, 2015, in databases including Medline/Embase/Cochrane Central Register of Controlled Trials (CENTRAL), and PubMed. The results of various publications on meta-analyses were combined from published double-blind, placebo-controlled, parallel-group trials of  $\beta$ -blockers in thousands of patients with heart failure from a variety of investigators and research labs. The odds ratios (ORs) and 95% confidence intervals (CIs) were presented from a number of meta-analysis studies of patients with heart failure.

**Statistical analysis.** Statistical analysis was conducted using the fixed-effect by (Mantel and Haenszel) and random-effect methods (6). The patients were regarded as a single unit of analysis to investigate the therapeutic benefits of  $\beta$ -blockers on SCD, CVD, and all-cause mortality. Similar results were obtained using either method, but only the random-effect results were reported. The efficacy was determined by odds ratios (ORs) with a 95% confidence interval (CI). The heterogenic nature of the trials was evaluated using the  $\chi^2$  test (6). The  $\chi^2$  test values of 25, 50 and 75% were defined as low, moderate, and high levels of heterogeneity, respectively (7). The results from the meta-analysis were documented only in the case of the  $\chi^2$  value being <75%. The sensitivity analysis was conducted for each outcome measure to evaluate the contribution of each trial to the total estimate by removing single trials one at a time and performing the analysis based on the remaining trials. The statistical analysis was conducted in a two-tailed manner.  $P < 0.05$  was defined as statistically significant. The data were processed utilizing RevMan software (version 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

## Results and Discussion

**Meta-analysis of  $\beta$ -blockers.** In the meta-analysis by Lechat *et al* (1), 18 trials that included 3,023 patients with heart failure, with 1,305 treated with placebo and the remaining 1,718 patients with a  $\beta$ -blocker were reported. Of these patients, 1,513 patients had heart failure due to idiopathic dilated cardiopathy while 1,445 patients had heart failure due to ischemic heart disease (IHD). Most of the patients were taking diuretics, digitalis and an angiotensin-converting enzyme (ACE) inhibitor and exhibited NYHA class II or III symptoms. Only  $\leq 5\%$  patients had class IV symptoms, and class I patients were included in only two trials. The mortality rate for patients receiving placebo was 11.9% (156 deaths in 1,305) compared to 7.5% for patients receiving  $\beta$ -blocker (130 deaths in 1,718), indicating that the  $\beta$ -blocker significantly reduced the risk of death [95% CI, 12-47%,  $P = 0.003$  (Peto's method)]. When hospitalization was compared, 223 hospitalizations were reported from the placebo group (17.1%) and 166 from the  $\beta$ -blocker group

(9.6%), suggesting that the  $\beta$ -blocker significantly reduced the risk of hospitalization ( $P < 0.001$ ). We combined morbidity and mortality and the results showed that 25.4% patients in the placebo group died or were hospitalized while only 239 such events occurred in the  $\beta$ -blocker groups (16.0%). This result showed that the  $\beta$ -blocker treatment was associated with a 37% reduction in risk (95% CI, 24-49%),  $P < 0.001$ .

By contrast, the patients treated with  $\beta$ -blocker were 32% more likely to show improvement in NYHA class ( $P = 0.04$ ) and 30% less likely to experience worsening of NYHA class ( $P = 0.03$ ). Patients in the placebo group presented with a mean unweighted value for left ventricular ejection fraction of  $0.23 \pm 0.04$  compared with  $0.31 \pm 0.04$  in the  $\beta$ -blocker groups, suggesting a significant increase in ejection fraction by  $\beta$ -blockers ( $P < 10^{-9}$ ). Based on the assumption that the duration of treatment was the same as the mean follow-up (7 months), it was calculated that 38 patients required treatment to prevent 1 case of death, 24 patients to prevent 1 case of hospitalization for heart failure, and 15 patients to prevent 1 combined endpoint. The present findings also suggest that  $\beta$ -blockers probably improved survival and correlated with relatively fewer lethal events. However, the fact that selective and non-selective  $\beta$ -blockers showed different effects on mortality suggested that future studies are required before a conclusion on the ability of  $\beta$ -blockers to improve survival are created. In addition, novel information was obtained from a few ongoing trials of selective (CIBIS II and MERIT) and non-selective (BEST and COPERNICUS)  $\beta$ -blockers. A meta-analysis of randomized controlled trials on  $\beta$ -blockers in the prevention of sudden cardiac death (SCD) in patients with heart failure has been conducted by Al-Gobari *et al* (5).

