Meta-Analysis Comparing Usefulness of Beta Blockers to Preserve Left Ventricular Function During Anthracycline Therapy

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The purpose of this analysis was to evaluate the cardioprotective benefit of β blockers in preventing anthracycline-induced cardiotoxicity (AIC) in breast cancer patients. Anthracyclines are the cornerstone treatment for breast cancer. Yet, their use has declined in the last decade due to associated AIC. Although β blockers may protect left ventricular (LV) function, previous trials were underpowered with equivocal results. The authors systematically searched online databases through August 2018 for studies evaluating effectiveness of β blockers in preventing AIC in breast cancer patients. We analyzed 9 studies including 771 patients. Data on converting-enzyme inhibitors, trastuzumab, or other malignancies were excluded. The primary outcome was comparison of postchemotherapy LV ejection fraction (LVEF) between β blocker and placebo. Secondary outcomes were changes in global longitudinal strain, LV end-diastolic diameter (LVEDD), and diastolic function parameters, as assessed by 2D echocardiogram and MRI. The mean pre-chemotherapy LVEF was >60% in all studies. Our pooled analysis demonstrated significantly higher LVEF postchemotherapy in the β blocker group in comparison to placebo: mean difference −3.84 with 95% confidence interval [−(6.19 to 1.48) p = 0.001]. The absolute change in EF also favored β blockers: mean difference −3.66 with 95% confidence interval [−(6.20 to 1.12) p = 0.005]. Diastolic function, global longitudinal strain, and LVEDD were also preserved by β blockers, but only LVEDD reached statistical significance. In conclusion, this study suggests that β blockers during anthracycline chemotherapy may prevent cardiotoxicity by preserving LV function. **(Am J Cardiol 2019;124:789−794)**

Abbreviations: BB, Beta Blocker; LVEDD, Left Ventricular End-Diastolic Diameter; GLS, Global Longitudinal Strain; E/A, Mitral Inflow Velocity; E/e', Ratio of Peak Early Diastolic Transmitral Velocity to Mitral Annular Velocity

Breast cancer is the most common cancer in women and is a major public health concern worldwide, with an estimated 1.7 million cases and 521,900 deaths in recent years.[1] Although the occurrence of breast cancer is pervasive, mortality rates have declined due to improved treatment and early detection.[2] Anthracycline is the mainstay chemotherapy in the treatment of breast cancer, with more than 80% of patients receiving an anthracycline-based chemotherapy regimen.[3] In the 1960s, cardiotoxicity was recognized as a side effect of anthracycline that results in left ventricular (LV) dysfunction, often with overt heart failure (HF).[2,4] This is attributable to oxidative stress and activation of apoptotic pathways that result in myocardial injury and cell death.[2,5] Decline in left ventricular ejection fraction (LVEF) may occur with even minimal exposure of 150 mg/m^2 and deteriorates exponentially with accumulating anthracycline doses.[2,4] Even in patients with preserved LVEF, the reduction in LV strain and remodeling has significant clinical implications.[2,5] As a result, anthracycline use has declined over the last decade, which has limited life-saving treatment options.[3] This has incited the search for prophylactic cardioprotective agents, such as β blockers. Their antioxidant, antiapoptotic, and vasodilating properties suggest they may be effective at preventing anthracycline-induced cardiotoxicity (AIC).[6] Previous studies investigating their benefit have demonstrated equivocal results.[7−16]

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Methods

The report of this protocol-driven systematic review follows the Cochrane Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[17] Two investigators independently reviewed abstracts and full-length articles to assess eligibility. A systematic search of online databases for key words "anthracycline," "cardiotoxicity," "AIC," "doxorubicin," "adriamycin," "breast cancer," "beta blocker," and "carvedilol" through August 2018. Eligibility included random control trials (RCT) that assessed the role of β blockers in the prevention of cardiotoxicity in breast cancer patients who underwent anthracycline chemotherapy. Cardiotoxicity was primarily defined as a reduction in LVEF after receiving anthracycline. Trials also assessed other parameters of diastolic and systolic function. Although some trials included angiotensin-converting-enzyme inhibitors or trastuzumab, we did not include these arms. Both men and women were included. Although carvedilol was the most common intervention, we included all β blockers. We excluded any RCT that was not predominantly (>60%) conducted in breast cancer patients.

