The Role of Prophylactic Renin-angiotensin System Inhibitors for the Prevention of Anthracycline-induced Cardiotoxicity Among Adult Cancer Patients: A Meta-analysis

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Abstract

Introduction: Anthracycline is a cornerstone in the treatment of various cancers. One major limitation to its use is cardiotoxicity. Renin angiotensin system (RAS) inhibitors have been shown to attenuate myocardial injury, initial data is promising in its use as prophylaxis for anthracycline-induced cardiotoxicity. The aim of the study is to determine effectiveness of prophylactic RAS inhibitors in preventing anthracycline-induced cardiotoxicity and adverse cardiac events among adult cancer patients

Methods: Systematic search of databases PUBMED, MEDLINE, EMBASE, and CENTRAL was done. Selection criteria were: 1) randomized controlled trials (RCT) 2) adult cancer patients with normal ejection fraction and without heart failure symptoms 3) RAS inhibitors as prophylaxis versus placebo 4) development of cardiac events, all-cause mortality and left ventricular ejection fraction (LVEF) reduction as outcomes. Two reviewers independently assessed the trials. Disagreements were resolved with a third reviewer. Test for effect of intervention, heterogeneity, trial quality and risk of bias were assessed using the Cochrane Review Manager Software version 5.3.

Results: Five RCTs involving 530 adult patients, with average age of 50± two years old, and average follow-up from six months to three years were included. Combined clinical outcomes of heart failure, cardiac events and all-cause mortality showed an RR of 0.27(95%CI 0.18, 0.40),p<0.00001, in favor of RAS inhibitors. There is same benefit in LVEF preservation with mean difference of 4.37%(95%CI 1.20, 7.55;p=0.007). Exploratory subgroup analysis showed significant benefit in LVEF preservation with combined RAS inhibitor and beta-blocker, with mean difference of 2.45%(95%CI 1.27, 3.63). There is overall significant heterogeneity (I^2=95%). Excluding one article with high-risk population, after sensitivity analysis, showed same benefit but reduced heterogeneity.

Conclusion: Renin angiotensin system (RAS) inhibitors may be used as prophylaxis for cardiotoxicity. As prophylaxis, it reduced the clinical outcome of cardiac events, heart failure, and all-cause mortality among cancer patients needing anthracycline. Combined RAS inhibitor and beta-blocker limits LVEF reduction.

Keywords: renin-angiotensin system, anthracyclin-induced cardiotoxicity

Introduction

Anthracyclines remain to be one of the cornerstones in the treatment of various hematologic and solid cancers.[1] It is among the most widely used and accepted chemotherapeutic regimen for both adult and pediatric population. However, one major limitation to its use is its established acute and chronic cardiac toxicity.[2-4] Billingham and collaborators and Mackay and collaborators, both demonstrated the structural effect of this drug class on the myocardium, leading to a dose-dependent and potential irreversible cardiac dysfunction leading to heart failure.[5-6]

There have been varying definitions for cardiotoxicity induced by anthracyclines, as a consequence, there is lack of a consensus definition for cardiotoxicity.[7] Cardiotoxicity may be predicted by a baseline left ventriular ejection fraction (LVEF) less than 50% or a reduction in LVEF by more than 10% during treatment, or to a level less than 50% during or after treatment.[8] The European Society of Medical Oncology (ESMO) guidelines state that a decline of LVEF to <50%, the chemotherapy should be put on hold for three weeks to reassess and treat left ventricular (LV) dysfunction, while at an LVEF of <40% it should be discontinued and other options be considered.[7-9]

At present, there is no accepted regimen to provide cardioprotection from damage induced by anthracyclines.[7,8,10] Modification of anthracycline structure, dosing regimen and

