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INNOVATION IN CARDIOLOGY: IS THERE A NEED FOR A GENDER-SPECIFIC APPROACH?

ליאור פרל

המערך הקרדיולוגי

המרכז הרפואי רבין

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FULL DISCLOSURE

- EQUITY IN FEMALE PATIENTS R&D.
- 2 PRE-CLINICAL PROTOTYPES.
- NO OWNERSHIP.
- NOT A CEO OF THE COMPANY!

INTRODUCTION

- Perception of cardiovascular disease are still commonly taken to be a health problem only for men, leaving women with an inadequate prevention vulnerable to CVD.
- CVD is the major cause of death in women older than 65 years of age. In Europe, CVD cause a greater proportion of deaths among women (51%) than men (42%) overall, i.E. They kill twice as many women as all forms of cancer combined.

European Heart Journal - Cardiovascular Pharmacotherapy (2017) 3, 163–182

Drug Pharmacokinetics and Pharmacodynamics

- Women and men differ in body composition and physiology and they present differences in drug pharmacokinetics (absorption, distribution, metabolism, and excretion) and pharmacodynamics.
- It is not rare that they may respond differently to cardiovascular drugs

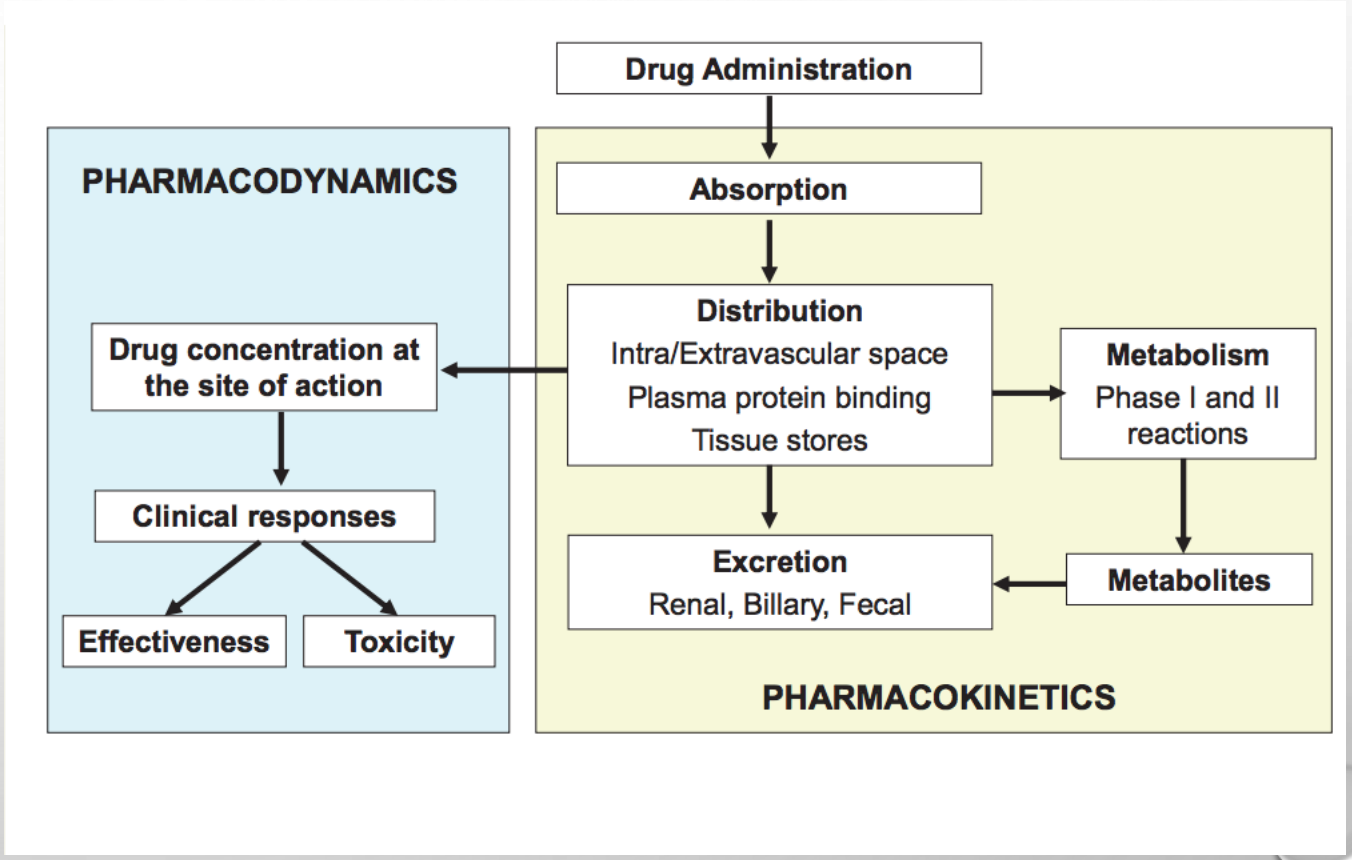

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Table I Gender differences in absorption, distribution, metabolism, and excretion

Parameter	Sex differences
Drug bioavailability	
Absorption	M > W
Gastric acid secretion	M > W > P. Decreases absorption of weak acids but increases absorption of weak bases in M
Gastric emptying	M > W > P. E inhibit gastric empting
Gastrointestinal transit times	
Gut metabolism	M = W
Body composition	
Body surface area	M > P > W. Absorption increases when body surface is larger
Organ (heart) size	M > W
Organ blood flow	Greater blood flow to skeletal muscle and liver in M; greater to adipose tissue in W. Blood flow increases during P
Total body water	M > P > W
Plasma volume	P > M > W. Varies during the menstrual cycle and P
Body fat content	W > M
Cardiac output	M > P > W. Increase rate of distribution in M
Pulmonary function	M > P > W. Increase pulmonary elimination in M
Drug distribution	
Volume of distribution	W > M. Higher Vd for lipophilic drugs in W M > W. Higher Vd for hydrophilic drugs in M
Plasma protein binding to	
Albumin	M = W. P and OCP reduce plasma albumin and increases free drug plasma levels
α1-acid glycoprotein	M > W. E, OC and P decrease its plasma levels
Globulins	E increase sex-hormone binding, corticosteroid-binding and thyroxine-binding globulins
Drug transporters	
Hepatic P-glycoprotein	M > W
OCT2	M > W. E downregulates OCT2
OATP1B1-3	M > W
Drug metabolizing enzymes and transporters	
Phase I metabolic reactions (hydrolysis, oxidation, reduction) mediated via cytochrome P450 (CYP) isoforms	CYP1A2: M > W. Decreased in pregnancy and by OCP CYP2B6: W > M CYP2C9: M = W CYP2C19: M = W Decreases in pregnancy and by OCP CYP3A4: W > M. Increases by OCP CYP2D6: M > W. E induces and OCP decreases CYP2D6 activity CYP2E1: M > W. Increases by OCP
Phase II metabolism	
Uridine diphosphate glucuronosyltransferases (UGTs 1/2)	M > W. Increase by OCP and E and during pregnancy
N-Acetyltransferases	M = W
Catechol-O-methyltransferase	M > W
Acetyl-/Butyryl-cholinesterase	M > W
Xantine-oxidase	W > M
Gastric alcohol dehydrogenase	M > W. Higher alcohol plasma levels in W
Drug excretion	
Renal blood flow	M > W. Renal Cl increases during P
Glomerular filtration rate	Drugs actively secreted by the kidney may show sex differences in renal excretion
Tubular secretion/reabsorption	

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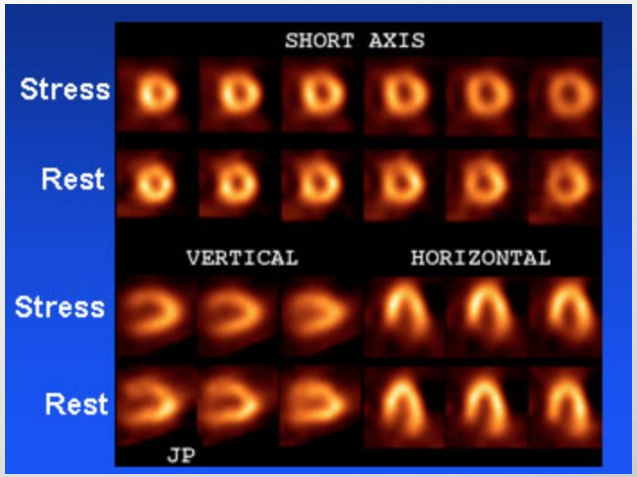
Table 2 Sex-related differences in drug pharmacokinetic parameters