Statistical analysis was conducted with *The Cochrane Collaboration RevMan 5.3*. To compare the final mean LVEF, we performed inverse variance of continuous outcomes to demonstrate the mean difference at 95% confidence interval (CI). For the change from baseline LVEF, we used generic inverse variance to estimate the mean difference. We calculated the mean change of LVEF by subtracting the final LVEF from the baseline; the associated SE was derived using either the given confidence interval or given p value. The calculations were performed within *RevMan* and using the methods as outlined by the *Cochrane Handbook for Systematic Reviews*.[20] The secondary outcomes included LV global longitudinal wall strain (GLS), transmitral flow (E/A), ratio of peak early diastolic transmitral velocity to mitral annular velocity (E/e'), and left ventricular end-diastolic diameter (LVEDD). The GLS was determined by calculating the mean of the individual strain segments (p values computed by *RevMan*) as outlined by previous studies and the *American Society of Echocardiography*.[18,19] All secondary outcomes were analyzed by generic inverse variance to limit the imprecision of the pooled effect estimate with few studies of various sample sizes and incongruent data reporting. To maintain plot uniformity, values that demonstrated reduction were given negative signs (−), whereas those that increased were expressed as positive (+) numbers.

Outcomes were evaluated for heterogeneity using the chi-squared test with an associated p value <0.05 considered as significant. The percent of variability in the effect estimate that was attributable to heterogeneity was determined by the I^2 statistics. The DerSimonian and Laird random effects model was used when I^2 exceeded 30% suggesting there was at least moderate heterogeneity. Sensitivity and subgroup analyses were performed for potential sources of heterogeneity. A funnel plot was created to assess for publication bias of the primary outcome. All outcomes were graded according to the *Cochrane* GRADE protocol.[20]

Results

The search yielded 460 citations. We excluded 6 duplicates and screened 454 abstracts, of which 11 full text articles were reviewed. Of these, 9 met our inclusion criteria.[9–18] These are outlined in Table 1. A total of 771 patients (396 BB and 375 placebo) were included for analysis. Baseline characteristics of included trials with inclusion/exclusion criteria, chemotherapy regimens, and type and dose of β blockers are delineated in the supplementary index. The mean follow-up duration was 5.5 ± 0.92 months. The mean age was 48 ± 4 years in the β blocker group and 47 ± 5 years in the placebo group. Although most of the patients were women (96%), men were included in 2 trials.[12,15] The majority of the patients had baseline LVEF >60%. Of the 9 studies, 6 reported E/A, 4 reported E/e', 5 reported LVEDD, and 3 reported GLS. 2D echocardiography was performed in 8 trials with 1 trial allowing for multigated acquisition scan at the operator's digression; cardiac MRI was utilized in 1 trial. Carvedilol was used in 7 trials; metoprolol succinate and nebivolol were each studied in 1 trial. Sensitivity analysis was performed for 2 trials that initially met our inclusion criteria, but were found to be outliers.[9,10]

Our primary outcomes of postchemotherapy mean LVEF and change in mean LVEF from baseline favored β blockers. These are shown in Figure 1. The average final LVEF among trials showed a mean difference −3.84 with 95% CI [(−6.19, −1.48) p = 0.001, I^2 91%]. The mean difference of LVEF change was −3.66 with 95% CI [(−6.20, −1.12) p = 0.005, I^2 90%]. The greatest absolute change in LVEF was 15.7% and the lowest was <1.0% with the mean final LVEF >50% for all trials. There was significant heterogeneity among our primary outcomes, which could not be accounted for by subgroup analyses of types of cancers (Salehi et al and Kalay et al included lymphoma), anthracycline doses (cut-off values ±400 mg/m^2) types of β blockers (Gulati et al used metoprolol and Kaya et al used nebivolol) or dose of carvedilol (cut-off values ±12.5). Nevertheless, we are moderately confident in our effect estimate due to the following evidence: all trials were RCT; assessing postchemotherapy LVEF by 2 methods demonstrated similar results, which also reflected the trends of the individual trials; the publication bias funnel plot was visually symmetric; and subgroup analyses did not significantly differ from our pooled results.

