Statins to mitigate cardiotoxicity in breast cancer patients treated with anthracyclines and/or trastuzumab: A systematic review and meta-analysis

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Background

- Due to advances in treatment and early detection, nearly 90% of women with breast cancer are living at least 5 years following their diagnosis
  - Living longer, there is increased risk for the development of long-term, late effects of cancer treatment
  - **Cardiotoxicity** may arise either during or after breast cancer treatments such as anthracyclines and/or trastuzumab
- Recent evidence has suggested the potential for **statin** use, a lipid-lowering drug, during treatment to mitigate the risk of cardiotoxicity in patients receiving cardiotoxic chemotherapy
- **Research Question:** Does statin use lower the risk of cardiotoxicity among breast cancer patients who receive treatment with anthracyclines and/or trastuzumab?

Methods

- Systematic review of the literature was conducted using PubMed, Embase, Web of Science, ClinicalTrials.gov, and Cochrane Central
- Inclusion criteria: samples with breast cancer patients, treated with anthracyclines and/or trastuzumab, and statins used during cancer therapy
- Exclusion criteria: case reports, reviews, guidelines, editorials, letters, and non-human research.
- Two reviewers independently performed study selection and data extraction
- **Random-effects model** using inverse variance weighting:
  - **Exposure:** Statin use among breast cancer patients treated with anthracyclines and/or trastuzumab
  - **Primary outcome:** Pooled relative risk of cardiotoxicity defined as 1) incidence of symptomatic heart failure or 2) having a reduction in left ventricular ejection fraction of >10% from baseline to an absolute value of <50%
  - **Secondary outcome:** Weighted mean differences of the mean change in left ventricular ejection fraction from baseline (before statin use) to the time of collected outcome

Results

Table 1. ***Characteristics of included studies***

First Author (Year)	Study design	Sample size #exposed/ #unexposed	Cancer type	Cardiotoxic chemotherapy	Matching criteria (exposed/unexposed)
Primary Outcome: Incidence of cardiotoxicity (n = 4)					
Calvillo-Arguelles (2019)	Retrospective study	43/86	Breast cancer	Trastuzumab therapy	Matched on age and anthracycline exposure status (1:2)
Nabati (2019)	Randomized trial	38/39	Breast cancer	Anthracycline-based chemotherapy	Randomized on 1:1 ratio
Seicean (2012)	Retrospective study	67/134	Breast cancer	Anthracycline-based chemotherapy	Matched on propensity score (1:2)
Tase (2013)	Retrospective study	144/288	Breast cancer and gastric cancer	Anthracycline-based chemotherapy	Matched on propensity score (1:2)
Secondary Outcome: Mean change in left ventricular ejection fraction (n = 3)					
Calvillo-Arguelles (2019)	Retrospective cohort study	43/86	Breast cancer	Trastuzumab therapy	Matched on age and anthracycline exposure status (1:2)
Nabati (2019)	Randomized trial	38/39	Breast cancer	Anthracycline-based chemotherapy	Randomized on 1:1 ratio
Chotenimitkhun (2015)	Prospective cohort study	14/37	Breast cancer, leukemia, and lymphoma	Anthracycline-based chemotherapy	-

Table 2. ***Random effects model for incidence of cardiotoxicity***

Studies	RR	95% CI	random-effect RR	% Weight
Calvillo-Arguelles (2019)	0.476	[0.193, 1.176]		27.68
Nabati (2019)	0.684	[0.209, 2.235]		16.15
Seicean (2012)	0.348	[0.125, 0.965]		21.72
Tase (2013)	0.538	[0.239, 1.211]		34.45
IV pooled RR	0.492	[0.306, 0.792]		100.00
test for heterogeneity: χ^2=0.79, df=3, p=0.85, I^2=0%				
test for overall effect: z=2.92, p=0.003				

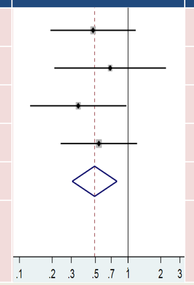
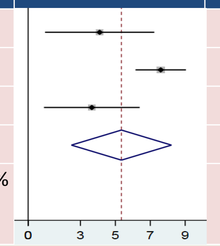


Table 3. ***Random effects model for weighted mean difference (WMD) of left ventricular ejection fraction change***

Studies	WMD	95% CI	Random effect MD	% Weight
Calvillo-Arguelles (2019)	4.100	[0.969, 7.231]		28.91
Nabati (2019)	7.600	[6.155, 9.045]		39.67
Chotenimitkhun (2015)	3.650	[0.906, 6.394]		31.42
IV pooled WMD	5.347	[2.480, 8.214]		100.00
test for heterogeneity: χ^2=8.58, df=2, p=0.014, I^2=76.6%				
test for overall effect: z=3.66, p<0.001				



Conclusions

- **Statins are associated with decreased overall risk of cardiotoxicity**
  - May mitigate development of cardiomyopathy among cancer patients treated with anthracyclines and/or trastuzumab
- Limitations: small sample sizes, included mostly retrospective designs, pooling results from randomized and non-randomized studies
- Further research is warranted to understand if statin use can be safely used to prevent or mitigate cardiotoxicity from breast cancer treatment

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