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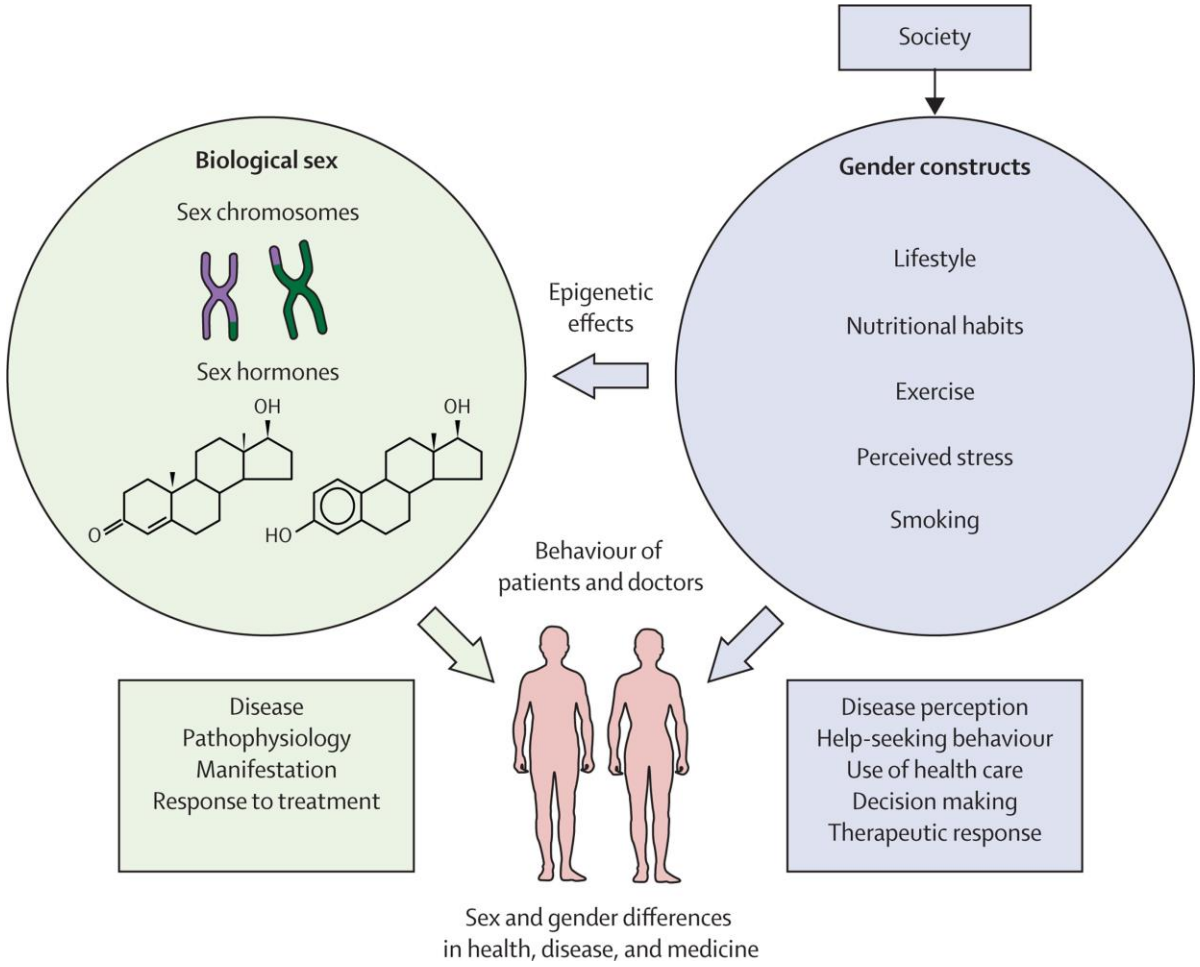
Hart en Vaat Instituut

