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Research Article

# Beta-Blockers for Primary Prevention of Anthracycline-Induced Cardiac Toxicity: An Updated Meta-Analysis of Randomized Clinical Trials

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*Aim*. Cardiotoxicity is a well-recognized complication of chemotherapy with Anthracyclines. However, results from trials evaluating beta-blockers for prevention are controversial. Therefore, we performed a meta-analysis to find whether prophylactic administration of beta-blockers can help prevent Anthracyclines-induced cardiotoxicity. *Methods*. We assessed randomized trials and observational studies where a prophylactic intervention was compared with a control arm in patients with a normal left ventricular ejection fraction (LVEF) receiving Anthracyclines. The primary outcome was EF reduction. The secondary outcome was the development of Cancer Therapeutics–Related Cardiac Dysfunction (CTRCD), defined as a decrease in the LVEF of >10% to a value of <53%. *Results*. We included 17 trials comprising 1291 patients (671 patients in the intervention arm and 620 in the control arm). Carvedilol was administered in eight studies, and others used bisoprolol, metoprolol, or nebivolol. Compared with baseline, LVEF reduced in both intervention and control groups after chemotherapy (MD = −1.93%, 95% CI: -2.94, -0.92, $p = 0.001$, $I^2 = 72.1\%$ vs. MD = −4.78%, 95% CI: -6.51, -3.04, $p = 0.001$, $I^2 = 91.6\%$, respectively). LVEF was less reduced among the beta-blocker receivers (MD = 3.44%, 95% CI: 1.41–5.46, $p = 0.001$, $I^2 = 94.0\%$). Among the eight studies reporting the incidence of CTRCD, 45 out of 370 participants in the intervention arm and 54 out of 341 in the control arm were reported to experience this complication (RR = 0.76; 95% CI: 0.53,1.09; $I^2 = 24.4\%$; $p = 0.235$). *Conclusion*. Treatment with beta-blockers prevents dilatation of the left ventricle, development of diastolic dysfunction, and reduction of LVEF. However, these hemodynamic effects do not translate into a significant reduction in CTRCD incidence and prevention of hospitalization for heart failure or cardiac death.

## 1. Introduction

Treatment with anthracyclines, a potent family of antineoplastic agents, has increased the survival rate of many cancerous patients, especially those with breast cancer and hematologic malignancies. However, this effect is at the expense of dose-related cardiotoxicity [1]. The incidence of heart failure (CHF) increases with the cumulative doxorubicin doses, and a dosage of 400, 500, and 550 mg/m$^2$ results in 5%, 16%, and 26% CHF incidence rates, respectively [2]. Several strategies for the primary prevention of anthracycline-induced cardiotoxicity have been implemented. These have mainly focused on either the reduction of cardiotoxicity potency (using a less cardiotoxic derivative, continuous infusion, or liposomal encapsulation) or the administration of cardioprotective agents (dexrazoxane, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or beta-blockers) [3, 4]. Beta-

measure the LA maximum volume and peak TR velocity indices. Notably, the result attained for the e' index was positive and that attained for the E/e' parameter was negative. Hence, specific conclusions can be made using these results. Therefore, we recommend that future studies should include all relevant parameters.

Our pooled analyses showed that 45 out of 370 participants in the intervention arm and 54 out of 341 participants in the control arm (from eleven studies) developed with CTRCD defined as a dramatic (more than 10%) reduction in LVEF (RR = 0.76; 95% CI: 0.53,1.09; $I^2 = 24.4\%$; $p = 0.235$). This finding does not accompany the beneficial finding of beta-blocker therapy on cardiac function indices such as LVEF. In fact, it needs to be clarified whether beta-blockers only impose beneficial hemodynamic effects or they may implement protective effects on the cardiac myocytes [4]. CTRCD has multifactorial pathophysiology. One of the key contributors is oxidative stress, caused by the generation of free-radical oxygen species due to interactions between doxorubicin and nicotinamide adenine dinucleotide dehydrogenase. As a result of oxidative stress, the integrity of the membranes of the cell and mitochondria is compromised, leading to myocardial cell injury and death. In an emerging theory, topoisomerase 2b inhibition has been implicated in the process of inducing the apoptosis of the cardiomyocytes [4]. Future experimental studies are needed to see if beta-blockers can affect any of these cascades, if true myocardial preservation happens or if just modification of the hemodynamic system is observed.

Our study had some limitations. Primarily, the review was limited to adult patients considering the variations between the adult and pediatric populations. The chief limitation, however, is the heterogeneous nature of the primary pooled data. This is a result of variations in methodology as well as differences in patient characteristics, including the breast cancer type/stage, level of immunocompetence, volume status, cardiovascular risk factors, underlying LV dysfunction, comorbidities, compliance, and disease predisposition. There is also unavoidable variability in the measurement techniques in the studies as the measured outcomes of echocardiograms are device dependent and subject to interobserver variability. Finally, we should also mention the fairly short (mean: 6 months) follow-up periods of the trials. Consequently, the rates of clinical events are very low, and the comparisons are weakened.

## 5. Conclusions

It can be concluded that treatment with beta-blockers has a statistically significant benefit in preventing a decline in cardiac systolic and diastolic function during anthracycline therapy which does not translate into a clinically significant reduction of the incidence of CTRCD, and in the prevention of hospitalization for heart failure or cardiac death. Therefore, routine administration of these medications for primary prevention of CTRCD cannot be recommended. Future investigations on selected high-risk populations, such as those with borderline primary LVEF or those receiving very high dosages of anthracyclines with a long duration of follow-up, are needed to see if these populations can gain a clinical benefit from such interventions or not.

## Data Availability

Data will be available based on request from the corresponding author.

## Ethical Approval

This study has been ethically approved by local ethical committee of Shiraz University of Medical Sciences.

## Conflicts of Interest

All authors declare that they do not have any conflict of interest.

## Authors' Contributions

A.A. was assigned in conception of the study. A. A. and A.K. were responsible for the design of the study. A. K., A.KB., M. S., M. H., and F.A. were assigned in data analysis. A. A. and A.K were assigned in data interpretation. A. A., A.K., A.KB., M. S., M. H., and F.A were responsible for writing initial draft. A. A., A.K., A.KB., M. S., M. H., F. A., and P.S. were charged in critical revision. final approval: A. A., A.K., A.KB., M. S., M. H., F. A., and P.S. were tasked in final approval.

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## Supplementary Materials

*Supplementary 1*. PRISMA 2020 Checklist.

*Supplementary 2*. Supplementary Figure 1: forest plot of LVEF difference between both group at the end of the studies. Supplementary Figure 2: results of analysis of each study effect on pooled LVEF in beta-blocker receivers. Supplementary Figure 3: forest plots of mortality, development of cardiomyopathy, hospitalization, and development of heart failure. Supplementary Figure 4: forest plot of risk of developing pathologic troponin level. Supplementary Figure 5: forest plot mean difference (MD) and 95% confidence interval (CI) of BNP in intervention and placebo arms at the end of the study. Supplementary Figure 6: meta-analysis of echocardiographic parameters.

## References

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