Figure 2 demonstrates the secondary outcomes. Compared with placebo, the mean difference with 95% CI in LVEDD was [−0.44 (−0.88, −0.01) p = 0.05, I^2 49%]; GLS [−2.46 (−5.41, 0.49) p = 0.10, I^2 87%]; E/A [−0.06 (−0.15, 0.04) p = 0.24, I^2 62%]; and E/e' [−0.36 (−1.00, 0.29) p = 0.28, I^2 61%]. Although only LVEDD reached statistical significance, the trend toward β blockers was apparent. We downgraded these secondary outcomes to a low grade of evidence due to the variability of parameters assessed by the individual trials, which limited our statistical power.

Discussion

AIC is most commonly defined as reduction in LVEF after anthracycline-based chemotherapy. The primary

Table 1
Individual trial outcomes and results

Trial	Primary outcomes	Important results
Avila	LVEF decrease from baseline of ≥10% between in carvedilol versus placebo after chemotherapy at 6 months	No significant difference in the changes of LVEF after chemotherapy among the groups There was statistically less diastolic dysfunction with beta blockers; no difference in BNP Troponin (TnI) was significantly increased with placebo, but unchanged with carvedilol
Beheshti	Change in LVEF and myocardial strain among carvedilol and placebo measured 1 week after chemotherapy (3 to 4 months)	No significant difference in the changes of LVEF after chemotherapy among the groups Carvedilol significantly improved GLS in contrast to placebo
Elitok	Change in LVEF, fractional shortening and myocardial strain among carvedilol and placebo after chemotherapy at 6 months	No significant difference in the changes of LVEF after chemotherapy among the groups No difference in diastolic parameters Carvedilol significantly improved GLS in contrast to placebo
Guglin	LVEF decrease from baseline of ≥10% between in carvedilol versus placebo after chemotherapy at 6 months	LVEF significantly decreased >10% with placebo, but not carvedilol
Gulati	LVEF change from baseline in metoprolol versus placebo after chemotherapy at 12 months	Mean LVEF was significantly lower with placebo, while it was unchanged with carvedilol Myocardial strain and troponin were similar in both groups Metoprolol demonstrated worse diastolic outcomes and higher BNP
Kalay	LVEF change from baseline in carvedilol versus placebo after chemotherapy at 6 months	Mean LVEF was significantly lower with placebo, while it was unchanged with carvedilol There was statistically less diastolic dysfunction in the carvedilol group
Kaya	LVEF and pro-BNP change from baseline in nebivolol versus placebo after chemotherapy at 6 months	Mean LVEF was significantly lower with placebo, while it was unchanged with nebivolol There was statistically less diastolic dysfunction in the carvedilol group BNP was significantly increased with placebo, but unchanged with nebivolol
Nabati	LVEF change from baseline in carvedilol versus placebo after chemotherapy therapy at 6 months	Mean LVEF was significantly lower with placebo, while it was unchanged with carvedilol There was statistically less diastolic dysfunction in the carvedilol group Troponin (TnI) was significantly increased with placebo, but unchanged with carvedilol
Salehi	LVEF change from baseline in carvedilol versus placebo after chemotherapy at 4 months	No significant difference in the changes of LVEF after chemotherapy among the groups No difference in diastolic parameters

Figure 1a.

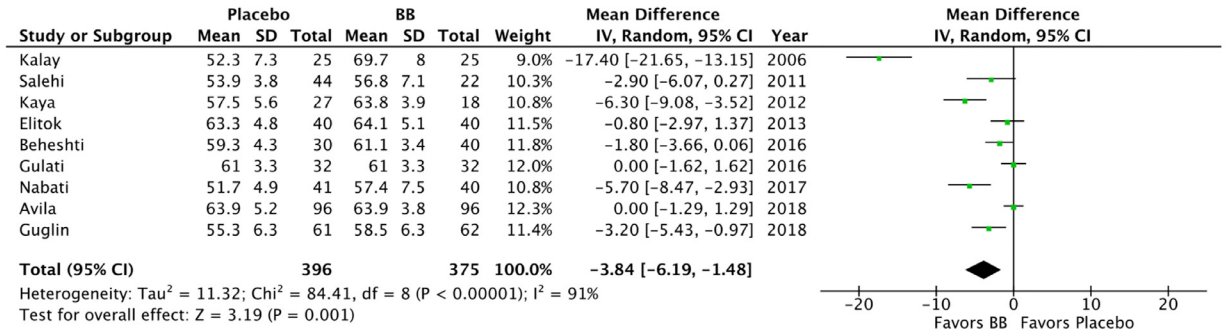


Figure 1b.