Drug class	Outcomes in females
Anaesthetics: propofol	Plasma propofol levels decline more rapidly in W at the end of infusion
Alcohol	Lower gastric alcohol dehydrogenase activity in W. Higher plasma concentrations in W as compared with M following an equivalent drink
Antidepressants	Higher AUC and C_{max} in W
H1-antihistamines	Slower metabolism and elimination in W
Antipsychotic drugs[a]	Higher plasma levels and Vd and lower Cl in W. Reduce the dosage in W or increase dosage in M. Olanzapine is more rapidly eliminated in M than in W
Aspirin	Bioavailability and plasma levels of aspirin and salicylate are higher in W possibly due to lower activity of aspirin esterase, larger Vd and lower Cl in W than in M. Differences disappear with OCP
Benzodiazepines	Lower initial plasma levels due to larger Vd, and possibly higher Cl, in W. OC reduce their Cl. Higher plasma levels of free diazepam in W
Beta-receptor agonists	W are less sensitive
Beta blockers: metoprolol, propranolol	W have higher plasma levels due to a smaller Vd and slower Cl. Drug exposure to metoprolol increases by OC
	Renal Cl of atenolol and metoprolol increases during P due to enhanced hepatic metabolism
Calcium channel blockers	Faster Cl of verapamil, and nifedipine in W. Increased bioavailability and decreased clearance of oral verapamil in W compared with M
Digoxin	W have higher serum digoxin concentrations due to reduced Vd and lower Cl. Drug Cl increases during P
Glucocorticoids	Oral Cl and Vd of prednisolone are higher in M. Prednisolone clearance was reduced by OC
Heparin	W had higher plasma levels and APTT values than M due to a lower Cl
Iron	Oral absorption of iron is greater in W than in M
Isosorbide mononitrate	W had significantly higher serum plasma concentrations compared with men, probably due to the lower body weights in females
Labetalol	Labetalol concentrations are 80% higher in W
Lidocaine	W has a larger Vd and may require a higher i.v. bolus dose than M. Higher free plasma levels in W receiving OCP, as alpha 1-acid glycoprotein levels are reduced by oestrogens
μ-opioid (OP3) receptor agonists[b]	Slower onset and offset of action in W
Neuromuscular blocking drugs[c]	Lower Vd, higher plasma levels, faster onset and prolonged duration in W due to the higher body fat and lower Vd
Paracetamol	Lower plasma levels and higher Cl in M due to increased activity of the glucuronidation pathway. OCP increase drug clearance
Procainamide	Plasma levels are higher (30%) in W due to a lower BMI and Vd
Quinidine	Plasma protein binding decreases during P
Selective serotonin reuptake inhibitors[d]	W present higher plasma levels, probably related to sex-related activity of various CYP enzymes
Statins	Higher plasma levels of lovastatin and simvastatin in W
Theophylline	Metabolism is faster and half-life is shorter in W than in M. Plasma protein binding decreases and the Vd increases during P
Torasemide	Higher C_{max} and lower Cl in W than in M
Tricyclic antidepressants	Free plasma concentrations of imipramine, clomipramine, and nortriptyline are higher during pregnancy
Verapamil	W display faster Cl of verapamil after i.v. administration probably due to the higher activity of CYP3A4 or lower activity of P-gp; lower Cl in W after oral administration
Vorapaxar	C_{max} and AUC are 30% higher in women but no dose adjustment is required
Warfarin	Higher free plasma levels in W
Zolpidem	Plasma levels and AUC are higher, and Cl is lower in W

European Heart Journal - Cardiovascular Pharmacotherapy (2017) 3, 163–182

BREAST ATTENUATION IN SPECT

- Attenuation artifacts are the most common sources of error in myocardial single-photon emission computed tomography (SPECT) imaging.
- Breast artifacts are the most frequent causes of false positive planar images in female subjects.
- Studies show attenuation in **40%** of patients with anterior ischemia.



Nurkalem Z, et al. J Digit Imaging. 2008 Dec;21(4):446-51.

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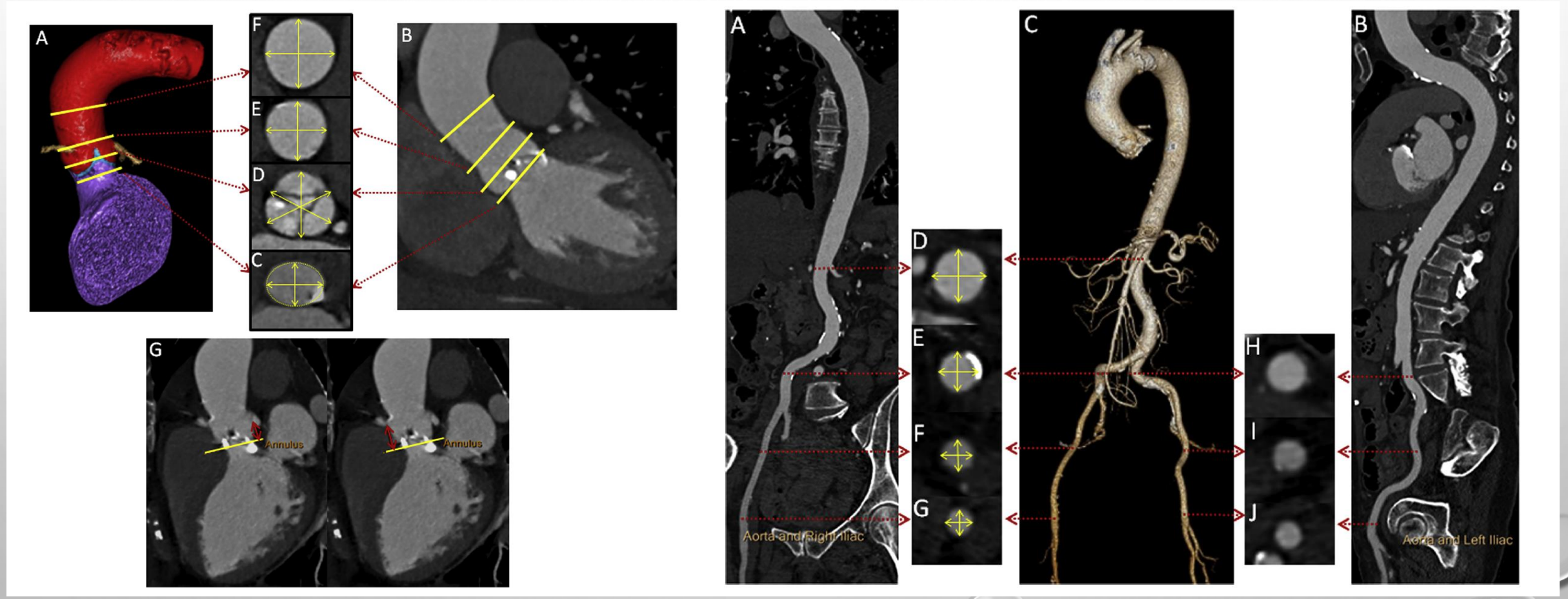
SEX DIFFERENCES IN AORTIC ROOT AND VASCULAR ANATOMY IN PATIENTS UNDERGOING TAVI: A COMPUTED TOMOGRAPHIC STUDY



A. Hamdan et al. Jour of Card Computed Tomography 11 (2017) 87e96

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Gender specific anatomic measurements of the aortic root.

