Application of Framingham Risk Score in HER2+ breast cancer patients referred to a cardio-oncology clinic

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Introduction

•Breast cancer (BC) is the most common malignancy in North American women

•15-20% of BC tumours overexpress HER2-neu, a growth factor receptor

•Several HER2-neu targeted therapies currently in use have significantly improved cancer survival

•However, these therapies may also increase the risk of cardiotoxicity

•The Framingham risk score (FRS) is a validated tool that calculates the 10 year risk of cardiovascular disease[1]

•This tool may be useful for the prediction of cardiotoxicity in patients receiving HER2 targeted therapy

Objectives

1) To determine if traditional and novel CVD risk factors outlined in the FRS can be applied to a HER2+ BC population at risk of cardiotoxicity

2) To correlate FRS with i) cardiotoxicity; ii) CVD-related hospitalizations or deaths and hospitalizations

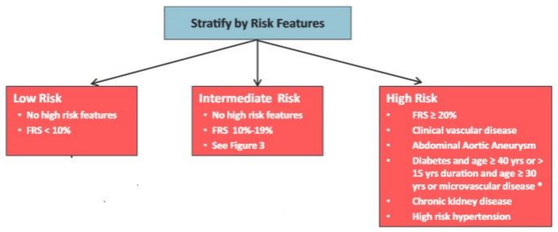
Methodology

HER2+ BC patients seen at the COC from Oct 2008-Aug 2014 (n=206)

Retrospective chart review of demographic, clinical and pathological characteristics of patients (stage of disease, cardiac outcomes, serum biomarkers and cardiac imaging abnormalities)

Application of FRS based on 2012 CCS guidelines[1]

High risk based on co-morbidities + past CV events (n=37)



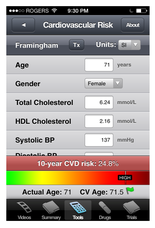


Figure 1a (above left): FRS stratification algorithm[1]; **Figure 1b (above right):** Screenshot of Lipids mobile app[2]

Calculation of 10-year absolute risk of CVD using mobile app (continuous FRS)

Missing (n=50)

Stratification of patients into low, intermediate and high risk

Statistical analyses conducted to determine associations between FRS and cardiovascular outcomes

Results

Retrospective chart review was completed for a total of 206 HER2+ breast cancer seen at the cardio-oncology clinic (COC) at the Ottawa Hospital (TOH).

Table 1: Baseline Patient Characteristics		Patients		Missing	
		n	%	n	%
All Patients (n)		206	-	-	-
Age at diagnosis	Median (range)	56 (23-87)	-	-	-
Sex	Female	201	98%		
Clinical Stage	Early (0, I, II)	137	67%		
	Late (III, IV)	66	32%	2	1%
Receptor Status	ER+	127	62%		
	PR+	101	50%	4	2%
	HER2+	206	100%	-	-
Node status	Node+	105	51%	2	1%
CVD risk factors					
Age	<50	70	34%		
	50-59	58	28%		
	60-69	51	25%		
	>=70	25	12%	2	1%
Sex	Male	5	2%	-	-
Body Mass Index	Median (range)	26 (17-46)			
	Underweight (<18.5)	11	5%		
	Normal (18.5-24.9)	77	37%		
	Overweight (25-29.9)	69	33%		
	Obese (>=30)	49	24%	-	-
Clinical Atherosclerosis		5	2%	-	-
Renal Function, eGFR (mL/min/1.73m^2)	Kidney disease (<45)	8	4%		
	45-60	18	9%		
	>=60	177	86%	3	1%
Fasting lipid profile (mmol/L)					
Total cholesterol	Median (range)	5.2 (2.9-9.2)	-		
	>5	102	50%		
HDL	Median (range)	1.5 (0.7-2.7)	-		
Male (n=5)	<1.0	3	60%		
Female (n=201)	<1.2	34	21%		
Tchol/HDL ratio	Median (range)	3.4 (1.9-7.8)	-		
	> 4.5	30	15%	41	20%
Smoking history		71	34%	-	-
Blood pressure (mmHg)					
Systolic BP	Median (range)	130 (96-198)	-		
Diastolic BP	Median (range)	75 (42-118)	-	10	5%
Hypertension (Clinically documented)		66	32%	-	-
Diabetes mellitus		25	12%	-	-
Cardiac Imaging					
Baseline ECG	Normal	121	59%		
	Abnormal	85	41%		
	LVH	8	-	-	-
Prechemo-LVEF testing modalities	ECHO	125	61%		
	MUGA	73	35%		
	Other	4	2%	4	2%
Prechemo-LVEF	Median	61	-	-	-
Baseline LVEF (before Trastuzumab)	Median	60	-	-	-
Adjuvant Therapy		203	99%	-	-
Targeted Regimen	Trastuzumab (T)	201	98%		
	TDM-1 + T	2	-		
	Lapatinib +T	8	-		
	Lapatinib + T + Xeloda	4	-		
	Pertuzumab +T	1	-	-	-
Chemotherapy with T	Anthracycline CT + T	153	74%		
	Non-anthracycline CT + T	46	22%	3	1%