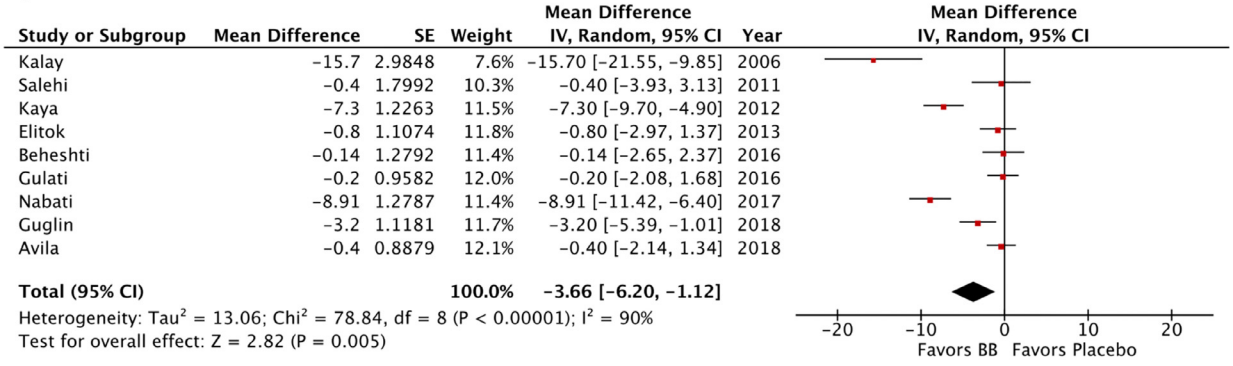


Figure 1. Primary outcomes. (A) Final LVEF postanthracycline with β blockers versus placebo; (B) change in LVEF postanthracycline with β blockers versus placebo.

Figure 2a.

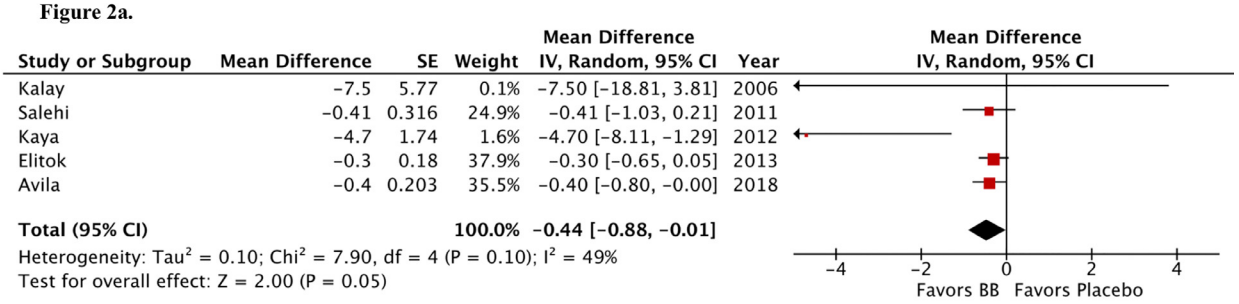
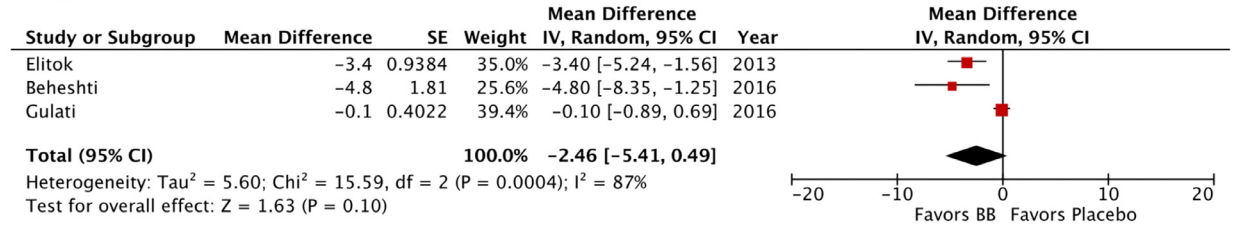


Figure 2b.