Parameters	All (n = 506)	Men (n = 243, 48%)	Women (n = 263, 52%)	*P* value	*P* value for index
Annulus					
Area	455 ± 108 (247 ± 50)	517 ± 107 (268 ± 51)	404 ± 75 (299 ± 42)	<0.001	<0.001
indexed to height	278 ± 66	303 ± 62	250 ± 42		<0.001
Area derived diameter	23.9 ± 2.8 (13.1 ± 1.6)	25.5 ± 2.6 (13.3 ± 1.5)	22.4 ± 1.9 (12.8 ± 1.6)	<0.001	<0.001
indexed to height	14.6 ± 2.0	15 ± 1.8	14.1 ± 1.6		<0.001
Perimeter	75.9 ± 9.1 (41.4 ± 5.1)	81 ± 8.2 (42.2 ± 4.7)	71.8 ± 7.5 (40.8 ± 5.3)	<0.001	0.001
indexed to height	46.3 ± 6.0	47.6 ± 5.6	44.6 ± 5.4		<0.001
Perimeter derived diameter	24.2 ± 2.9 (13.2 ± 1.6)	25.8 ± 2.6 (13.5 ± 1.5)	22.6 ± 2.2 (12.9 ± 1.9)	<0.001	<0.001
indexed to height	14.6 ± 2.1	15.2 ± 1.8	14.2 ± 1.7		<0.001
Max diameter	27.0 ± 3.2 (14.7 ± 1.8)	28.8 ± 3.0 (15.0 ± 1.7)	25.5 ± 2.6 (14.5 ± 1.9)	<0.001	0.001
indexed to height	16.4 ± 2.2	16.9 ± 2.0	15.9 ± 1.6		<0.001
Min diameter	21.5 ± 2.8 (11.7 ± 1.5)	22.9 ± 2.7 (12.0 ± 1.4)	20.3 ± 2.2 (11.5 ± 1.5)	<0.001	0.001
indexed to height	13.1 ± 1.8	13.5 ± 1.8	12.6 ± 1.3		<0.001
Mean diameter	24.2 ± 2.8 (13.2 ± 1.6)	25.7 ± 2.7 (13.5 ± 1.5)	22.9 ± 2.2 (13.0 ± 1.6)	<0.001	<0.001
indexed to height	14.8 ± 1.9	15.2 ± 1.8	14.3 ± 1.3		<0.001
Ellipticity index	1.26 ± 0.1	1.26 ± 0.1	1.26 ± 0.1	0.78	–
Sinus of Valsalva					
Mean diameter	34 ± 4.6 (18.5 ± 2.8)	36.3 ± 3.8 (18.9 ± 2.5)	31.8 ± 4.2 (18.1 ± 3.0)	<0.001	0.001
indexed to height	20.6 ± 3.5	21.2 ± 3.0	19.9 ± 2.9		<0.001
Sino-tubular junction					
Max diameter	28.6 ± 3.7 (15.6 ± 2.2)	30.5 ± 3.9 (15.9 ± 2.2)	26.3 ± 2.9 (15.0 ± 2.2)	<0.001	0.012
indexed to height	17.4 ± 2.5	17.8 ± 2.4	16.8 ± 1.7		<0.001
Min diameter	27.9 ± 3.6 (15.2 ± 2.2)	29.8 ± 3.6 (15.5 ± 2.2)	26.3 ± 2.9 (15.0 ± 2.2)	<0.001	0.011
indexed to height	17.0 ± 2.6	17.4 ± 2.3	16.4 ± 1.8		<0.001
Mean diameter	28.0 ± 4.1 (15.2 ± 2.4)	29.8 ± 4.2 (15.5 ± 2.4)	26.3 ± 3.4 (15.0 ± 2.4)	<0.001	0.009
indexed to height	17.1 ± 2.8	17.4 ± 2.6	16.4 ± 2.0		<0.001
Ellipticity index	1.03 ± 0.07	1.2 ± 0.06	1.03 ± 0.08	0.64	–
Coronary ostia					
Height left coronary ostium	13.1 ± 2.8 (7.2 ± 1.6)	14.1 ± 2.9 (7.3 ± 1.6)	12.3 ± 2.4 (7.0 ± 1.6)	<0.001	0.020
	7.9 ± 1.9	8.3 ± 1.8	7.7 ± 1.5		<0.001
Height right coronary ostium	15.8 ± 3.1 (8.6 ± 1.7)	17.1 ± 3.2 (8.9 ± 1.7)	14.8 ± 2.6 (8.4 ± 1.7)	<0.001	0.001
indexed to height	9.6 ± 1.9	10.0 ± 2.0	9.1 ± 1.8		<0.001

A. Hamdan et al. Jour of Card Computed Tomography 11 (2017) 87e96

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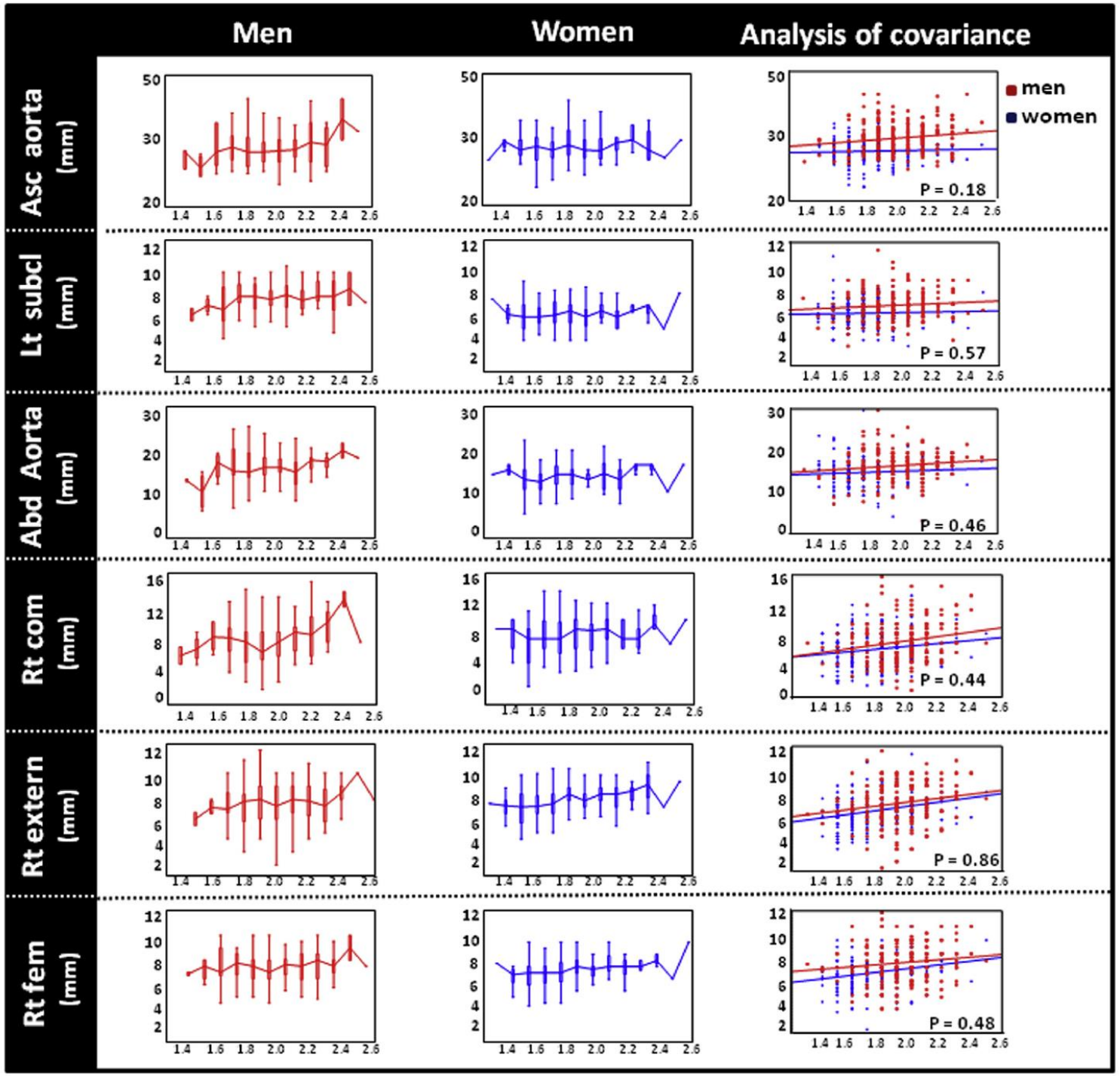