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schedules all geared toward mitigating its effects have been encouraged and prescribed, but despite this, cardiotoxicity continues to be a problem.[11] Symptomatic patients are managed as cases of overt heart failure with referral to a cardiologist being advocated by guidelines.[7,12] Dexrazoxane is an iron chelator that reduces the incidence of contractile dysfunction and is advocated by some.[7,11] However, because dexrazoxane can potentially reduce tumor response rates and the lack of a significant effect on improving overall survival has prevented the administration of this drug from becoming a universal practice.[11]

Data from experimental models suggest that the cardiac renin-angiotensin system (RAS) plays an important role in the development of anthracycline-induced cardiomyopathy and that treatment with RAS inhibitors protects against chemotherapy-induced cardiotoxicity. Potential mechanisms identified are reduction in the formation of reactive oxygen species and preservation of mitochondrial respiratory efficiency all of which leads to attenuation of myocardial dysfunction and irreversible damage. The positive outcomes of animal studies have led to postulation that these drug classes specifically angiotensin converting enzyme (ACE) inhibitors and angiotension receptor blocking agents (ARBs) may have a potential role in cardioprotection in patients who will receive anthracycline therapy.[13-16]

Several systematic reviews and meta-analyses regarding anthracycline-induced cardiotoxicity and various cardioprotective agents had been published in recent years.[17-19] These covered patients from both adult and pediatric populations who were diagnosed with different cancer types. Taken together these studies used varying outcome measures to document cardiotoxicity. In the systematic review and meta-analysis of Kalam and collaborators the following drugs had similar efficacy in reducing anthracycline-induced cardiotoxicity: dexrazoxane, beta-blockers, statins, and angiotensin antagonists.[18]

In the latest systematic review and meta-analysis of Yun et al, they were able to show an association among groups given beta-blockers and/or ACE inhibitors with higher LVEF compared with the control group. Exploratory subgroup analysis also showed benefit in giving prophylactic agents to those with higher cumulative dose of anthracyclines versus those with lower cumulative dose.[20]

In recent years, several newer studies on the potential role of RAS inhibitors in limiting cardiotoxicity had since been published specifically for the adult population of cancer patients receiving anthracyclines. This review was conducted to systematically analyze all available data from randomized controlled trials on the role of RAS inhibitors in preventing anthracycline-induced cardiotoxicity and adverse cardiac events among adult cancer patients.

General Objectives

To determine the efficacy of giving prophylactic RAS inhibitors in preventing anthracycline-induced cardiotoxicity and adverse cardiac events among adult cancer patients

Specific Objectives

1. Primary Endpoint: To measure the efficacy of RAS inhibitors in preventing the occurrence of adverse cardiac events (sudden death, death resulting from a cardiac cause, overt heart failure, and life-threatening arrhythmias requiring treatment) during the 6 months and one-year follow-up.
2. Secondary Endpoint: To measure the efficacy of RAS inhibitors in preventing chemotherapy-induced cardiotoxicity defined as an absolute decrease >10 percent units in rest LVEF associated with a decline below the normal limit value (50%).

Methods

The study was reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) proposed by the Cochrane collaboration. The methods of the analysis and inclusion criteria were specified in advance and documented in a protocol available from the corresponding author upon request. All references and authors were acknowledged and identified properly.[21-22]

Electronic searches

Two independent researchers (K.M.M. and J.H.V.) systematically searched MEDLINE, CENTRAL (Cochrane Central Register of Controlled Trials) and Embase for relevant studies using a combination of Medical Subject Headings (MeSH) term and corresponding free-text terms using the search terms "anthracyclines", "cardiomyopathy", "cardiotoxicity" "Heart Failure", "Renin-Angiotensin Sytem Inhibitors", "Angiotensin-Converting Enzyme Inhibitors", and "Angiotensin-Receptor Antagonist".

The researchers also looked into the World Health Organization International Clinical Trials Registry Platform, Current Controlled Trials (http://www.controlled-trials.com webcite), ClinicalTrials.gov and the Clinicaltrialsregister.eu for potentially eligible studies including completed and ongoing RCTs, which could possibly post their interim results online. There was no restriction regarding to language and publication period.