SEXE VERSCHILLEN IN HART- EN VAATZIEKTEN
VROUW SPECIFIEKE RISICOFACTOREN

Chahinda Ghossein, MD, PhD, FESC

Cardiologist

SEKSE, GENDER EN DE INTERACTIE



STERFTE DOOR DE JAREN HEEN

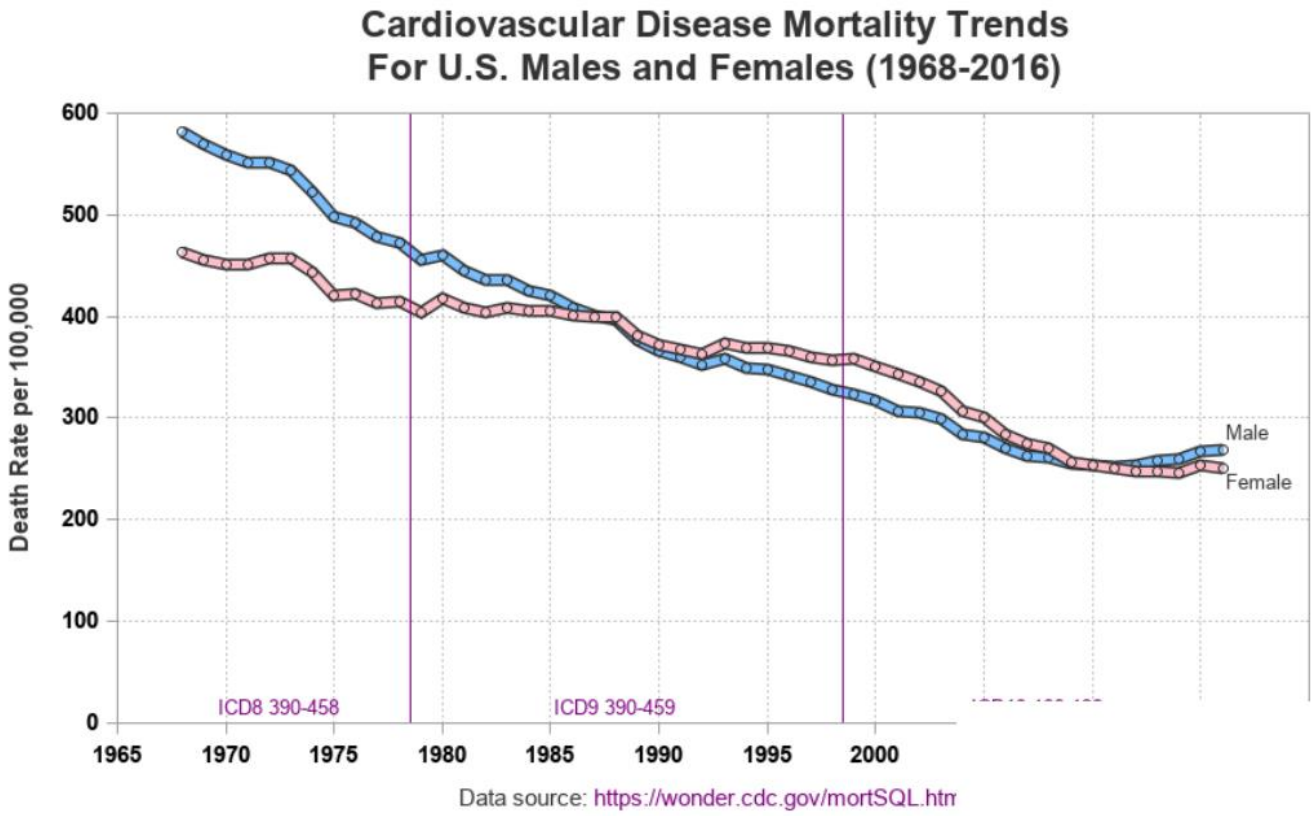
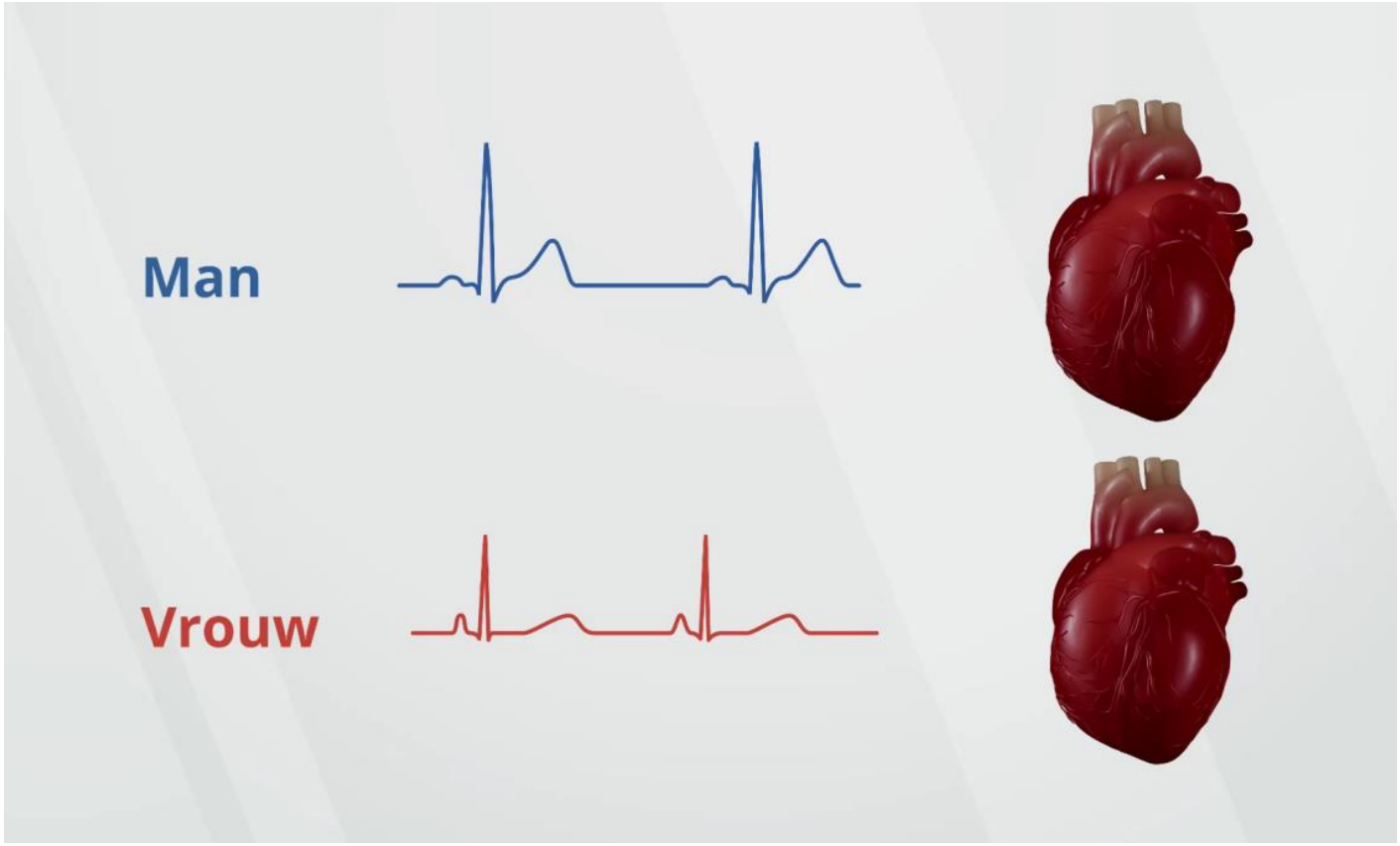