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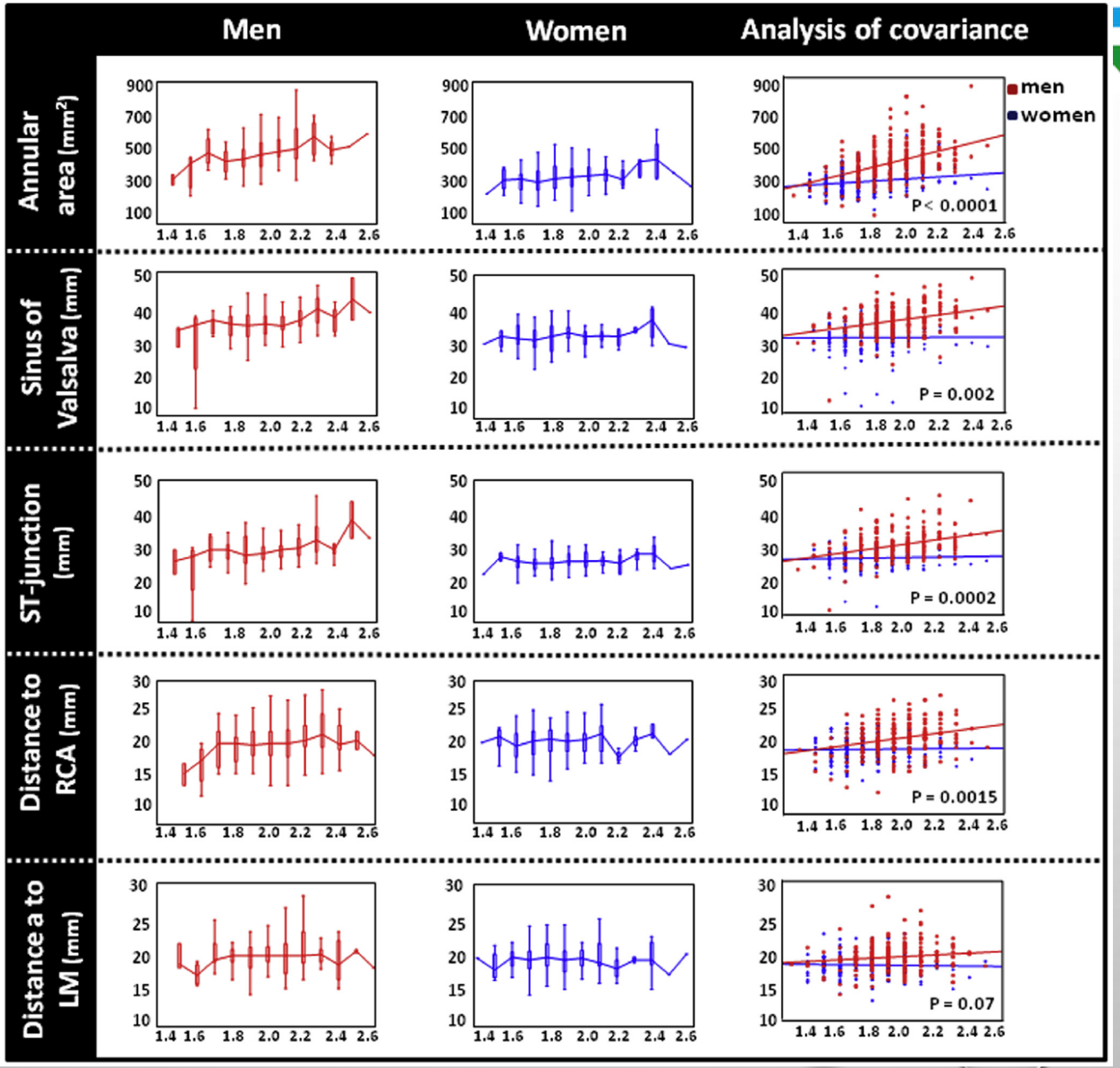

