CHRONIC HEART FAILURE – PATHOPHYSIOLOGY AND MECHANISMS

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Cell growth, survival, and differentiation signal transduction pathways in advanced failing myocardium (gender dependent differences)

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Background: HER (1–4) family (tyrosine kinase receptors) regulate cell growth/survival/differentiation via RAS/MAPK/AKT pathways, what is crucial in heart failure (HF). However overexpression of the HER gene occurs in cancer, provide proliferative and antiapoptosis signals, so anti-HER treatment has been intensely evaluated, but in HF is controversial.
Aim: Elucidate the expression of HER2/HER4/RAS/MAPK/AKT expression in HF with regard to gender.
Material: 24 HF, compared to 23 non-failing hearts (NFH). HF patients presented dilated left (LV EF19% ±6,6%), right (RVD 41mm ±8.5mm) ventricle, elevated NTproBNP (5844pg/ml ± 5696pg/ml).
Methods: In HF vs NFH in LV/RV, the expression HER2 on protein (ELISA), mRNA (IDHS01001580_m1), levels also HER4 (IDHS00955525_m1), RAS (IDHS00243115_m1), MAPK (IDHS00946872_m1), AKT1 (IDHS00178289_m1), GAPDH -internal control (IDHS03929097_g1) on mRNA levels were measured (TaqMan RTPCR quantitative).
Results: See table. The HER2 expression on protein/mRNA levels, HER4/RAS/MAPK/AKT1 on mRNA levels were reduced (both LV/RV) in HF, with relation to patient's gender, but not to the HF etiology.
Conclusions: In HF (both ventricles) we observed gender dependent, significant reductions in expression pro-life pathways, so additional HER inhibition could be potentially unsafe in HF population. So close monitoring during such treatment should be maintained.
Funding Acknowledgements: Scientific Grant from Institute of Cardiology Warsaw, Poland

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Accumulating evidence for deleterious effects of digoxin in heart failure and atrial fibrillation: an updated meta-analysis

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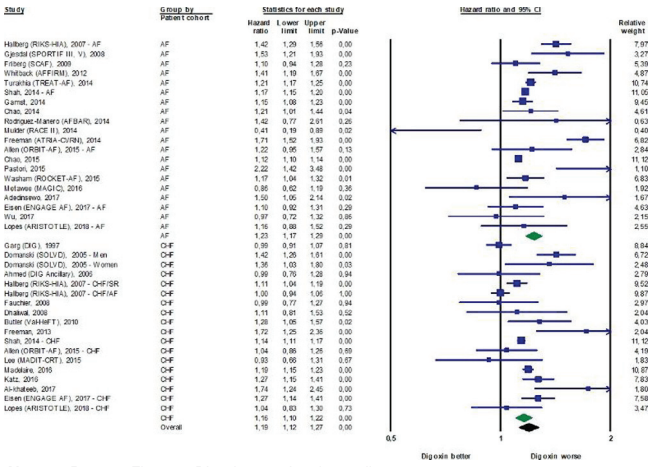
Background: In 2015 three independent meta-analyses demonstrated that digoxin therapy is associated with an increased mortality risk in patients with atrial fibrillation (AF) and with congestive heart failure (CHF). Although a series of studies has been published since then with further safety concerns, the most recent guidelines for AF still recommend this therapy as a class I indication.
Purpose: To perform an extended meta-analysis on digoxin-associated mortality including all studies published since 2015.
Methods: We performed a systematic review and random-effect meta-analysis on publications up to December 2017 reporting data on digoxin associated mortality in subjects with AF or CHF.
Results: Based on the adjusted survival data of all identified 31 trials comprising a total of 636.934 patients, digoxin use was associated with an increased relative risk of all-cause mortality (HR 1.19, 95% CI, 1.12–1.27, $p<0.01$). In the subgroup of patients with AF (N=502.299), treatment with digoxin was associated with an increased mortality risk (HR 1.23, 95% CI, 1.17 to 1.29, $p<0.01$), in the subgroup of patients with CHF (N=134.635) digoxin use was again associated with a higher risk for all-cause mortality compared with individuals not treated with cardiac glycosides (HR 1.16, 95% CI, 1.10–1.22, $p<0.01$). The sensitivity analysis of studies reporting data on new digoxin users (N=41.687) demonstrated an even more elevated risk for all-cause mortality (HR 1.47, 95% CI, 1.15 to 1.88, $p<0.01$).
Conclusion: This systematic review and meta-analysis including the most recent publications confirms that digoxin use is associated with an increased mortality risk in contemporary AF or CHF patient populations