Table I Standard echocardiographic and Doppler measurements

Chamber	Parameter	Normal values
Left ventricle	LV end-diastolic dimension (mm)	≤58.4 (M), ≤52.2 (F)
	LV end-systolic dimension (mm)	≤39.8 (M), ≤34.8 (F)
	LV EDV index (mm/m^2)	<75 (M), <62(F)
	LV ESV index (mm/m^2)	<32 (M), <25(F)
	Relative wall thickness	≤0.42
	LVM index (g/m^2)	≤102 (M), ≤88(F)
	LVEF, biplane (%)	≥52 (M), ≥54(F)
	Transmitral *E* velocity (cm/s)	<50
	Transmitral *E* velocity DT (ms)	>160 to < 220
	Transmitral *E/A* ratio	>0.8 to < 2.0
	Septal annular e′ velocity (cm/s)	>7
	Lateral annular e′ velocity (cm/s)	>10
	LV *E*/e′ (average) ratio	<14
Left atrium	Maximal LAVi (mL/m^2)	≤34
Thoracic aorta	Annulus (cm/m^2)	≤1.4 (M and F)
	Sinus of Valsalva (cm/m^2)	≤1.9 (M), ≤2.0 (F)
	Sinotubular junction (cm/m^2)	≤1.7 (M and F)
	Proximal ascending aorta (cm/m^2)	≤1.7 (M), ≤1.9 (F)
Right ventricle	RV basal diameter (mm)	<42
	RV mid diameter (mm)	<36
	RVOT proximal diameter (mm)	<36
	RVOT distal diameter (mm)	<28
	TAPSE (mm)	>17
	Tricuspid annular s′ velocity (cm/s)	>9.5
	Fractional area change (%)	>35
Right atrium	RAVi (mL/m^2)	<30 (M), <28 (F)