Other resources

The researchers also reviewed the reference lists of all full-text papers and correspond with all trial authors to

identify any trials that we may have missed. The reference sections and citation lists of the retrieved literature, including original research articles, reviews, editorials and letters were also reviewed for potentially relevant studies.

Eligibility criteria

The included studies met all of the following criteria:

1. A randomized controlled trial as study design
2. Study population of patients with any type of cancer ages 19 years old and above with normal ejection fraction (EF) and no history of heart failure symptoms who will be receiving any anthracycline containing chemotherapy regimen
3. Renin Angiotensin System (RAS) Inhibitors either alone or in combination with other cardioprotective agents, as prophylactic intervention arm versus placebo. Prophylaxis was defined as administration of intervention prior to any evidence of clinical heart failure and/or reduction of EF to less than 50%.
4. Primary outcome of measures include either change in EF from baseline to a predefined follow up period and a primary clinical endpoint – cardiac events, all cause mortality. The differences in types and preparation of anthracycline, dosing regimen, treatment duration, length of follow up, length and timing of intervention were taken into account but as long as they fulfill the four predefined criteria they were eligible for inclusion.

Studies which included patients who already have known cardiac dysfunction or previous chemotherapy-related heart failure or cardiac dysfunction, EF < 50% or multiple organ failure were excluded from the analysis. Studies with outcome measures that did not include measurement of EF were also excluded in the articles for review. For the purpose of this study, the researchers focused on measurement of EF and clinical endpoints as primary outcomes.

Data extraction and quality assessment

After duplicate studies were removed and articles were screened based on the inclusion criteria, the authors reviewed the full-text articles independently. The eligibility of each study was determined by consensus among the authors. Eligible studies were reviewed independently and data were extracted based on the cochrane data extraction template.

Selection of studies

Two members of the review team (K.M.M. and J.H.V.) independently triaged the titles and abstracts identified by the search to remove those that are clearly inappropriate. The remaining papers were found to have clear inclusion criteria applied to them. Disagreements about study inclusion were resolved by discussion with a third review author. All trials excluded from the review were given reasons for exclusion, such as `not a randomized trial' or `inappropriate control'. All randomized controlled trials (RCTs) in languages other than English were to be translated into English, however none of the included trials were found to be in a non-English text.

Data extraction and analysis

Two reviewers (K.M.M. and J.H.V.) independently extracted data from each study with uniform electronic forms specifically created for this study and the following data were extracted and recorded: trial characteristics (country, details of study procedure, sample size, study period, follow-up duration and funding), intervention characteristics, patient characteristics (inclusion criteria, background treatment, age, gender). (Appendix 1)

Risk of bias assessment

The bias risk of individual studies were assessed with the domains recommended by the cochrane collaboration tool including random sequence generation, allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting (reporting bias).

Statistical method

The aggregate data from each study were summarized by entering the data in the Cochrane Review Manager Software version 5.3.To examine the outcomes, the inverse variance fixed-effect model was used to calculate the weight mean difference (WMD) and 95% CI interval if there was no significant or substantial heterogeneity; otherwise, the random effects model was used. Both the maximally adjusted and unadjusted effect sizes with 95% CIs were recorded, if available. Any discrepancies were resolved by discussion or consensus with a third reviewer (DLS), the data extracted from each study was carefully checked by another reviewer (LLA) before performing final analyses.

Heterogeneity between studies was assessed using Cochran Q test (based on pooled RR from the Mantel–Haenszel test) and also by using the I^2 statistic interpreted as I^2 less than 0-30% was assessed as minimal heterogeneity, 30% to 50% as moderate and >50% as substantial heterogeneity

A forest plot was constructed to show the overall effect of intervention against control in all the studies grouped together. Data were also analyzed by subgroups of either single RAS inhibitor or in combination with another cardioprotective agent.