In many studies,  $\beta$ -blockers have been shown to decrease SCD in HF patients, whereas other studies have shown mixed results. The results of several studies of large randomized control trials of  $\beta$ -blockers have been previously reported (3). The new findings have been summarized in a systematic review that currently presents available data on the use of  $\beta$ -blockers. A meta-analysis was also performed to analyze randomized controlled trials comparing the efficacy of  $\beta$ -blockers in the prevention of SCD in patients with heart failure (2). In a total of 30 trials, 24,779 patients were randomized to receive  $\beta$ -blocker or placebo/control. The study was performed following the preferred reporting items for systematic reviews and meta-analysis guidelines. The eligible studies presented an analysis on the incidence of SCD in patients with heart failure. Further inclusion criteria were: therapeutic regimen  $> 30$  days and follow-up time period of  $> 3$  months. Any studies that recruited patients  $< 8$  years, randomization to  $\beta$ -blocker versus an ACE (without placebo) and/or  $\beta$ -blocker in both arms were excluded from the analysis. The pre-defined markers comprised SCD, cardiovascular death (CVD), and all-cause mortality. In addition, these pre-defined markers were studied according to intention-to-treat. The analysis results suggested that the use of  $\beta$ -blockers was associated with significantly fewer cases of SCD, CVD and all-cause mortality. Therefore, according to data analysis, the number of patients required to receive  $\beta$ -blocker to avoid 1 case of SCD was 43, the number to avoid 1 case of CVD was 26 and the number to avoid all-cause mortality over a 12-month period was 21. Treatment with  $\beta$ -blockers decreased the risk of SCD by 31%, CVD by 29%

Table I. Randomized trials of  $\beta$ -blockers for the prevention of sudden cardiac death.

Authors (year)	No. of patients	Name of drug	Comparator	Daily maintenance dose	Follow-up	Jaded (reference) patients of (months) scoring (mg)	Refs.
Anderson <i>et al</i> (1985)	50	Metoprolol	Control	61	19	3	(8)
Beta-Blocker Evaluation of Survival Trial Investigators (2001)	2,708	Bucindolol	Placebo	152	24	5	(11)
No authors listed (1997)	415	Carvedilol	Placebo	12.5	19	4	(12)
Chadda (1986)	3,837	Propranolol	Placebo	180/240	25	5	(13)
Bristow <i>et al</i> (1994)	139	Bucindolol	Placebo	12.5/50/200	3	5	(14)
Bristow <i>et al</i> (1996)	345	Carvedilol	Placebo	12.5/25/50	6	5	(15)
Dargie (2001)	1,959	Carvedilol	Placebo	50	15.6	5	(16)
No authors listed (1999)	2,647	Bisoprolol	Placebo	10	15	5	(17)
No authors listed (1994)	641	Bisoprolol	Placebo	5	23	5	(18)
Witchitz <i>et al</i> (2000)	124	Celiprolol	Placebo	100	12	5	(19)
Colucci <i>et al</i> (1996)	366	Carvedilol	Placebo	100	15	5	(20)
Packer <i>et al</i> (2002)	2,289	Carvedilol	Placebo	50	10.4	5	(21)
de Milliano <i>et al</i> (2002)	59	Metoprolol	Placebo	150	6	5	(22)
Conraads <i>et al</i> (2012)	116	Nebivolol	Placebo	5/10	6	5	(23)
Engelmeir <i>et al</i> (1985)	25	Metoprolol	Placebo	92	12	4	(24)
Fisher <i>et al</i> (1994)	50	Metoprolol	Placebo	87	6	5	(25)
Hansteen <i>et al</i> (1982)	560	Propranolol	Placebo	160	12	5	(26)
Krum <i>et al</i> (1995)	49	Carvedilol	Placebo	50	4	5	(27)
Waagstein <i>et al</i> (1993)	383	Metoprolol	Placebo	108/115	18	3	(28)
No authors listed (1999)	3,991	Metoprolol	Placebo	159/170	12	5	(29)
Metra <i>et al</i> (1994)	40	Carvedilol	Placebo	50	4	4	(30)
Olsen <i>et al</i> (1995)	60	Carvedilol	Placebo	81	4	5	(31)
Packer <i>et al</i> (1996)	1,094	Carvedilol	Placebo	60	6	5	(32)
Pollock <i>et al</i> (1990)	19	Bucindolol	Placebo	200	3	4	(33)
No authors listed (2000)	426	Metoprolol	Placebo	156	6	5	(34)
Flather <i>et al</i> (2005)	2,128	Nebivolol	Placebo	7.7	21	5	(35)
Sturm <i>et al</i> (2000)	100	Atenolol	Placebo	89	24	5	(36)
Uhlir <i>et al</i> (1997)	91	Nebivolol	Placebo	2.5/5	3.5	5	(37)
Wisnibaugh <i>et al</i> (1993)	24	Nebivolol	Placebo	5	3	5	(38)
Woodley <i>et al</i> (1991)	50	Bucindolol	Placebo	175	3	5	(39)