Abstract P2777 – Figure 1. Digoxin associated mortality

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Effect of cardiovascular risk factors on left ventricular ejection fraction in HER2 positive breast cancer patients who were treated in adjuvant setting with trastuzumab

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Background: Trastuzumab has improved survival for women with HER2 positive breast cancer, but its use is associated with an increased risk of cardiotoxicity, that can be manifested by symptomatic and asymptomatic left ventricular dysfunction. Cardiovascular risk factors (CVRF) such as hypertension, hyperlipidaemia, diabetes mellitus, obesity and physical inactivity can worsen the cardiotoxic effect of anti HER 2 therapy.
Purpose: To assess the effect of cardiovascular risk factors (hypertension, obesity, hyperlipidaemia and diabetes mellitus) on left ventricular ejection fraction (LVEF) in HER2 positive breast cancer patients who were treated in adjuvant settings with trastuzumab.
Methods: 73 HER2 positive breast cancer patients (average age 57years) were involved in this study. They were all treated in adjuvant settings with trastuzumab for one year. LVEF was assessed by echocardiography at the beginning and at the end of the treatment with trastuzumab. We divided all patients into two groups: a group of 33 patients with CVRF and group of patients without CVRF (40 pts). The group of patients with CVRF was divided into three subgroups: a subgroup of patients with one CVRF (15 pts), subgroup of patients with two CVRF (11 pts) and subgroup of patients with three CVRF (7 pts). There were no pts with 4 CVRF.
Results: At the end of trastuzumab treatment patients with CVRF showed a greater decrease of LVEF by 7.45% (from 67.70±5.83% to 60.24±4.22%; p=0,000) than patients without CVRF by 4.99% (from 68.73±6.50% to 63.74±6.65%). Compared to the baseline values, at the end of the treatment with trastuzumab, reduction of LVEF in subgroup of pts with one, two and three CVRF was 7.50%, 9.58% and 4.0%. Out of three examined CVRF, the reduction of LVEF was the highest and similar in pts who had hyperlipidaemia by 7.84% (from 67.71±6.34%; to 59.87±3.94%; p=0.0001) and in pts with arterial hypertension (67.52±5.45% to 60.40±4.25%, p=0.0000; by 7.11%).
Conclusion: In HER2 positive breast cancer patients who were treated in adjuvant settings with trastuzumab, those with cardiovascular risk factors had a higher decrease of LVEF than pts without cardiovascular risk factors. Presence of two CVRF has a great impact on LVEF reduction during treatment, and significant influence on LVEF reduction had the presence of hyperlipidemia and arterial hypertension.

Abstract P2776 – Table 1

	HER2 protein/LV	HER2 mRNA/LV	HER2 protein/RV	HER2 mRNA/RV	HER4 mRNA/LV	HER4 mRNA/RV
NHF	13,49±3,93	0,2±0,09	17,4±5,59	0,03±0,25	0,03±0,29	0,006±0,45
HF	3,09±0,55	0,001±0,29	2,83±0,47	0,002±0,34	0,0001±0,1	0,0001±0,07
p NHF vs HF	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p<0.0001
Men HF	3,17±0,008	0,0005±0,3	3,04±0,007	0,0007±0,37	0,00008±0,081	0,00005±0,066
Women HF	2,72±0,011	0,0073±0,19097	2,18±0,0073	0,012±0,17	0,00074±0,2218	0,0009±0,1011
p Men vs Women	p=0.6374	p<0.0001	p=0.8751	p<0.0001	p=0.0005	p=0.0005
	RAS mRNA/LV	RAS mRNA/RV	MAPK mRNA/LV	MAPK mRNA/RV	AKT mRNA/LV	AKT mRNA/RV
NHF	0,025±0,35	0,0019±0,61	0,1224±0,28	0,0197±0,31	0,1408±0,16	0,0278±0,19
HF	0,00006±0,34	0,0001±0,18	0,0004±0,13	0,0006±0,25	0,015±0,21	0,015±0,22
p NHF vs HF	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p=0.0001	p=0.0043
Men HF	0,00003±0,289	0,00008±0,142	0,0002±0,123	0,0003±0,275	0,008±0,232	0,008±0,231
Women HF	0,0003±0,6748	0,0003±0,4936	0,0016±0,1868	0,0024±0,0848	0,0511±0,0838	0,0539±0,1243
p Men vs Women	p<0.0001	p<0.0001	p<0.0001	p<0.0001	p=0.1879	p=0.0053