Table I. Summary of the studies included

Study	No. of pts	Age	Study Design	Type of cancer	Anthracycline and dosage	Intervention	Follow Up
Cardinale, et. al 2006	114	E: 47±11 C: 44±13	Prospective, randomized clinical study	Acute myeloid leukemia Breast cancer Ewing's sarcoma Hodgkin's disease Myeloma Non-Hodgkin's lymphoma	Varied Anthracycline regimens and dosing (Epirubicin, Idarubicin, etc.)	Enalapril	Cardiac evaluation was performed at baseline and at one, three, six, and 12-month
Georgakopoulos, 2010	147	E: 47.4±16.2 C: 49.1±19.4	Prospective, parallel group, randomized, controlled study	Lymphoma	Doxorubicin ~380mg/m^2 – as the maximal cumulative dose	Metoprolol or Enalapril or no concomitant treatment	36-month follow up
Dessi, et. al 2013	49	E: 52.9±9 C: 53±10	Phase II placebo (PLA)-controlled randomized trial	Endometrium Salivary gland Non Hodgkin's lymphoma Breast Ovary Lung (NSCLC)	Epirubicin 400 ± 30 (SD) mg/m^2 – as the maximal cumulative dose	Telmisartan	18-month follow-up
Bosch, et. al 2013	90	E: 49.7±13.9 C: 50.9±13.2	Randomized, controlled study	Hematological malignancies	Varied regimens and dosing of AC E: 139 ± 188 mg/m^2 C: 133 ± 182 mg/m^2	Enalapril and Carvedilol	six months
Gulati, et. al 2016	130	E: 51.7±10.7 C: 50.8±9.2	2x2 factorial, randomized, placebo-controlled, double-blind	Breast Cancer	Epirubicin	Candesartan and Metoprolol	six months

Abbreviations: E – experimental; C - Controlled

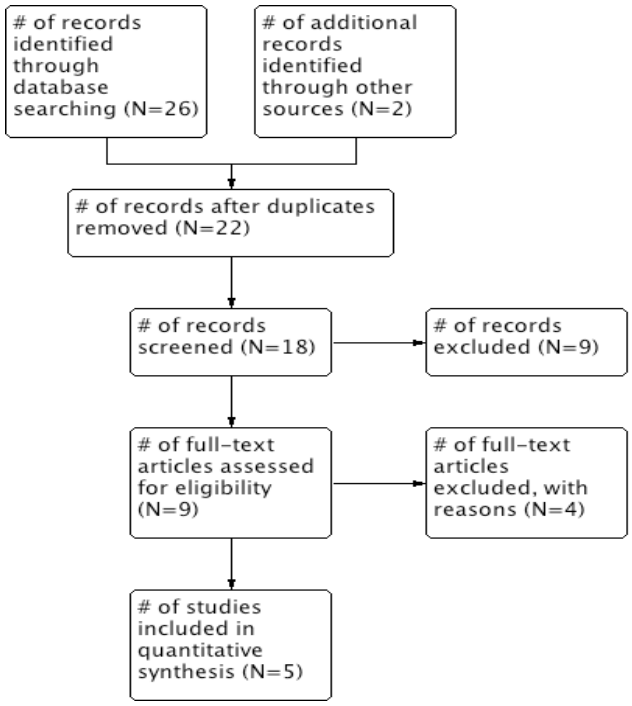

Figure 1. PRISMA flowchart of study selection

Results

During the search, there were 28 studies derived from the search terms used, and an additional two studies were found from other sources and references through other studies. A total of nine studies were screened, however one study that was listed at clinical trials.gov was unpublished and could not be retrieved even after contacting the primary investigator. A total of nine full articles were subjected for review. Among the nine studies, four were excluded.[23-26] Two of the four were found to be preliminary trials of a more recent study already obtained, and the other article was excluded due to absence of desired measured outcome.[36-37] A total of five studies were included for qualitative and quantitative synthesis. (Figure 1 and Table I)

The remaining five studies were all randomized controlled trials (n=530), with an average follow-up of 15.6 months. Average age of patients was 50 ± two years and patients had varied oncologic diseases requiring anthracycline regimens, but majority had lymphoma and breast cancer. Baseline characteristics were cited in all studies, and all studies included patients of normal EF, without baseline heart failure and coronary disease (Table I). [22-27]

Enalapril was used in three studies as preventive therapeutic agent. However, in one of those studies, Enalapril and Carvedilol were used in combination. The

Figure 2. Risk of bias assessment

two other studies used an angiotensin-receptor blocker (telmisartan and candesartan) as preventive therapy.