and all-cause mortality by 33%. These results confirmed the mortality benefits of  $\beta$ -blocker drugs, which should be recommended to all heart patients similar to those included in these trials. The features of trials and study quality are listed in Table I (5), and included 30 randomized controlled trials of  $\beta$ -blocker with a total of 24,779 cardiac patients.

After the Medline database and the Cochrane Library were searched, 441 studies were chosen to be reviewed according to the inclusion and exclusion criteria. Of these studies, 361 were excluded for the following causes: non-randomized study (n=349), lack of placebo or inactive control group (n=11), and enrollment of patients <18 years (n=1). The full texts of the remaining 81 articles were obtained for further review. Based on the detailed review, another 51 trials were excluded due to the following reasons: absence of placebo or control (n=9), duplicate report or substudy (n=16), absence of a  $\beta$ -blocker arm (n=10), outcome of no interest (n=15) and use of

$\beta$ -blockers in both arms (n=1). For features of studies (Table I), the mean follow-up time was 11.51 months (0.96 year) and all but one trial was placebo-controlled (8). The Jadad scoring was utilized (9). The trials were scored between 3 and 5, suggesting high quality. The studies were analyzed following the intention-to treat paradigm. The risk of SCD was most prominent in heart failure patients who had absolute risk of SCD in 1 year between 4 and 13% (10).

A randomized trial was conducted to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure [Al-Gobari *et al* (5)]. For the efficacy of  $\beta$ -blockers, 3,764 cases of death were reported in the 24,779 patients included in the present analysis, comprising 1,597 SCDs. The SCD incidence was 5.27% (n=673/12,768) in the  $\beta$ -blocker group relative to 7.69% (n=924/12,011) in the placebo/control group (P<0.00001). The cardiovascular mortality rate was 10.84% (n=1,236/11,398)