Table 2: Patient outcomes		Patients		Missing	
		n	%	n	%
CV-related hospitalizations or deaths		30	15%		
CV-related Hospitalizations		28	14%	-	-
Causes	CHF	7	25%		
	Other	21	75%		
CV-related Deaths		5	2%	-	-
Causes	CHF	1	20%		
	Other	4	80%		
Cardiac Function					
Final LVEF (%)	Median (range)	57(10 -80)		9	4%
	<50	33	16%		
	50-54	31	15%		
	>=55	133	65%		
Changes in LVEFs from baseline	Median (range)	1.7 (-40 to +22)			
	>= 10% Increase	21	10%		
	Within +/- 9.9% of baseline	132	64%		
	>= 10% decrease	38	18%	15	7%

Table 3: Description of co-morbidities or past CV events that stratified patients into high risk FRS group

Condition	Description
Clinical Atherosclerosis	Clinically documented atherosclerosis
Abdominal aortic aneurysm	Clinically documented abdominal aortic aneurysm
High risk diabetes mellitus	DM and i) Age >40, ii) 15 yr of duration and iii) Age >30 or with microvascular disease
High risk chronic kidney disease	eGFR <=45mL/min/1.73m^2
High risk hypertension	Hypertension + 3 RF: male, age >55, smoking, Tchol/HDL-C>6, left ventricle hypertrophy, family history of premature CVD, ECG abnormalities
Past CV event or surgery	Past medical history of CV event or surgery (ex. CABG, stent)

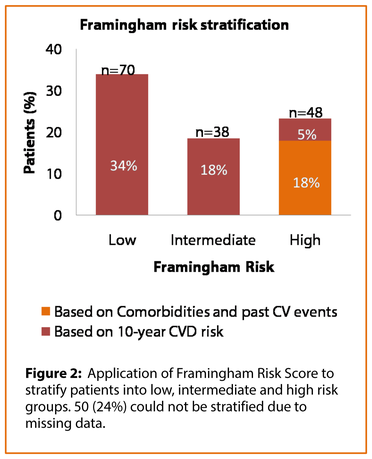


Figure 2: Application of Framingham Risk Score to stratify patients into low, intermediate and high risk groups. 50 (24%) could not be stratified due to missing data.

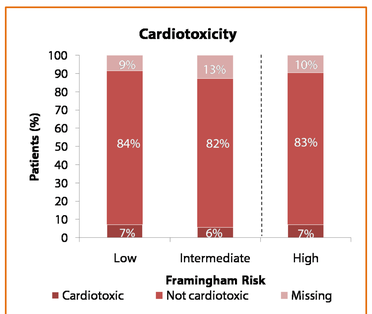


Figure 2: Framingham risk and the prevalence of cardiotoxicity defined as final ejection fraction <50% and decrease in EF by >=10%. Patients were grouped into high vs. low and intermediate risk and cardioxic vs. not cardiotoxic for statistical analyses. No correlation was found between the continuous FRS and cardiotoxicity (r=0.03, p=0.75); or FRS groups and cardiotoxicity (p=0.08 p=0.33).