Risk of bias (Figure 2) was assessed in all the included trials. The study of Georgakopoulous et al had unclear risks because there was no mention of blinding of the outcome assessment, of allocation concealment, and of blinding of participants.[29] Blinding of the outcome assessment may have significant effect in the measurement of LVEF, however blinding of participants and allocation concealment were not found to significantly affect the objective outcome being measured, which was the change in LVEF post chemotherapy.

Effect of preventive therapy on EF is depicted in Figure 3. In the forest plot the mean difference in the reduction of EF from baseline to six months of follow up was compared between the control arm and the intervention of either RAS inhibitors alone or in combination with a beta blocker. The average time frame of follow up which was reported in all of the studies included were six months and has been the basis of comparison in this review.

Subgroup analysis was done based on the combination of agents. Combined agents of RAS inhibitor with a beta-blocker (Carvedilol) showed benefit in preventing cardiotoxicity with a significant mean difference of 2.45 (95% CI 1.27, 3.63). Control groups were found to have significant reduction in LVEF by 2.45% compared with the group given combined agents of RAS inhibitor with another drug as prophylaxis. Subgroup analysis of RAS alone showed mean difference of 5.37 (95% CI -5.61, 16.34) when compared with the control group; although nonsignificant with a p=0.34. This was also found to have significant heterogeneity at I^2=95%. The combined effect of all five trials had an overall mean difference of 4.37 (95% CI 1.20, 7.55), p=0.007. There was also an overall significant heterogeneity among all the five trials with an I^2 of 95% (Figure 3).

Sensitivity analysis was done to determine the effect of removing the study by Cardinale et al study and its effect on the overall outcome. This yielded with an overall mean difference of 2.24 (95% CI 1.21, 3.27), p<0.0001. Heterogeneity was also decreased to I2=50%. Despite the adjustment, there is still benefit of limiting the reduction in LVEF by a mean difference of 2.20%. (Figure 4)

In terms of clinical endpoint, Compared to the intervention group, the control group had a higher incidence of death, heart failure symptoms or LVEF <50% and/or decrease by 10% from baseline with an overall RR 0.27 (95% CI 0.18, 0.40), p<0.00001. This was represented by two of the five trials gathered that compared clinical endpoints with the use of RAS inhibitor. (Figure 5)

Discussion

This meta-analysis explored the role of RAS inhibitors to prevent anthracycline-induced cardiotoxicity. The principal finding of this meta-analysis is that RAS inhibitors, with or without beta-blockers, are able to reduce the combined clinical outcome of heart failure, cardiac events, and all-cause mortality. Two of the five trials included were able to demonstrate this result.[27,28] One of which used a combination of RAS inhibitors with beta-blocker,[28] while the other study made use of RAS inhibitor alone.[27] The heterogeneity, although significant, does not affect the overall result since both studies clearly showed benefit in decreasing the risk of cardiac events.

Overall, there was a significant LVEF preservation among those given RAS inhibitors. However, this was particularly significant in the exploratory subgroup analysis of combined RAS inhibitors and beta-blockers. In the meta-analysis of Yun et al. they were able to demonstrate an association of beta-blocker treatment and/or angiotensin antagonist treatment with higher LVEF compared with control.[20] The combination of beta-blocker and angiotensin antagonist treatment as prophylaxis, however, was demonstrated only by the study of Cardinal.[27] The addition of the study of Gulati in this meta-analysis further strengthens the benefit of combined beta-blocker with RAS inhibitor.

