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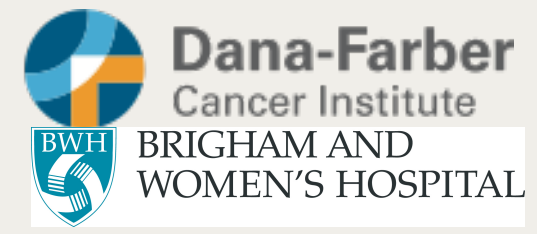
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Statins to mitigate cardiotoxicity in breast cancer patients treated with anthracyclines and/or trastuzumab: A systematic review and meta-analysis

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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	-

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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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: $\chi^2=0.79$, $df=3$, $p=0.85$, $I^2=0\%$
 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: $\chi^2=8.58$, $df=2$, $p=0.014$, $I^2=76.6\%$
 test for overall effect: $z=3.66$, $p<0.001$