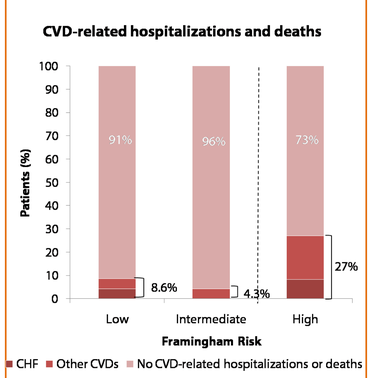


Figure 3: Framingham risk and the prevalence of CHF and other CVDs leading to hospitalizations or deaths. Patients were grouped into high vs. low and intermediate risk and CHF/other CVDs vs. no CVD-related hospitalizations and deaths for statistical analyses. No association was found between the continuous FRS and CHF (OR=1.01, CI=0.91-1.11, p=0.85), or FRS groups and CHF (Fisher's exact test; p=0.25). **CVD-related hospitalizations and deaths were associated with continuous FRS (logistic regression; OR=1.06, CI=1.00-1.11, p=0.045) and with FRS groups (Fisher's exact test; p=0.01; estimated RR=3.25, CI=1.49-7.08)**

Table 4: Specific causes of CVD-related hospitalizations and deaths

Condition	Hospitalizations	Deaths
CHF	7	1
Cardiac arrhythmia	7	1
Pericaridial-related	4	1
Changes in BP	3	0
Myocardial Infarction	3	1
Cardiac tamponade	1	1
Enlarged aortic aneurysm	1	0
Other	2	0
Total	28	5

Conclusion

- The majority of reviewed patients were successfully stratified using the Framingham Risk Score (FRS) (n=156)
- Application of FRS in this cardio-oncology population showed that 34% (n=70) were at low risk <10%, 18% (n=38) were at intermediate risk (10-20%) and 23% (n=48) were at high risk (>=20%) of developing CVD in the next 10 years. 50 (24%) could not be determined due to missing data
- CVD-related hospitalizations and deaths is associated with continuous FRS and FRS groups

Significance of this study

•FRS is a well-established tool accessible to the patient and clinician in multiple formats[3]

•Previous studies have not shown an association the FRS and CV outcomes[3]

•We applied the 2012 Update of the Canadian Cardiovascular Society Dyslipidemia Guidelines in this study that include traditional and novel CVD risk factors

•This is a preliminary step to see how the FRS can be applied in a breast CA population at risk of developing cardiotoxicity

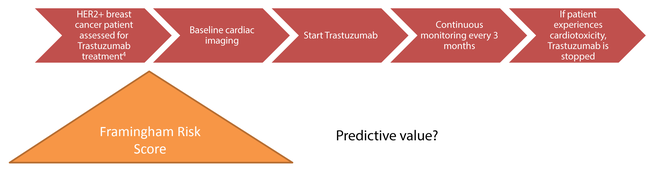


Figure 3: How Framingham Risk Score can be used to predict a subset of patients receiving Trastuzumab who experience cardiotoxicity

Future directions

•Adjust for confounders to elucidate predictive value of FRS for cardiovascular outcomes

•Compare associations in control populations

•Investigate other existing clinical risk tools to see if their application can be used to predict cardiovascular outcomes or decreases in LVEF[5]

•Examine the possibility of prospective study to survey patients for parameters outlined in clinical risk tools

•Conduct cost-benefit analyses of using clinical risk tools compared to routine cardiac imaging

References

1. Anderson, T. , Grégoire, J., Hegele, R., Couture, P., Mancini, J., … Ur, E. (2012). 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol.*, 151-67.
2. Developed by Chow C., Leiter L., Brawer E., 2012.
3. Farolfi, A., Melegari, E., Aquilina, M., Scarpi, E., Ibrahim, T., Maltoni, R., ... Rocca, A. (2013). Trastuzumab-induced cardiotoxicity in early breast cancer patients: A retrospective study of possible risk and protective factors. *Heart, 99*, 634-639.
4. Mackey, J., Clemons, M., Cote, M, Delgado, D, Dent, S.,…Verma, S. (2008). Cardiac Management During Adjuvant Trastuzumab Therapy: Recommendations of the Canadian Trastuzumab Working Group. *Current Oncology, 15*, 24-35.
5. Johnson, C., Sulpher, J., & Stadnick, E. (2015). Evaluation, prevention and management of cancer therapy-induced cardiotoxicity: A contemporary approach for clinicians. *Curr Opin Cardiol., Epub ahead of print.*

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