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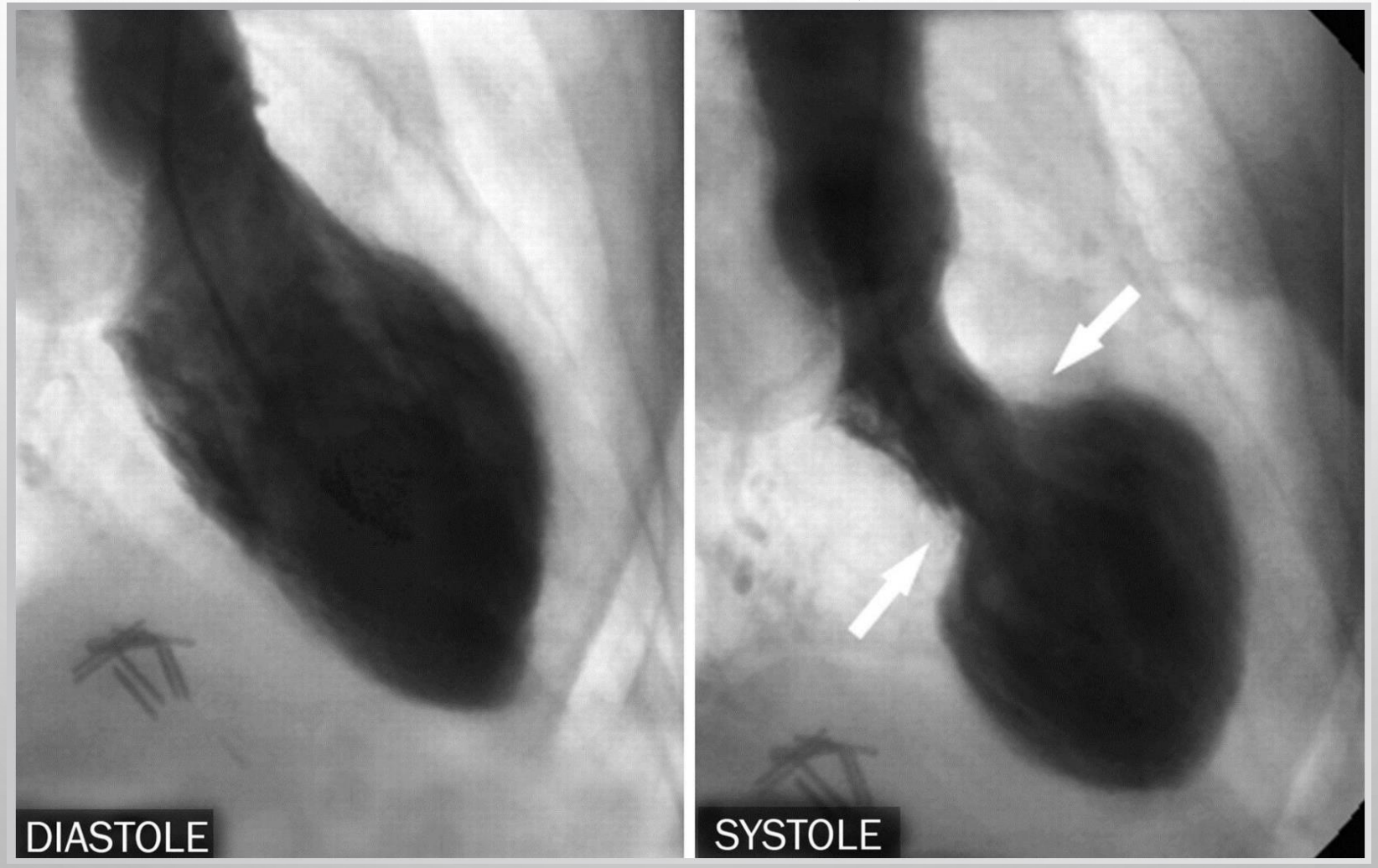
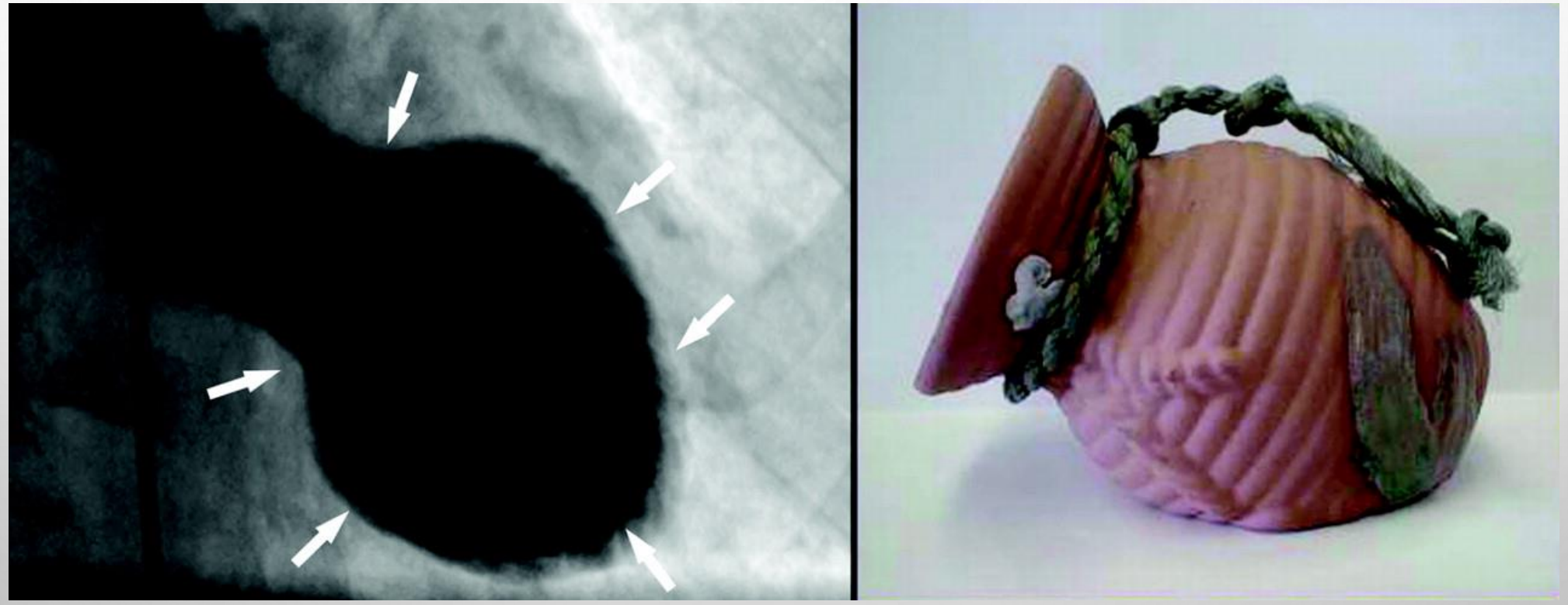
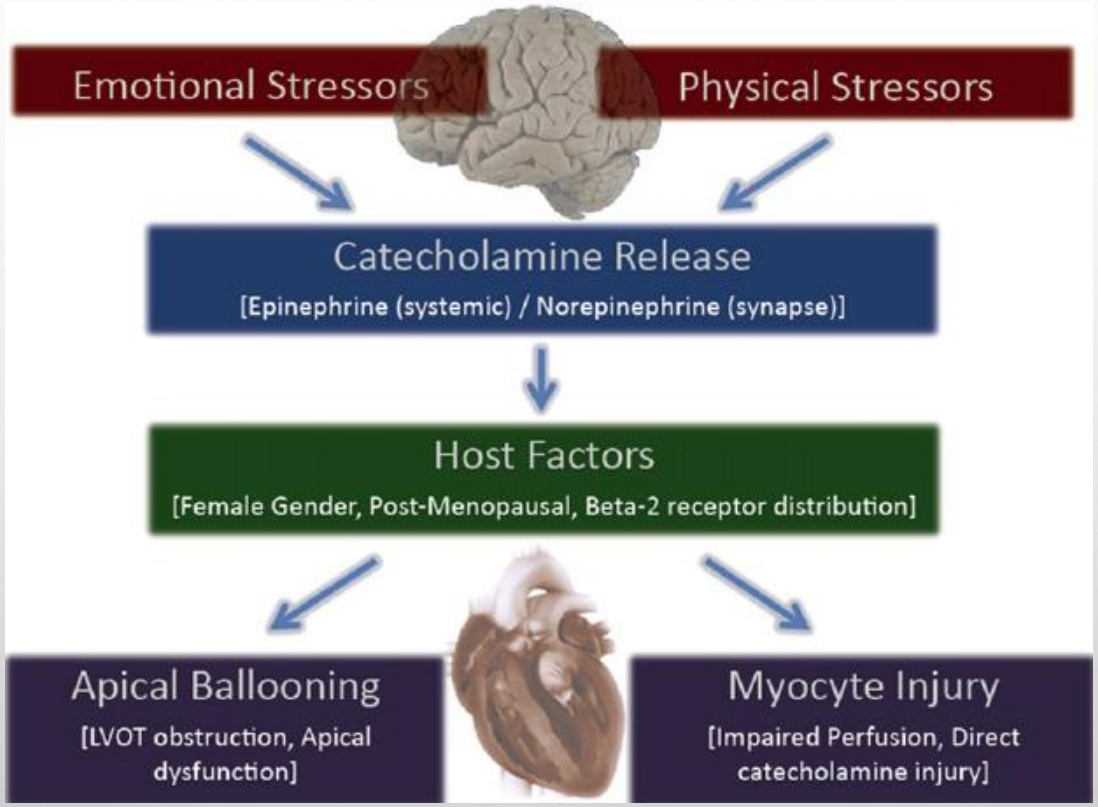
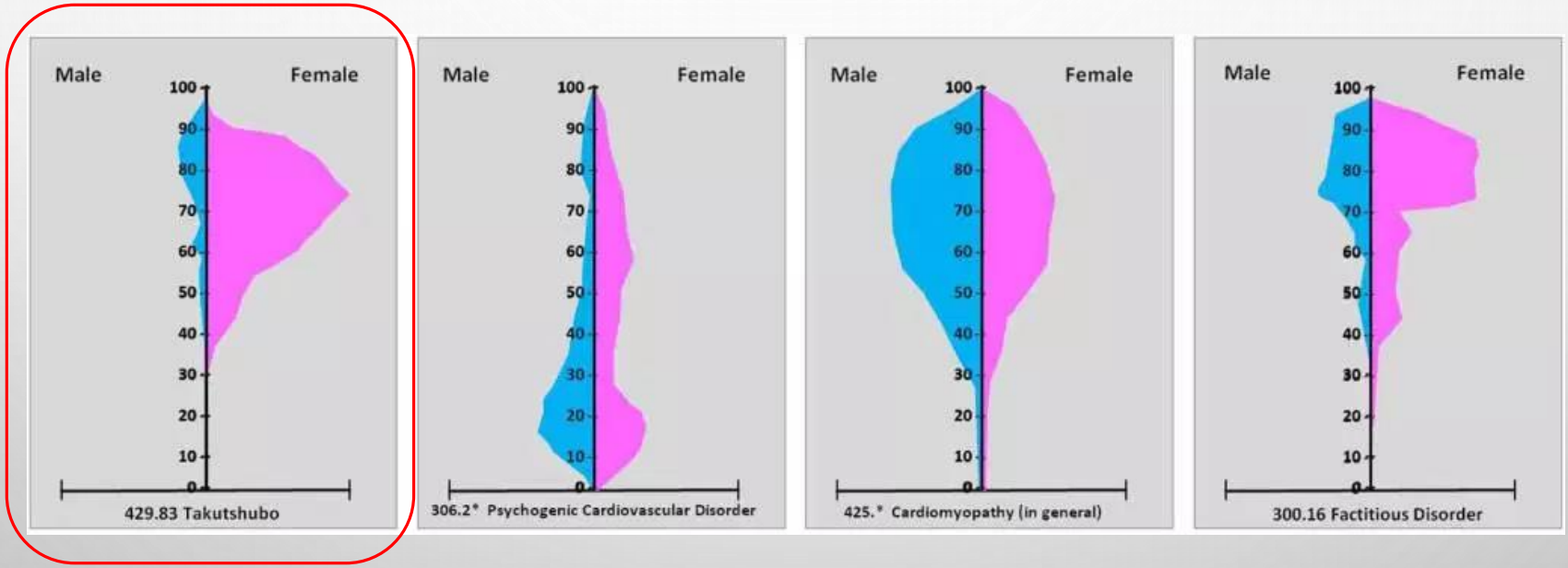
STRESS-INDUCED CARDIOMYOPATHY (TAKOTSUBO SYNDROME)