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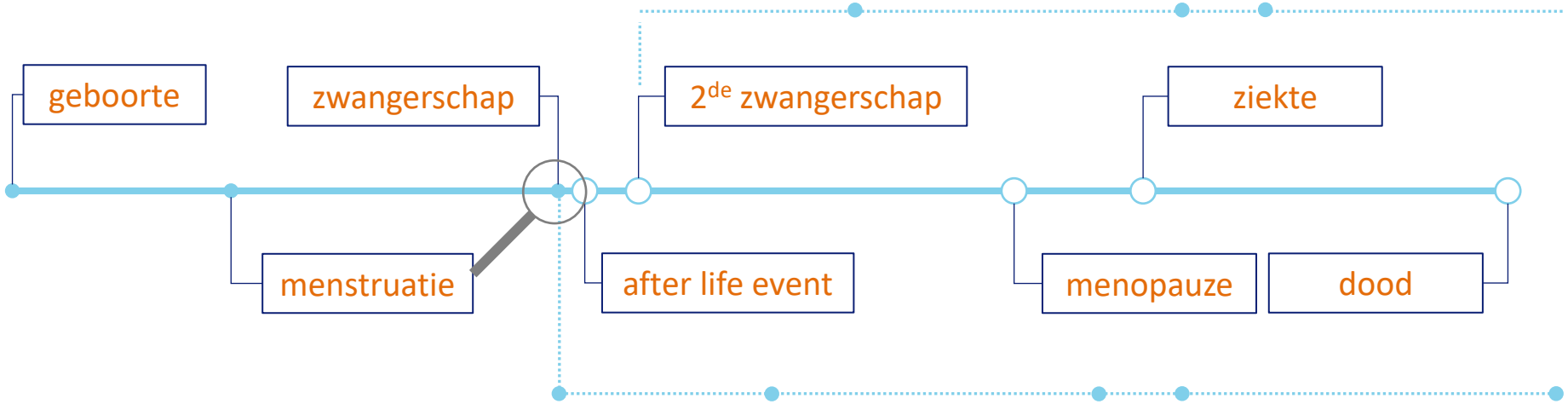
Levenslijn vrouw



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CONVENTIONELE RISICOFACTOREN

- Leeftijd >55jaar
- Roken
- Hoge bloeddruk
- Familale belasting: (man <55jaar, vrouw <65 jaar)
- Suikerziekte
- Perifeer vaatlijden
- Verstoord cholesterol (hoog LDL en laag HDL)
- Hoog triglyceride
- Nierfunctieverlies
- Reuma, auto-immuun ziekte
- Obesitas/overgewicht
- Stress

VERSCHILLEN IN KLASSIEKE RF

- Laag HDL predictiever dan hoog LDL
- Triglyceride predictiever in oudere vrouwen, vooral als >400 mg/dL
- Diabetes: verdubbelt het risico op fataal coronairlijden
- Roken:
  - Geassocieerd met 50% van alle hart events bij vrouwen
  - Risico verhoogd zelfs bij matig gebruik
  - Rokende vrouwen hebben 6x verhoogd risico op hartinfarct (vs. 3x bij mannen)
  - Risico is hoger bij vrouwelijke rokers op alle leeftijd

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Rich-Edwards, JW et al. NEJM 1995; Miller VT. Atherosclerosis 1994; Orth-Gomer K. Circulation 1997

VROUWSPECIFIEKE CV RISICOFACTOREN

Obstetrisch

- Menarche
- Polycysteus ovarium syndroom
- Vroege menopause/primaire ovariële insufficientie (POI)

Non-obstetrisch

- Vasculair aangedane zwangerschappen
  - Zwangerschapshypertensie
  - Preeclampsie
  - HELLP syndroom
- Herhaalde miskramen
- Onverklaarde subfertiliteit
- Vroeggeboorte
- Groeivertraagd kind
- Zwangerschaps diabetes