in the  $\beta$ -blockers group and 14.86% ( $n=1,585/10,666$ ) in the placebo/control group ( $P<0.00001$ ). The all-cause mortality rate was 12.82% ( $n=1,626/12,678$ ) in the  $\beta$ -blockers group and 17.80% ( $n=2,138/12,011$ ) in the placebo/control group ( $P<0.00001$ ) (5). According to the present analysis, the number of patients required to receive  $\beta$ -blocker to avoid 1 case of SCD was 43, the number to avoid 1 case of CVD was 26 and the number to avoid all-cause mortality in a year was 21. The forest plot comparison in SCD and all-cause mortality was performed between the  $\beta$ -blockers and placebo groups. The  $\chi^2$  value was relatively low in SCD, CVD, and all-cause mortality (0, 20 and 43%, respectively). In this meta-analysis of 24,779 randomized patients, the  $\beta$ -blockers were effective in preventing SCD, CVD, and all-cause mortality. A majority of patients with severe congestive heart failure combined with ventricular arrhythmias, including non-sustained ventricular tachycardia (4). As anti-arrhythmic agents,  $\beta$ -blockers treatment is associated with reduced morbidity and mortality in patients with CHF, and a markedly decreased risk of SCD. However, results from the present meta-analysis revealed a 32% decrease in SCD risk. As mentioned previously, the absolute risk of SCD within 1 year in patients with heart failure was 4-13% (10). In the present study, the 1-year absolute risk of SCD in the  $\beta$ -blocker and placebo/control groups was 5.5 and 8.10%, respectively. The mortality rates increased in the higher (NYHA) class, but the percentage of patients succumbing to heart failure (rather than from progressive pump failure) was highest in those with less severe HF (NYHA class II or III) (MERIT-HF) (29). It is well known that  $\beta$ -blockers decrease overall and cardiovascular mortality in heart failure patients. A meta-analysis was performed to analyze their effect on sudden death, their efficacy, and whether there was any difference between vasodilating and non-vasodilating agents (40). Randomized, clinical trials were reviewed to evaluate a  $\beta$ -blocker without intrinsic sympatho-mimetic activity. The trials comprised a control group treated with a placebo or standard treatment, and mortality was appreciated on an intention-to-treat basis, and documented for  $\geq 8$  weeks. In total, 21 trials with 5,849 patients (3,130 receiving  $\beta$ -blockers) were reviewed in the meta-analysis. The median length of treatment was 6 months. The majority of patients had mild or moderate heart failure and were treated with angiotensin-converting enzyme inhibitors, diuretics, and digitalis. The  $\beta$ -blockers significantly reduced overall mortality, cardiovascular mortality, and mortality due to pump failure and sudden death by 34-39%. The decrease in overall mortality in patients with IHD (30%) was no different from that among patients with non-IHD (26%) ( $P=0.08$ ). The reduction in overall mortality was greater with vasodilating than with non-vasodilating agents (45 vs. 27%;  $P=0.007$ ), particularly in patients without IHD (62%), compared with those with IHD (22%;  $P=0.03$ ) (40). The vasodilating  $\beta$ -blockers showed a greater effect on overall mortality than the non-vasodilating agents, particularly in patients with non-IHD.  $\beta$ -blockers generically available are subclassified and based on selective aspects of their action and include: acebutolol, bisoprolol, metoprolol, nadolol, propranolol, and timolol. The safety and effects of the  $\beta$ -blocker, nadolol, have been suggested in mild asthma by an open-label pilot study (41).  $\beta$ -blockers are currently applied with care in asthma patients because

their acute administration may be associated with worsening broncho-spasm. However, their effects and safety are yet to be adequately evaluated. The use of  $\beta$ -blockers in congestive heart failure is successful, despite previously recorded acute detrimental effects (7). However  $\beta$ -blockers have been shown to reduce mortality with their chronic use. Certain  $\beta$ -blockers are safe and useful in chronic asthma therapy. In such cases, open-label, pilot studies, were conducted to determine the safety and effects of escalating doses of the  $\beta$ -blocker, nadolol, administered  $>9$  weeks to 10 subjects with mild asthma. The dose escalation was performed on a weekly basis based on pre-determined safety lung function, asthma control, and hemodynamic parameters. The safety and effects of  $\beta$ -blockers on airway hyper-responsiveness, and indices of respiratory function have been described (6). Nadolol was effective in the cases of asthma. In 80% of tested patients, 9 weeks of treatment with nadolol resulted in a significant increase in PC20 in a dose-dependent manner, which reached 2.1-doubling doses at 40 mg ( $P<0.0042$ ). In addition, a dose-independent 5% reduction in mean FEV1 was found over the study period ( $P<0.01$ ). It was shown that in most patients with mild asthma, the dose-escalating administration of the  $\beta$ -blocker, nadolol, was well-tolerated and provided therapeutic benefits on airway hyper-responsiveness. These results suggest more testing of the drugs in large-scale studies.

Recently, Laroche *et al* described the role of  $\beta$ -blockers in hypertension in a meta-analysis of studies spanning over several years (42). The  $\beta$ -blockers are among the most commonly used drugs in the treatment of hypertension. After 45 years of studies their initial indication for hypertension has been questioned based on evidence from the meta-analyses of clinical trials. The  $\beta$ -blocker class consists of various agents with many pharmacokinetic and pharmacodynamic properties including lipo- and hydrophilicity, duration of action, intrinsic sympathomimetic activity, vasodilation, and metabolism linked to genetic polymorphisms (32).  $\beta$ -blockers are also used for cardiovascular conditions such as angina, pain in heart, rate control of atrial fibrillation, CHF, and after myocardial infarction (MI), and other indications such as migraine and essential tremor. Over 17 large-scale trials influencing the recommendations on the use of  $\beta$ -blockers in the treatment of hypertension are available (37).  $\beta$ -blockers have been used as a first-line treatment option for patients  $<60$  years of age, and are based on evidence from these large trials, which were supported by two of the meta-analyses. Matowa studied the use of  $\beta$ -blockers in patients of cardiac failure (43). A retrospective observational study was conducted by reviewing medical records (38). A total of 385 cardiac failure cases was included. The medical records of hospitalised patients for cardiac failure at the study center were abstracted. The results showed that 36 (9.4%) patients were prescribed with  $\beta$ -blockers and 7 patients had their  $\beta$ -blocker substituted for another. Atenolol, propranolol and carvedilol were prescribed to 30 (7.8%), 7 (1.8%), and 6 (1.6%) patients, respectively. Metoprolol and bisoprolol were not administered at all. More female (57.9%) than male (42.1%) subjects were included. The mean age was 41.9 (standard deviation, 24.0). The prevalence of hospital stay due to cardiac failure was 1.54%. It was concluded that the use of  $\beta$ -blocker was not common. Therefore, this evidence-based treatment regimen for managing cardiac failure in patients