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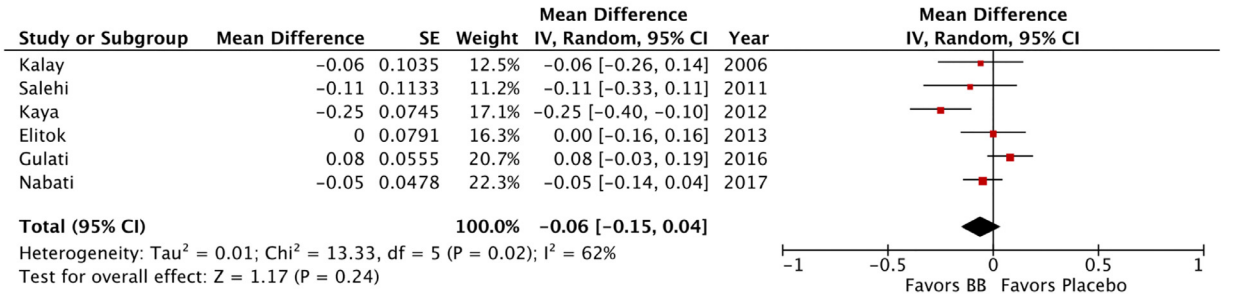

Figure 2d.

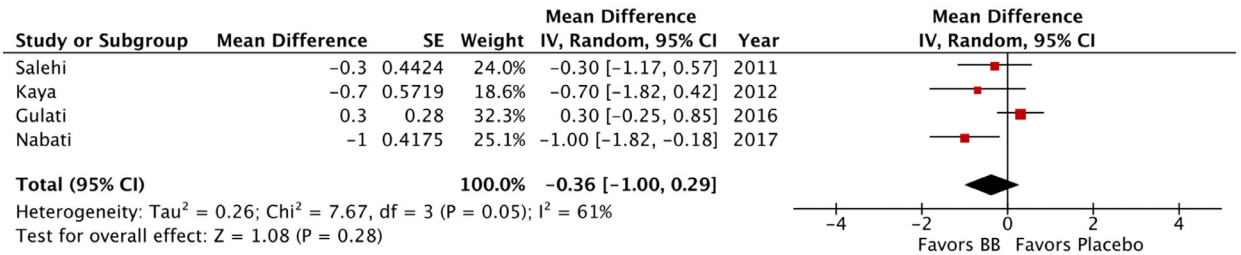

Figure 2. Secondary outcomes. (A) LVEDD postanthracycline with β blockers versus placebo; (B) GLS postanthracycline with β blockers versus placebo; (C) E/A postanthracycline with β blockers versus placebo; (D) E/e' postanthracycline with β blockers versus placebo.

outcome of our pooled results demonstrates that β blockers preserve LVEF by nearly 4% when compared with placebo. This modest outcome suggests that patients with borderline LVEF may achieve the most benefit. However, this finding may be due to the overall mean baseline LVEF >60% among the individual trials; whether patients with lower baseline LVEF would derive more benefit is uncertain. Although the long-term effects of marginal LVEF decline are unknown, there is an association between subclinical borderline LVEF and subsequent development of HF.[21,22] A large previous study of patients without structural heart disease who had asymptomatic LV dysfunction were 6× more likely to develop HF.[21] Even after adjusting for cardiovascular risk factors, age, and gender, those with borderline LVEF had greater risk of HF and death than patients with LVEF >55%. For every 5% decrease in LVEF, their risk of HF increased by 23%.[22]

The cumulative amount of anthracycline exposure is considered a determinant of LV dysfunction. This dose-dependent decline in LVEF occurs exponentially with increasing and cumulating doses of anthracycline. Incidence of cardiac events have been demonstrated in doxorubicin doses as low as 150 mg/m^2, (7%), which more than doubled with 350 mg/m^2 (18%), and vastly increased (65%) with 550 mg/m^2. Nearly half of patients may experience overt HF in doses ≥700 mg/m^2.[4] Our subgroup analysis of cumulative anthracycline dosing showed marginally greater benefit of β blockers among patients who received ≥400 mg/m^2. Suboptimal anthracycline dosing in efforts to avoid cardiotoxicity has become an imprudent practice.[3,23]