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MENARCHE

<12 jaar

>14 jaar

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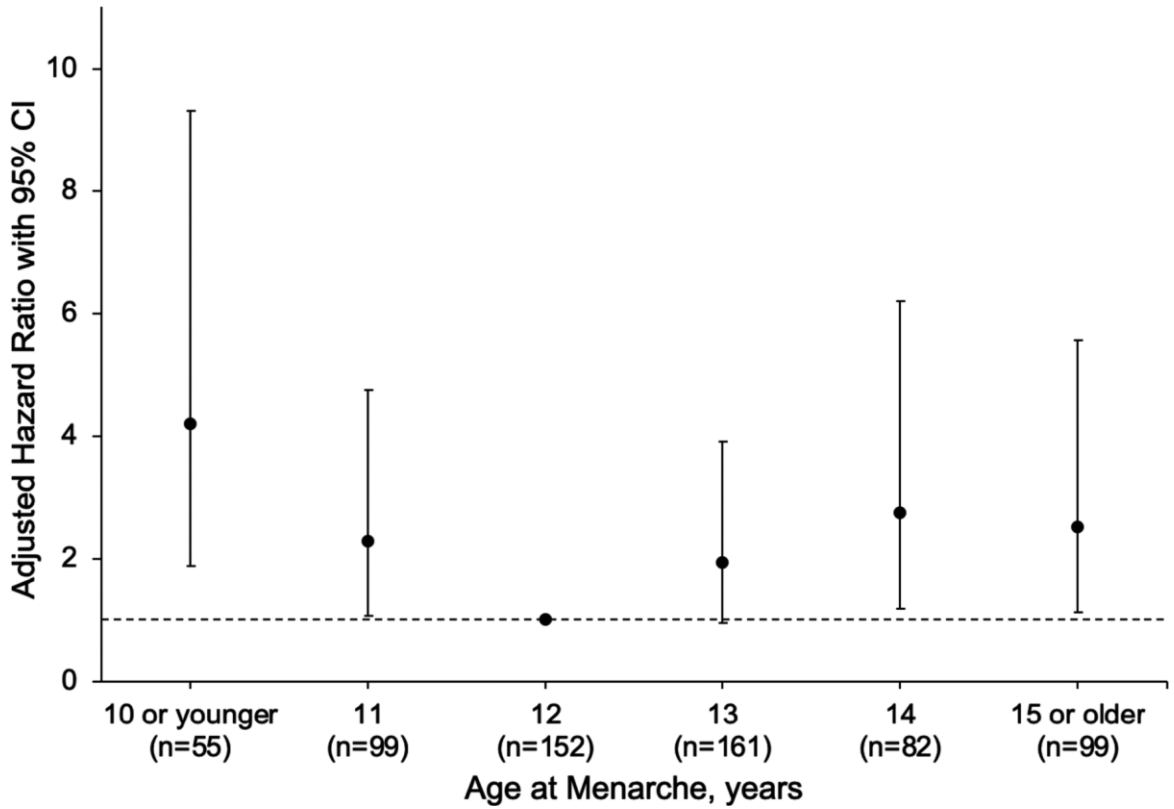

Julie J. Lee. JAHA. 2019

POLYCYSTEUS OVARIUM SYNDROOM

Diagnose:

- Oligo- annovulatie
- Hyperandrogenisme
- Ovariumcystes

Associatie:

- DM II
- Hypertensie
- Pro-atherogeen lipidenprofiel
- Metabool syndroom

HVZ:

- geen hoger risico op ischemisch hartlijden

- wel hoger risico op CVA/TIA

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MENOPAUZE

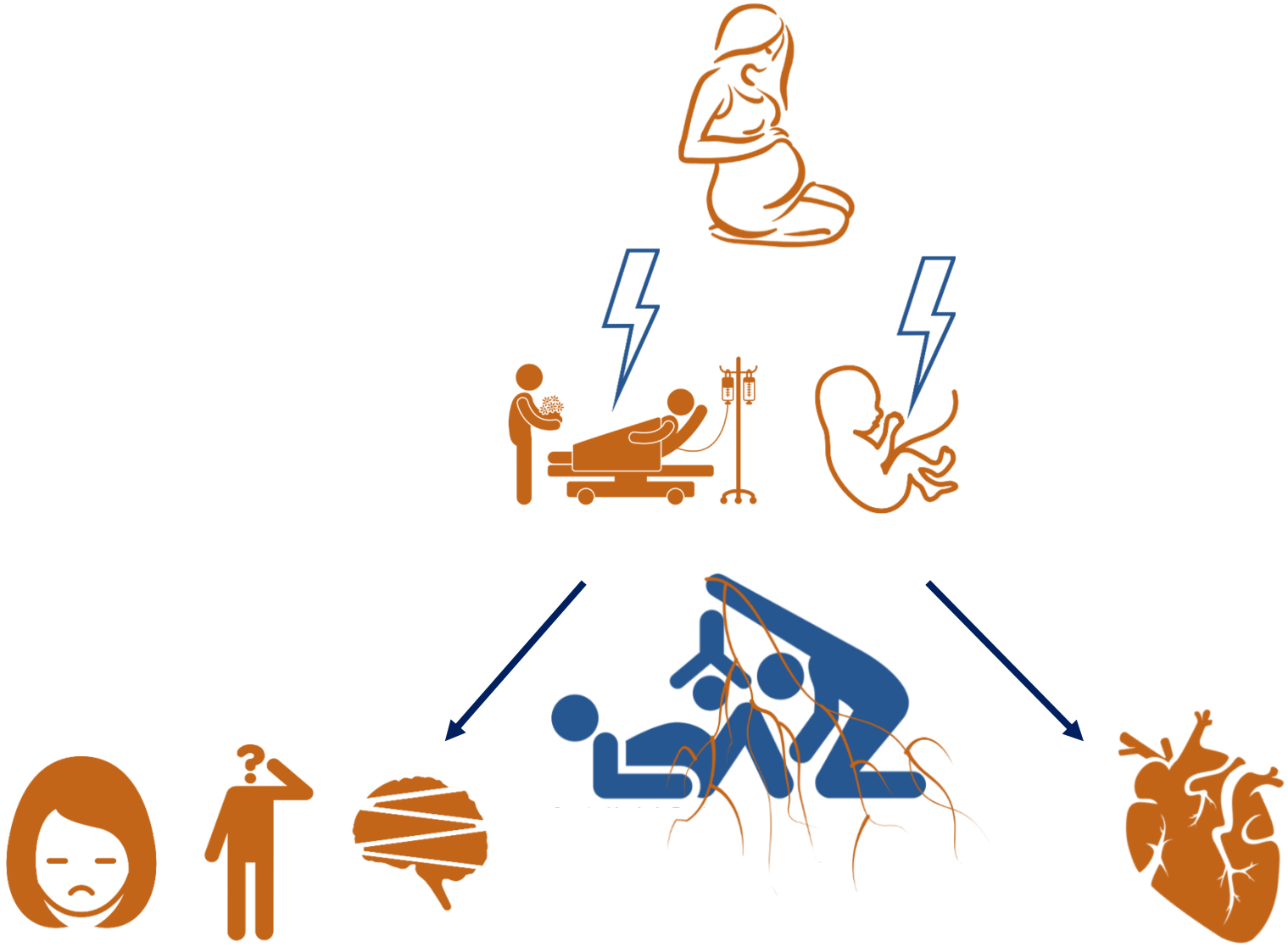
- 1 jaar uitblijven van menstruatie
- Gemiddeld: 51 jaar
- POI:
  - <40 jaar
  - 1%
  - 1.4x hoger risico op HVZ
- Ovariectomie <50 jaar
  - Verhoogt HVZ risico
- HRT tot normale menopauzeleeftijd tenzij….
  - Verhoogd risico op borstkaker
  - BRCA-dragerschap

Obstetrisch

Zwangerschap en bevalling
- 170 duizend bevalling jaarlijks in Nederland
- 5-10% placenta problemen

Placenta syndroom: preeclampsie, zwangerschapshypertensie, foetale groeirestrictie, placenta loslating, HELLP syndroom

Preeclampsie
- Definitie:
  - Verhoogde bloeddruk + proteïnurie
  - >20 weeks van de zwangerschap
- Endotheel ziekte



Ghossein-Doha et al.; Hypertension 2015
Melchiorre et al.; Hypertension 2015
Baecke et al.; Obstet &Gynecol 2009
Engelhard et al.; Gen Hosp Psychiatry 2002