from Zimbabwe, Africa, should be stressed. In a recent study, Bangalore *et al* analyzed the clinical outcomes of  $\beta$ -blockers for MI (44). Randomized trials including  $\geq 100$  subjects were mined from Medline/Embase/CENTRAL to assess the role of  $\beta$ -blockers in MI. All-cause mortality was defined as the primary outcome. The analysis was conducted by stratifying studies into reperfusion-era or pre-reperfusion-era trials. The results were obtained from 60 studies comprising 102,003 patients who met the inclusion criteria. In the acute MI studies, a significant interaction (Pinteraction, 0.02) was noted.  $\beta$ -blockers reduced mortality in the pre-reperfusion era [incident rate ratio (IRR), 0.86; 95% CI: 0.79-0.94] but not in the reperfusion era (IRR, 0.98; 95% CI: 0.92-1.05). In the pre-reperfusion era (IRR, 0.72; 95% CI: 0.62-0.83) [number needed to treat to benefit (NNTB)],  $\beta$ -blockers reduced cardiovascular mortality (IRR, 0.87; 95% CI: 0.78-0.98), MI (IRR, 0.78; 95% CI: 0.62-0.97), and angina (IRR, 0.88; 95% CI: 0.82-0.95), with no difference for other outcomes. In the reperfusion era,  $\beta$ -blockers reduced MI (NNTB=209) and angina (IRR, 0.80; 95% CI: 0.65-0.98) (NNTB=26) at the expense of increase in heart failure (IRR, 1.10; 95% CI: 1.05-1.16) [number needed to treat to harm (NNTH)=79], cardiogenic shock (IRR, 1.29; 95% CI: 1.18-1.41) (NNTH=90), and drug discontinuation (IRR, 1.64; 95% CI: 1.55-1.73), with no benefit for other outcomes. The benefits for recurrent MI and angina in the reperfusion era appeared to be short term (30 days). It was concluded that in the current regimen of treatment of MI,  $\beta$ -blockers do not provide clinical benefits on mortality but prevent recurrent MI and angina (short-term) with increase in heart failure, cardiogenic shock, and discontinuation of drug.

A recent meta-analysis was performed on  $\beta$ -blockers and their role in heart failure with preserved ejection fraction (HFpEF) (45).  $\beta$ -blockers are well known as drugs used for the care of heart failure; however, their role in HFpEF is not known. Thus, a meta-analysis was performed to evaluate the efficacy of  $\beta$ -blockers on mortality and morbidity in HFpEF patients. A systematic mining in PubMed, Embase, Scopus and Cochrane databases was conducted to locate the relevant trials on  $\beta$ -blockers and HFpEF. A random-effects model was performed to evaluate the effect of  $\beta$ -blockers on all-cause mortality and hospitalization due to HF. A total of 27,099 patients from 15 observational studies and two randomized control trials were included in the analysis. The  $\beta$ -blocker treatment significantly correlated with lower all-cause mortality. However, no change in HF hospitalization was found. In the two RCTs,  $\beta$ -blocker treatment did not result in significantly lower all-cause mortality or HF hospitalization ( $P>0.05$ ). These results were consistent with geographic region (USA versus rest of world) and ejection fraction subgroups. The subgroup analysis revealed that the beneficial survival effect of  $\beta$ -blocker was limited to studies with subjects of mean age  $<75$  years. The observational studies showed a significant benefit from the use of  $\beta$ -blockers for all-cause mortality, but not for HF hospitalization. The  $\beta$ -blockers in the two RCTs were not associated with a significant reduction in all-cause mortality or HF hospitalization, but the two trials were not adequately powered and had high loss to follow-up rates.