Heart Failure Clin 9 (2013) 217–223



Heart Failure Clin 9 (2013) 217–223

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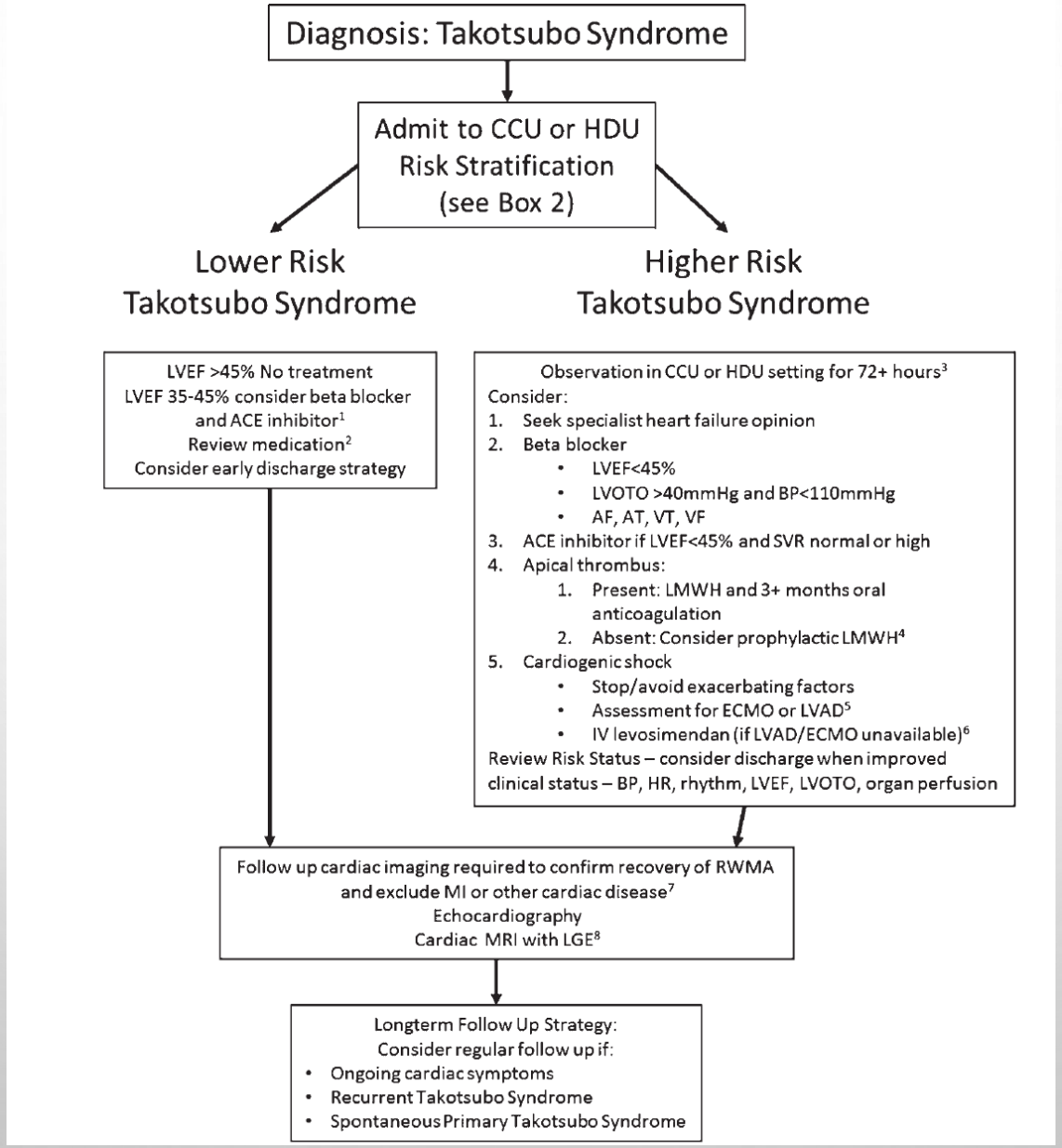
Table 3 In-hospital and long-term outcome of Takotsubo syndrome

Complication/outcome	Frequency
Acute complications	
Right ventricular involvement	18–34%
Acute heart failure	12–45%
LV outflow tract obstruction	10–25%
Mitral regurgitation	14–25%
Cardiogenic shock	6–20%
Arrhythmias	
Atrial fibrillation	5–15%
Ventricular arrhythmias	4–9%
Bradycardia, asystole	2–5%
Thrombus formation	2–8%
Pericardial tamponade	<1%
Ventricular wall rupture	<1%
In-hospital mortality	1–4.5%
Recurrence	5–22%
5-year mortality	3–17%

European Journal of Heart Failure (2016) 18, 8–27



European Journal of Heart Failure (2016) 18, 8–27

CARDIOVASCULAR SURGERY RISK FACTORS

Female preoperative risk factors	Male preoperative risk factors
Older age at presentation	Ejection fraction less than 35%
Angina Class 3 or 4	Three vessel disease
Urgent surgical interventions	Repeat operations
Preoperative IABP usage	Recent of significant history of smoking
Congestive heart failure	Renal failure
Previous percutaneous transluminal coronary angioplasty	Chronic obstructive pulmonary disease
Diabetes mellitus	
Hypertension	
Peripheral vascular disease	
Smaller body surface area	
Lower hematocrit	

Eur J Cardiothorac Surg. 2011;40(3):715-721.

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30-DAY MORTALITY FOLLOWING CABG

Author	*n*	Year	Mortality (Males vs Females)
Abramov	4823	2002	2.7% vs 1.8% ($p = 0.09$)
Aldea	1743	1999	1.5% vs 1.0% ($p = 0.33$)
Blankstein	15440	2005	4.24% vs 2.23% ($p < 0.0001$)
Carey	1335	1995	6.3% vs 3.1% ($p = 0.011$)
Christakis	7025	1995	3.5% vs 1.8% ($p < 0.0001$)
Doenst	1567	2006	7% vs 4% ($p = 0.026$)
Edwards	344913	1998	4.52% vs 2.61% ($p < 0.001$)
Hammar	3933	1997	3.0% vs 1.7% ($p < 0.01$)
Humphries	25212	2007	3.6% vs 2.0% ($p < 0.001$)
Koch	15597	2003	2.4% vs 1.4% ($p < 0.01$)
O'Connor	3055	1993	7.1% vs 3.3% ($p < 0.001$)
Ramstrom	220	1993	5.6% vs 2.4% ($p < 0.001$)
Vaccarino	15178	2002	5.3% vs 2.9% ($p < 0.001$)
Woods	5324	2003	3.16% vs 1.95% ($p = 0.007$)

Eur J Cardiothorac Surg. 2011;40(3):715-721.

POST ACUTE CARE

- WOMEN IN THE UNITED STATES ARE 4 TIMES MORE LIKELY THAN MEN TO BECOME WIDOWED AT AN OLDER AGE.

West LA, et al. 65+ in the United States: 2010. US Census Bur. 2014

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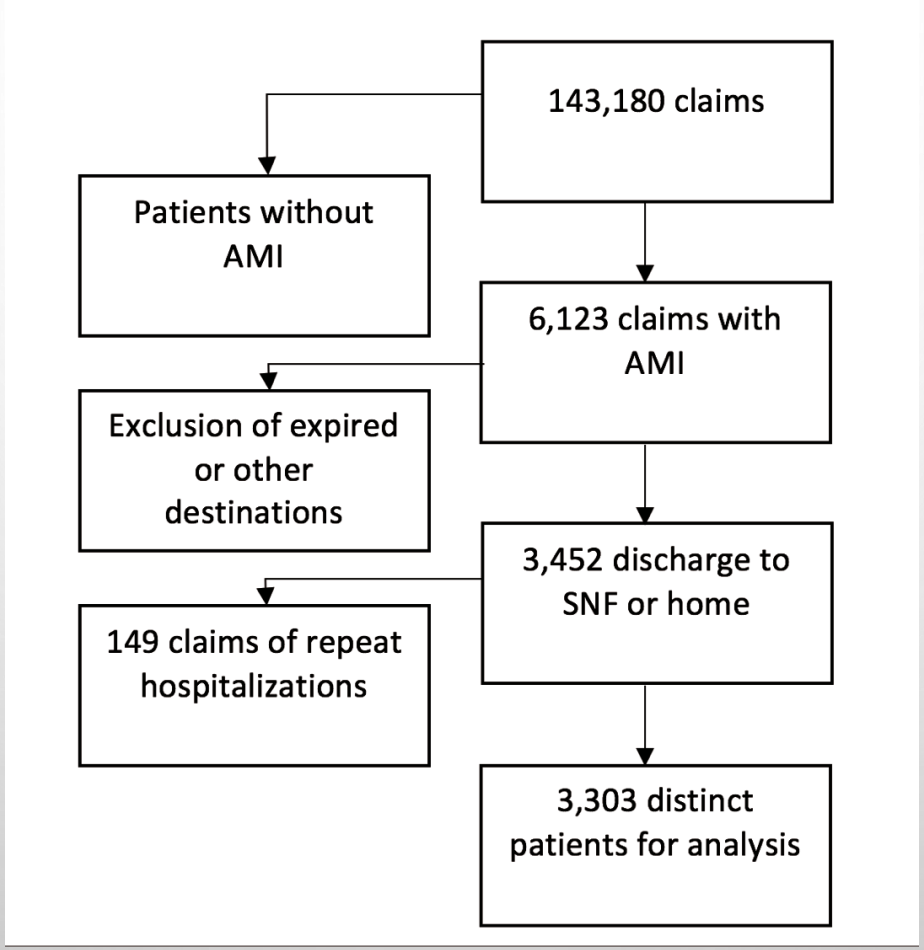
SEX DIFFERENCES IN DISCHARGE POST MYOCARDIAL INFARCTION