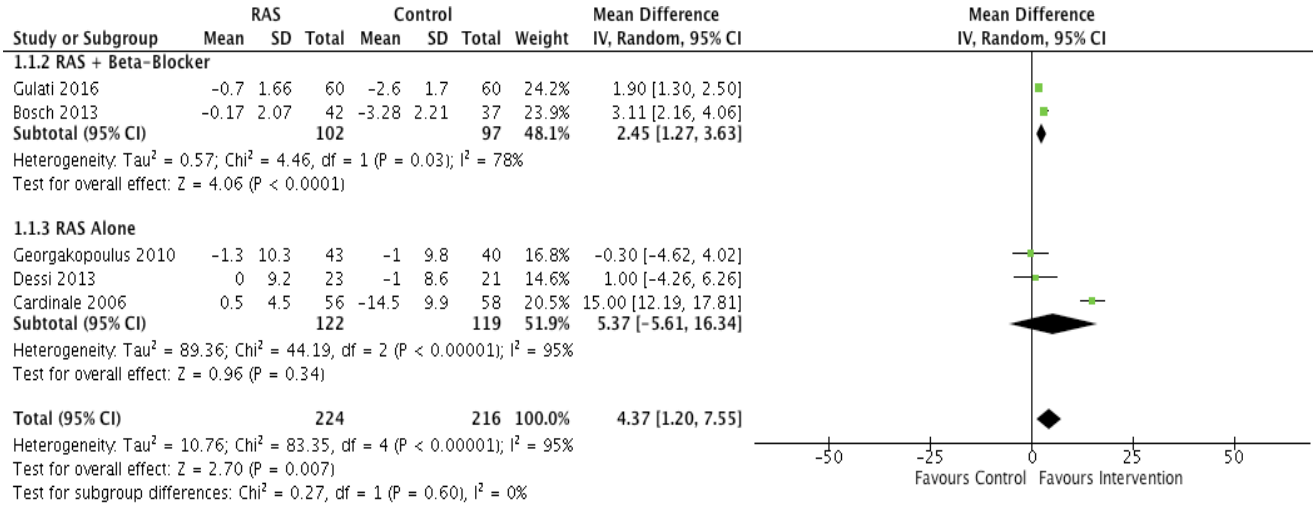

Figure 3.

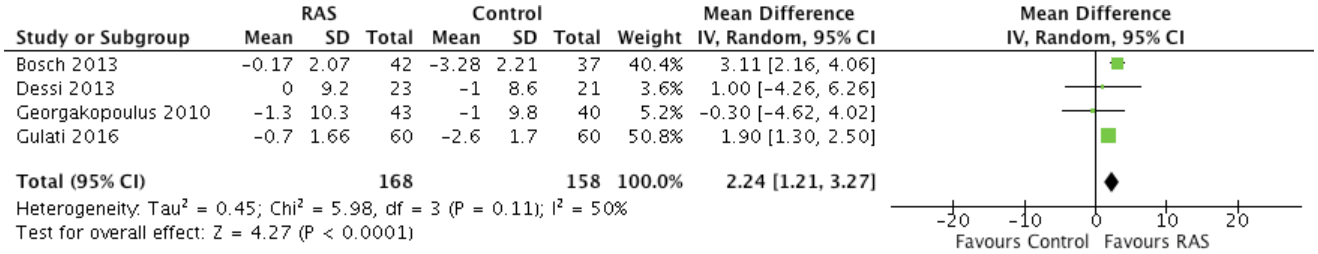

Figure 4. Forest plot showing the sensitivity analysis without the study of Cardinale 2006.