It is known that the improvement of LV function with β blockers is due to preservation of systolic function. However, β blockers improve LV function independent of LVEF. This is mediated by a reduction in LV filling pressures, even without changes in volume, demonstrated by improved myocardial compliance.[24] This is supported by our secondary outcomes, in which most trials demonstrated improved myocardial deformation, smaller change in LV diastolic cavity size, and less diastolic dysfunction among β blocker groups. Although these outcomes do not reach statistical significance in our pooled results, this trend can be appreciated (Figure 2). GLS measurement by speckle echocardiography has emerged as an early predictor of systolic dysfunction and remodeling even before overt LVEF reduction. We discovered a significant decrease in GLS among placebo groups after chemotherapy, whereas β blockers mitigated this in 2 of 3 studies.[7,8] The decreased GLS noted with anthracycline suggests that future reductions in LVEF are likely to occur.[25] LVEDD is another index of LV remodeling. Increased LV cavity size has been shown to more than double the risk of HF.[22] An increase in postchemotherapy LVEDD was seen with placebo, but not β blockers. The preservation of diastolic function was less clear due to the interdependent nature of these parameters. The *American Society of Echocardiography* recommends that diastolic function be assessed by multiple indexes, particularly when EF is normal and values are indeterminant.[26] Therefore, interpretations of our findings must be done with caution and in relation to other parameters.

The pathophysiology of AIC is multifactorial. Oxidative stress, secondary to production of free-radical oxygen species, from the interaction of doxorubicin and nicotinamide adenine dinucleotide dehydrogenase is a major contributor. This compromises the integrity of cellular and mitochondrial membranes, resulting in myocardial cell injury and death.[4] More recent theory implicates topoisomerase 2β inhibition, which results in cardiomyocyte apoptosis.[2,5] Anthracycline cardiotoxicity was historically considered to be irreversible, yet research shows that recovery of LV dysfunction is possible if addressed before symptom onset.[5,23]

Presently, there is lack of consensus on optimal AIC preventative strategies.[27] Standard HF therapies, such as angiotensin-converting-enzyme inhibitors and β blockers are promising, but their role in anthracycline treatment is equivocal.[7–16] The benefit of β blockers is largely attributed to their ability to reduce adrenergic signaling, mitigate ventricular remodeling and suppress renin-angiotensin-aldosterone axis stimulation. In addition, β blockers have pleiotropic benefits as free radical scavengers.[28,29] Pharmacologic studies exemplified how carvedilol prevents dysregulation of calcium handling during oxidative stress induced apoptosis of cardiomyocytes. The antioxidant properties of carvedilol were unsubstantiated among other β blockers.[29]

Beta blockers may offer more benefit in high-risk patients. Cardiotoxicity is increased among those with greater anthracycline exposure, underlying LV dysfunction, women, age >65 years or <18 years, black race, chest wall radiation, renal failure, and concomitant trastuzumab use. Genetic polymorphisms may also determine individual susceptibility to AIC.[2,3] A multidisciplinary approach to evaluate individual patient risk factors can identify those who are likely to derive the most benefit from prophylactic β blockers.[27]

The biggest limitation of this study is the significant heterogeneity of our primary pooled results. Methodological differences among the trials and patient characteristics, such as type and stage of breast cancer, immunocompetence, volume status, cardiovascular risk factors, underlying LV dysfunction, co-morbidities, compliance, and predisposition to disease all contribute to heterogeneity. There is also unavoidable variability in the measured outcomes of 2D-echocardiogram and cardiac MRI, as these are subjective to interobserver interpretation. Additionally, parameters of diastolic function and GLS were not consistently evaluated among the trials. Lastly, all trials had relatively short follow-up, occurring on average at 6 months; follow-up occurred at 4 months with 2 trials, and 12 months with 1 trial.

We conclude that β blocker administration during anthracycline chemotherapy prevents cardiotoxicity by mitigating the reduction in LVEF. Diastolic function may also be preserved with β blockers, although our interpretation of these results is limited.

Disclosures

The authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.046.

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