Perl L, et al. Coron Artery Dis. 2018 Jun 6. [Epub ahead of print]

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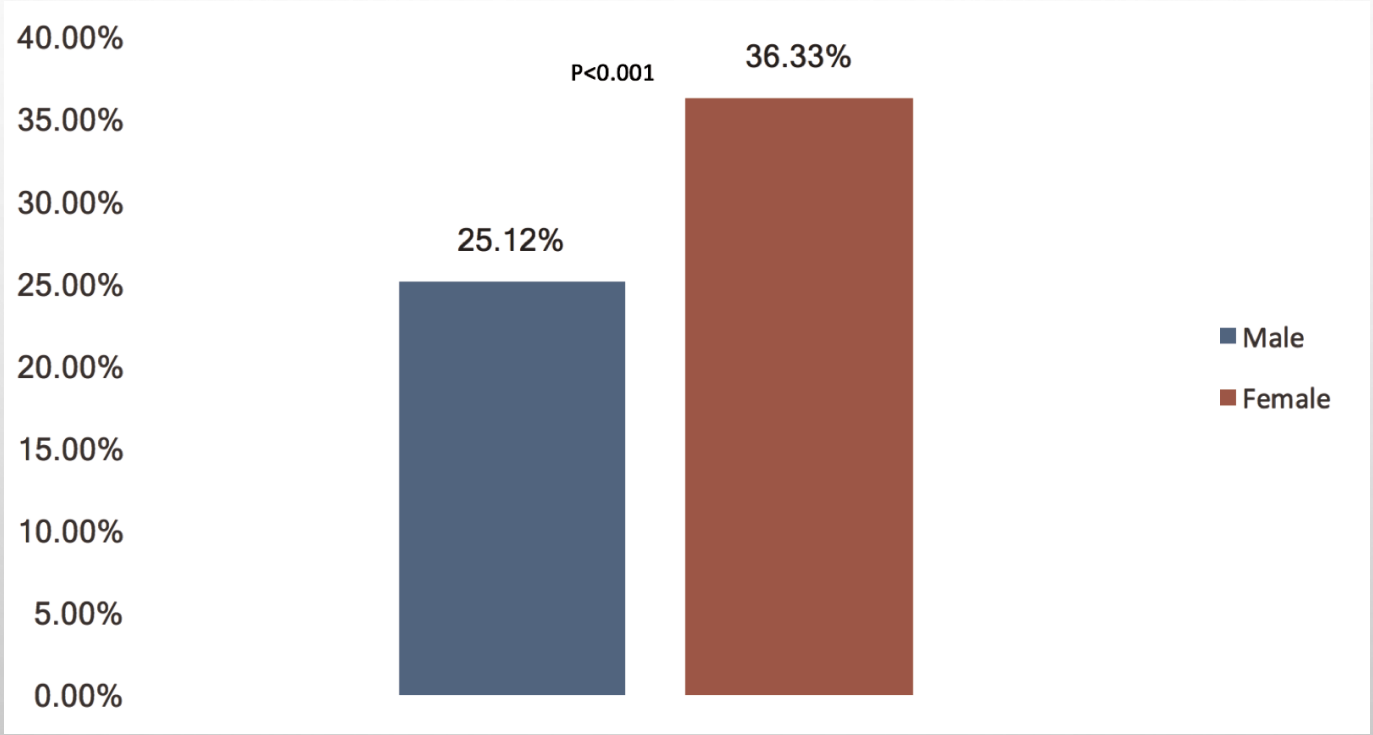
SEX DIFFERENCES IN DISCHARGE POST MYOCARDIAL INFARCTION

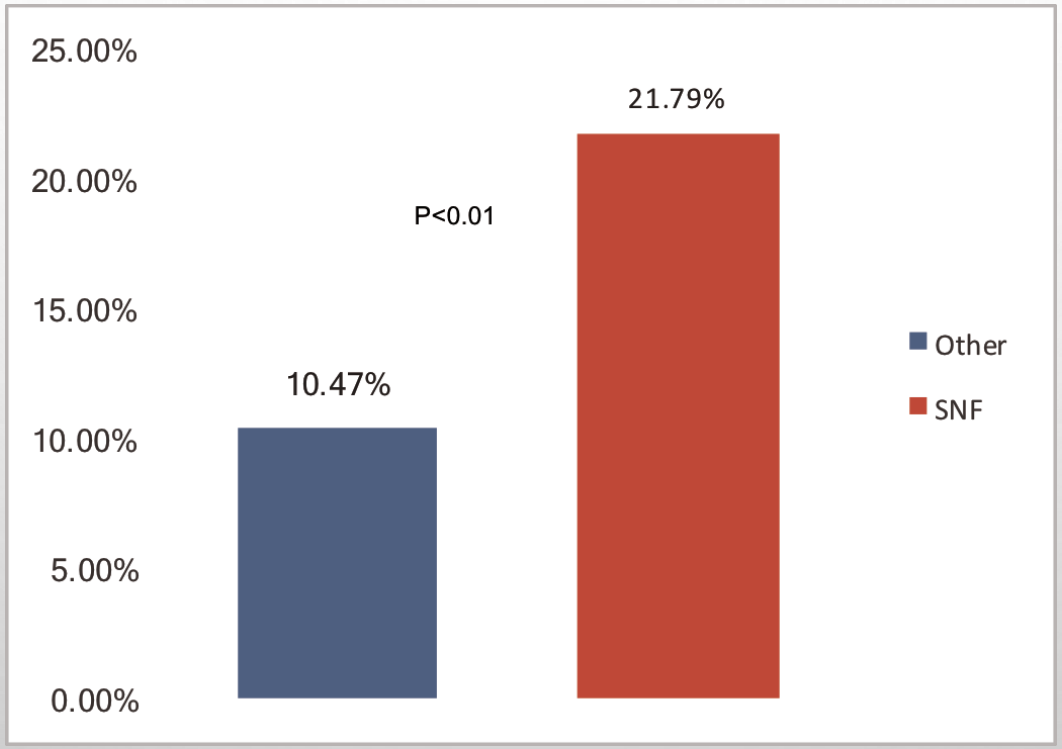
Rates of discharge to skilled nursing facilities



Perl L, et al. Coron Artery Dis. 2018 Jun 6. [Epub ahead of print]

SEX DIFFERENCES IN DISCHARGE POST MYOCARDIAL INFARCTION

Rates of death according to discharge destination



Perl L, et al. Coron Artery Dis. 2018 Jun 6. [Epub ahead of print]

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"OUTSIDE THE BOX" THINKING

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RECOMMENDATIONS FOR FUTURE CARDIOVASCULAR TRIALS IN WOMEN

Limit exclusion criteria and remove upper age limit to improve the generalizability of results and the projection of effectiveness in clinical practice
Women-only trials should be limited to the study of conditions unique to or predominate in women
Cardiovascular end points should include the scope of outcomes significant for women, including all acute coronary syndromes, fatal coronary heart disease, stroke (thromboembolic and hemorrhagic), and heart failure
Quality-of-life measures should be part of outcomes evaluated by gender
Gender-specific analyses should be conducted and published for both efficacy and safety
Reasons for nonadherence to interventions should be documented according to gender
Cost-effectiveness analysis should be conducted and gender-specific data published
Gender-specific power calculations should be conducted and published
Dissemination of results should include communication regarding any significant gender differences in efficacy and adverse effects

Circulation. 2011;124:2145-2154.