The benefit of  $\beta$ -blockers on prostate cancer mortality has been analyzed in a meta-analysis study of 16,825 patients (46).

The results suggested that  $\beta$ -blocker treatment correlated with decreased mortality in patients with prostate cancer. Data mining was performed from Medline (from 1 January 1966) and Embase (from 1 January 1974), through 10 September 2014, and the reference lists of pertinent articles were also located. The investigators independently screened and reviewed the eligibility of each study. The primary outcomes were defined as prostate cancer-specific mortality and all-cause mortality. The meta-analysis was conducted on the base of 4 studies including 16,825 patients. The results revealed that  $\beta$ -blocker treatment correlated with decreased prostate cancer-specific mortality without any heterogeneity between studies ( $Q=3.59$ ,  $I^2=16.5\%$ ,  $P=0.309$ ). No correlation with all-cause mortality (hazard ratio = 0.97, 95% CI: 0.90-1.04) was found. There was no significant heterogeneity between the 4 studies ( $Q=2.48$ ,  $I^2=0.0\%$ ,  $P=0.480$ ). The analysis indicated that  $\beta$ -blocker use was associated with reduced cancer-specific mortality among prostate cancer patients taking  $\beta$ -blocker drugs. Use of  $\beta$ -blockers improves and protects the condition of heart patients from heart failure, hypertension, cardiac arrhythmias, angina pectoris (pain in heart), glaucoma of eyes, headache and migraines, stress and anxiety as well as prostate cancer (42). The meta-analysis studies also indicated that  $\beta$ -blockers preserved ejection fraction in heart failure patients. Andrews *et al* conducted a meta-analysis to determine the efficacy of digoxin, verapamil, and  $\beta$ -adrenoceptor blockers as prophylaxis against supraventricular arrhythmias (SVAs) after coronary artery bypass graft surgery (CABG) (47). Randomized control trials were performed and 24 of 69 identified studies were included in the final analysis. The OR of developing SVAs after CABG in the treatment versus control groups was calculated. The pooled mean ventricular rate during SVA in patients who developed arrhythmia was also calculated. The digoxin and verapamil did not reduce the likelihood of SVAs after CABG (digoxin: OR, 0.97, 95% CI: 0.62-1.49; verapamil: OR, 0.91, 95% CI: 0.57-1.46). The likelihood of developing SVA in patients treated with  $\beta$ -blockers was markedly decreased compared with the controls (OR, 0.28; 95% CI: 0.21-0.36). The pooled ventricular rate when SVAs occurred was significantly decreased in each of the treatment groups. The prophylactic  $\beta$ -adrenoceptor blockers showed a protective effect against the development of SVAs in a selected population of patients undergoing CABG. However, no such beneficial effect was observed for digoxin or verapamil. The ventricular rate was reduced with all 3 agents in patients who developed the arrhythmia, although the ventricular rate reduction was not optimal clinically.

*Recent advances in adrenergic  $\beta$ -blockers and CHF.* To evaluate the efficacy of  $\beta$ -blockers in patients with heart failure and impaired ejection fraction, a network meta-analysis was performed (48). Data were mined from CINAHL (1982-2011), CENTRAL (1985-2011), Embase (1980-2011), Medline/PubMed (1966-2011), and Web of Science (1965-2011). Randomized trials that compared  $\beta$ -blockers with other  $\beta$ -blockers or other treatments were included. Data extraction was performed and the cause of death at the longest available follow-up was defined as the primary endpoint. The data were analyzed with ORs and Bayesian random effect 95% credible intervals, with independent extraction by