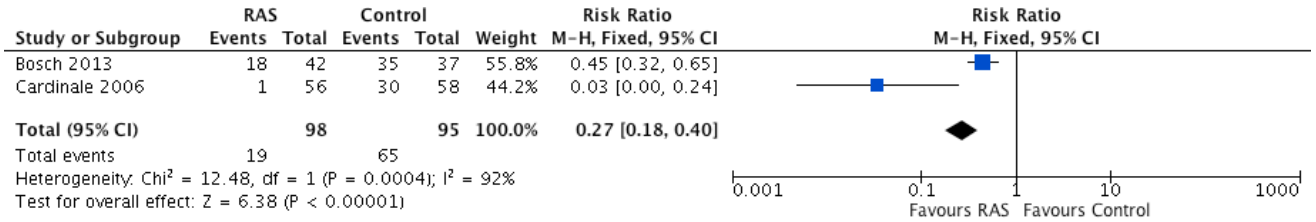

Figure 5. Forest plot showing control and treatment group and risk ratio for each study based on adverse cardiovascular outcomes death, heart failure symptoms or LVEF <50% and/or decrease by 10% from baseline

The subgroup analysis of RAS inhibitor alone showed potential benefit, but was largely affected by heterogeneity. Several factors were identified to be potential sources of this heterogeneity.

First was the difference in the type of anthracycline used. Among the included studies variability in the anthracycline investigated was noted. One study investigated only doxorubicin[26] while two others looked at epirubicin.[27,32] The fourth included study did not mention a specific anthracycline.[24] In this meta-analysis data from the single doxorubicin study showed a non-significant trend in favor of the control over the treatment intervention. This could be explained by differences among the anthracycline compounds in terms of their cardiotoxicity. In particular, it had been shown that the risk of clinical cardiotoxicity was lower with epirubicin compared to doxorubicin.[19]

Second was the dosage of anthracycline used. Toxicity from this class of agents was driven not only by type but also by cumulative dosing with higher doses increasing the likelihood and severity of heart failure.[5,6] Of the studies considered, three gave the cumulative anthracycline doses of participants, while the study of Bosch and collaborators[28] did not. The study of Georgakopolous and collaborators[26] used doxorubicin at a cumulative dose approaching the recommended lifetime limit of the drug (~400-550 mg/m^2).[29] Meanwhile, the studies of Dessi and collaborators and Gulati and collaborators[30,31] both used epirubicin but at different doses: for the former 400 mg/m^2 and for the latter 240, 360, or 400 mg/m^2, respectively. Notably, the equivalent dose of epirubicin could be estimated by multiplying the doxorubicin dose by two.[12] Thus the Georgakopolous and collaborators study used an estimated dose of about 800 mg/m^2 of epirubicin.[29] This higher dose compared to other studies might further explain the results of this study in favor

of the control over the treatment group. Moreover, the lack of uniform dosing given that anthracyclines cause toxicity at higher doses made comparisons of RAS inhibitor treatment effect more difficult to assess. In addition, considering that all doses given were within the acceptable range of doses for both doxorubicin and epirubicin could there be a 'threshold dose' where cardioprotection would no longer be effective?

Third was the presence of co-interventions. The combination of other chemotherapeutic agents and treatment modalities such as cyclophosphamide, taxanes, trastuzumab, and radiation were commonly used with anthracyclines and were themselves cardiotoxic.[17] Most of the studies accounted for these except the study of Dessi and collaborators.[31] In three of the four studies the effect of these factors was non-significant but for Bosch, radiotherapy was more often given to the treatment group. Despite this the result was still favorable for the treatment arm versus the placebo, suggesting a greater effect with the addition of Enalapril and Carvedilol.