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Table 5 **Suggestions to improve our understanding of gender differences in the effects of cardiovascular drugs**

1. Increase the number of women recruited in all phases of clinical trials
   - Include an adequate number of women unless adequately justified or enrol only woman when indicated
   - Limit the exclusion criteria to facilitate the extrapolation of the results to the general population
   - Gender-specific power calculations should be conducted and published
2. When designing and analysing the results of clinical trials gender-related cardiovascular endpoints should include outcomes important for women
3. Gender-specific PD/PK differences have not been investigated for many CV drugs and the clinical relevance of many gender-related differences remains unproven.
   a. Preclinical studies should consider sex differences in expression and function of target receptors, both for efficacy and safety
   b. Prospective clinical studies should be designed to better understand:
      - Sex differences in the pathophysiology and prevalence risk factors of CVD
      - Sex-related differences in the efficacy and safety of cardiovascular therapy and the mechanisms involved
      - The role of sex–gender on the PD/PK variations induced by pathological conditions
      - The potential interactions of CV drugs with endogenous or therapeutically supplied sex hormones
      - All this information should be correlated with the incidence of ADRs
   c. Gender-specific analyses should be conducted and cost-effectiveness analysis should be conducted and published for both efficacy and safety.
   d. Quality-of-life measures should be part of outcomes evaluated by gender
   e. Reasons for nonadherence to therapy and/or interventions should be documented according to gender
4. Disseminate the results regarding significant gender differences in CV drug efficacy/safety
   - Gender differences in PK/PD of CV drugs should be part of medical education and should be presented as an intrinsic characteristic of many drugs
   - Develop educational programmes to increase awareness of sex-specific differences in PD/PK of CV drugs
   - Sex-specific dosage recommendations for CV drugs should be included on their labels
   - Provide sex-specific data on drug efficacy and safety in all guidelines on CVD
5. Gender differences in dosing, efficacy, and safety of CV drugs are the first step to design safer and more effective personalized treatments

ADR, adverse drug responses; CV, cardiovascular; CVD, cardiovascular diseases; PD, pharmacodynamics; PK, pharmacokinetics.

European Heart Journal - Cardiovascular Pharmacotherapy (2017) 3, 163–182

INNOVATIVE SOLUTIONS BASED ON GENDER/SEX?

Society of Thoracic Surgery Gender-Specific Practice Guidelines for Females 2005
Use internal mammary artery for bypass
Maintain blood glucose 100–150 mg/dl
Maintain intraoperative hematocrit above 22%
Follow off-pump CABG indications when appropriate
Account for body size when administering anesthetic and sedative drugs
Maintain euthryroid state during surgery
Do not use hormone replacement therapy for postmenopausal females undergoing CABG

Eur J Cardiothorac Surg. 2011;40(3):715-721.

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CLINICAL TRIALS FOR TAKOTSUBO

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Save this study

Autonomic Modulation in Takotsubo Syndrome

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT03324529

Recruitment Status ⓘ: Not yet recruiting
First Posted ⓘ: October 27, 2017
Last Update Posted ⓘ: March 30, 2018

See **Contacts and Locations**

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New York University School of Medicine

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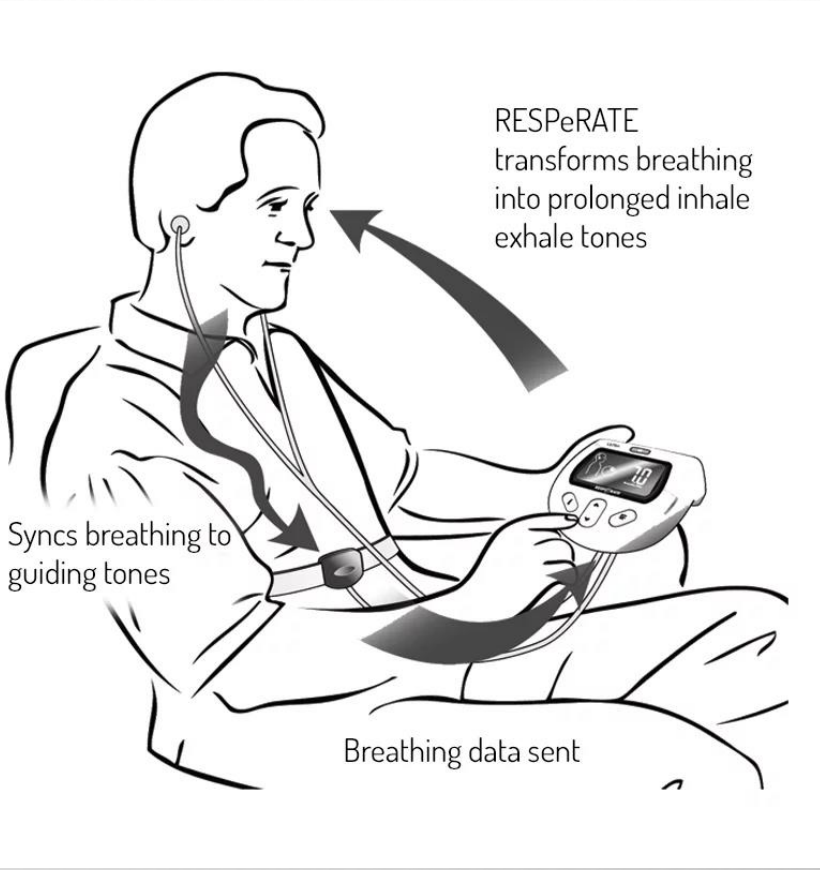
BEILINSON • HASHARON

CLALIT



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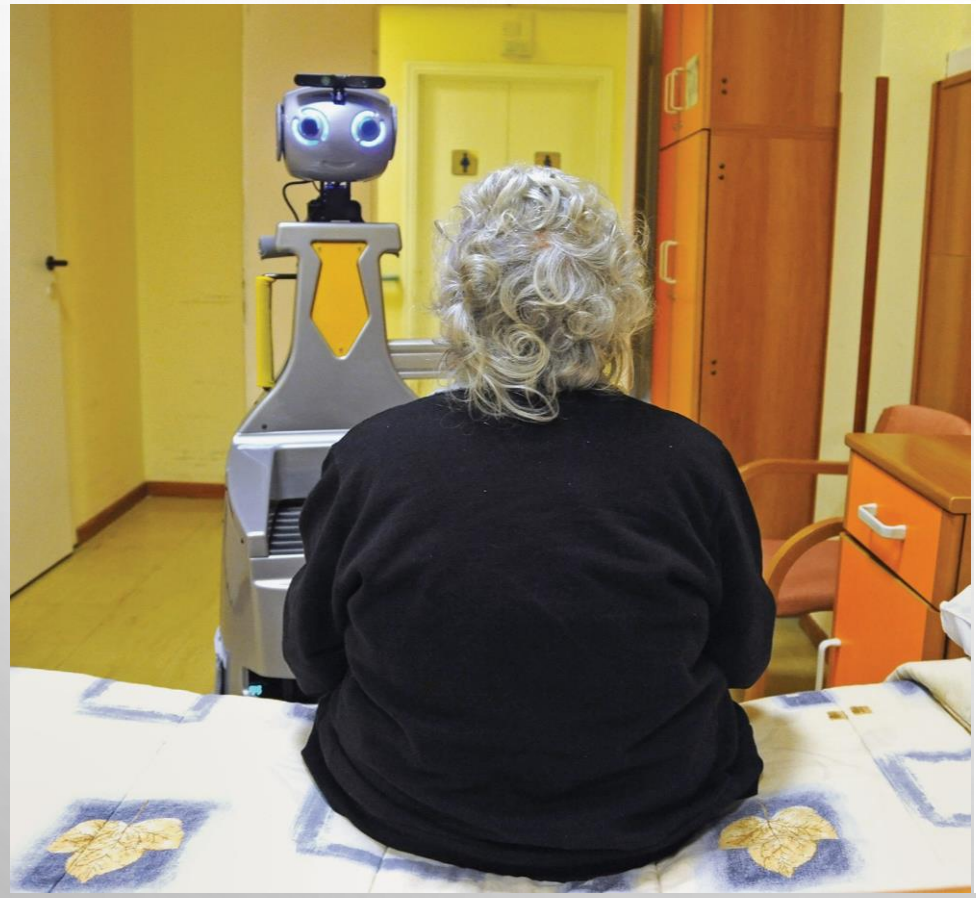
INNOVATION FOR ELDERLY PATIENTS



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