observers. A total of 21 trials were included and  $\beta$ -blockers including atenolol, bisoprolol, bucindolol, carvedilol, metoprolol, and nebivolol, were used. When compared with placebo or standard treatment after a median of 12 months,  $\beta$ -blockers showed significant beneficial effects (OR, 0.69, 95% CI: 0.56-0.80). However, when the different  $\beta$ -blockers were compared head-to-head for the risk of death, SCD, death due to pump failure, or drug discontinuation, no significant difference was revealed. Improvements in left ventricular ejection fraction were also similar irrespective of the individual drug studied. The beneficial effects of  $\beta$ -blockers in patients with heart failure and impaired ejection fraction was mainly because of a class effect, as no statistics from currently available trials evidenced the advantage of any single agent over other treatments. Ma *et al* conducted a meta-analysis on the correlation between  $\beta$ 1-adrenergic receptor gene Arg389Gly polymorphism and risk of heart failure in humans (49). The studies were mined from the PubMed, Embase, and China National Knowledge Infrastructure databases and two reviewers independently evaluated the studies. The 6 case-control studies with a total of 1,736 participants were included in the meta-analysis, including 882 cases with heart failure and 854 controls. The results showed no association between Arg389Gly polymorphism and heart failure. No publication bias was identified (all  $P > 0.05$ ).

The  $\beta$ 1-adrenergic receptor gene Arg389Gly polymorphism may not be associated with heart failure risk. Large-scale and well-designed studies are required to support these results. In a recent meta-analysis the role of  $\beta$ -adrenergic blockers in reducing perioperative cardiac risk in patients experiencing vascular surgery was investigated (50). This class of drugs may reduce the risk of perioperative cardiac complications in individuals experiencing major non-cardiac vascular surgery. The Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator searched the Specialised Register (January 2014) and the CENTRAL (issue 12, 2013). The databases were mined and reference lists were reviewed for relevant studies. The study included prospective, randomized controlled trials of perioperative  $\beta$ -blockers of subjects  $>18$  years experiencing non-cardiac vascular surgery. The two review authors independently carried out study identification and data extraction. The meta-analysis was carried out with a fixed-effect model with ORs and 95% CIs. The results from two double-blind, randomized controlled trials comparing perioperative effects of  $\beta$ -blockers (metoprolol) with placebo, on cardiovascular outcomes in subjects experiencing major non-cardiac vascular surgery were analyzed. A total of 599 subjects were included to be treated with  $\beta$ -blockers (301 subjects) or placebo (298 subjects). The outcomes were revealed only in a single study and neither of the studies reported on vascular patency/graft occlusion, which decreases the quality of evidence to moderate. There was no evidence to indicate that perioperative  $\beta$ -adrenergic blockade reduced all-cause mortality, cardiovascular mortality, non-fatal MI, arrhythmia, heart failure, stroke, composite cardiovascular events or re-hospitalisation at 30 days. However, there was strong evidence that  $\beta$ -adrenergic blockers increased the odds of intra-operative bradycardia (OR, 4.97, 95% CI: 3.22-7.65;  $P < 0.00001$ ) and intra-operative hypotension (OR,

1.84, 95% CI: 1.31-2.59;  $P = 0.0005$ ). The meta-analysis did not strongly support that perioperative  $\beta$ -blockers improve postoperative cardiac morbidity and mortality in subjects experiencing major non-cardiac vascular surgery. However,  $\beta$ -blockers provided some therapeutic benefits in patients with heart failure and reduced ejection fraction according to the recent network of meta-analysis.

In conclusion, results of the meta-analysis studies have shown a marked decreased in the incidence of overall mortality, cardiovascular mortality, and sudden death by 34-39%.  $\beta$ -blockers reduced mortality in patients with IHD by 30%, which was not significantly different compared to non-IHD patients (26%) ( $P = 0.08$ ). The reduction in mortality was greater with vasodilating than with non-vasodilating agents (45 vs. 27%;  $P = 0.007$ ), particularly in patients without IHD (62%), compared with those with IHD (22%;  $P = 0.03$ ) (40). The  $\beta$ -blockers with vasodilating effects demonstrated a better efficacy on reducing mortality than the non-vasodilating agents, especially in non-IHD patients. In a meta-analysis study, the results did not support that perioperative treatment with  $\beta$ -blockers correlated with decreased postoperative cardiac morbidity and mortality in individuals experiencing major non-cardiac vascular surgery. The effects of  $\beta$ -blockers on heart failure patients with impaired ejection fraction was primarily because of a class effect, since no statistics from present studies supported the advantage of any single agent over other agents.

In summary, the findings of the meta-analyses have shown that  $\beta$ -blockers preserved ejection fraction in heart failure patients. The  $\beta$ -blockers reduced MI, angina, heart failure, and cardiogenic shock. The effects for recurrent MI and angina in the reperfusion era cannot last for long (only 30 days). The use of  $\beta$ -blockers is therefore useful in controlling heart failure.

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