Fourth was that the timing of administration of prophylaxis varied between studies. In Georgakopoulos et al. it was concomitant to administration of anthracycline.[29] In Cardinale et al. it was given one month after the last cycle of high dose chemotherapy.[27] In Dessi et al. it was started one week before the beginning of treatment and up to six months after discontinuation; for Gulati et al. prior to initiating with titration up to maximum dose, in Bosch et. al it was started simultaneously at least 24 hours before the first cycle of chemotherapy.[28,30,31] This difference may significantly alter the dose response and subsequently the expected treatment effect, this in itself may account for the significant heterogeneity in the outcomes even with same cardioprotective agent. However as there is no acceptable consensus as to the optimal timing and definition of prophylaxis except that it should be given prior to an objective evidence of cardiac dysfunction then all the studies fulfilled the criteria as prophylactic agents. In the sensitivity analysis conducted removing the study done by Cardinale et al, to account for the striking difference in terms of provision of prophylaxis

In the study of Cardinale et al., the participants included in the study were those who had a significant troponin I elevation prior to the initiation of RAS inhibitor.[27] Troponin I was considered to be predictive of the cardiotoxic effect of anthracycline, hence this was the study's prerequisite criterion prior to inclusion of the participant in the study. This may have significantly affected the outcome leading to a more effective prevention of anthracycline-induced cardiotoxicity, when compared to the other studies, which did not have the same protocol. Determination of troponin I levels prior to prophylaxis treatment may potentially identify high-risk population among the cancer patients who are more predisposed to developing cardiotoxicity after being given an anthracycline regimen. Further studies may be conducted to compare high-risk from low-risk populations to determine if prophylactic treatment with RAS inhibitors to limit development of anthracycline-induced heart failure will be most beneficial among the high-risk population

Lastly, there was variability in the length of follow-up performed. The average follow up in the study was 15.2 months, which would be acceptable in assessing the acute cardiotoxicity associated with anthracyclines. However, a longer follow-up would be necessary in order to fully assess the incidence of chronic cardiotoxicity which would take as long as ten years to develop. In fact, ESMO guidelines would recommend assessment of cardiac function four and ten years after anthracycline treatment in individuals who received a cumulative dose of >240 mg/m^2 of doxorubicin and >360 mg/m^2 of epirubicin as was the case in most patients studied here.[31] As such, adequate surveillance and monitoring of anthracycline toxicity would need to be long and drawn out in order to more accurately determine the incidence of anthracycline-induced cardiotoxicity.

These potential causes of heterogeneity provide significant implications for future research. It warrants also a look into concerns regarding future trial protocols outcome measures (i.e. cardiac biomarkers vis-à-vis clinical endpoints), appropriate prophylaxis duration, timing of prophylaxis to initiation of treatment, consensus on schedule of surveillance and adequate length of follow-up. Each of these topics presents possible directions for research into this relevant area of survivorship, particularly in light of improving outcomes among patients being treated for cancer.

Anthracycline-induced cardiotoxicity is a known barrier in the improvement of cancer survivorship and strategies to mitigate its effect have been the subject of recent studies in the field of cardio-oncology.[32] The potential utility of renin angiotensin system inhibitors as possible cardioprotective agent is particularly promising, especially when combined with beta-blocker.

Conclusion

This systematic review and previous published studies have highlighted the potential role of RASi as cardioprotective agents. Both in reduction of EF and prevention of cardiac events, the studies included were able to show benefit in using RASi as prophylaxis to prevent anthracycline-induced cardiotoxicity. However, a significant benefit was noted more in the combination of RAS inhibitor with beta-blocker. This was supportive of the conclusion of Yun et al, which showed benefit in giving ACE inhibitor and/or beta-blocker.[30]

Cardinale et al. was identified to have affected the heterogeneity of the study. On further review, the study was

also different in the methodology; wherein the participants included in the study all had a baseline significant cardiac troponin I. This study may have potentially selected the population who may benefit more from RAS inhibitors as cardioprotective agents against anthracycline-induced cardiotoxicity.

The researchers recommend further randomized controlled trials be done on this topic. A comparison between those with significant Troponin I versus those without may possibly demonstrate the significance of identifying the population that may benefit more from RAS inhibitors as prophylaxis. Inclusion of more studies with similar methodologies may also decrease the heterogeneity, giving a more robust conclusion on the benefits of RAS inhibitors.

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