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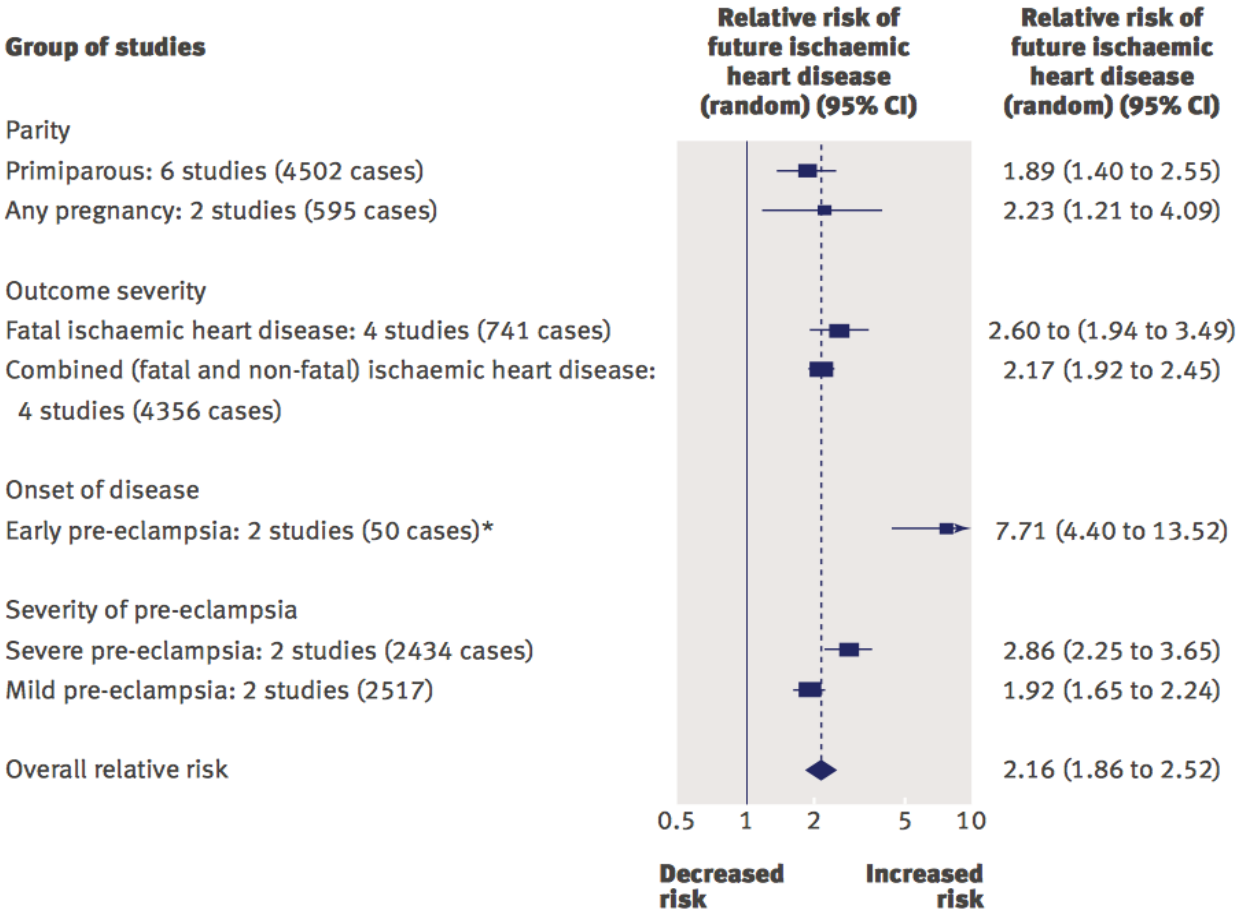
RISICO OP HARTINFARCT NA PREECLAMPSIE



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Bellamy et al; BMJ 2007

PE as a CV risk factor

Table 1. Risk ratios for CV risk factors for CVD		
Risk factor	Risk ratio for CVD	95% CI
Preeclampsia	2.2	1.9-2.5
Obesity	2.3	1.9-2.7
Smoking	2.9	2.4-3.5
Hypertension	2.9	2.6-3.4
Diabetes	4.3	3.5-5.2
Early preeclampsia	7.7	4.4-13.5
Familiar hypercholesterolaemia	8.5	5.3-13.8

Bellamy et al; BMJ 2007

Yusuf S et al. Lancet 2004

Umans-Eckenhausen; Circulation 2002

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ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3227–3337
doi:10.1093/eurheartj/ehab484

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice

Sex-specific conditions	In women with a history of pre-eclampsia and/or pregnancy-induced hypertension, periodic screening for hypertension and DM should be considered.[184–187]	IIa	B
	In women with a history of polycystic ovary syndrome or gestational DM, periodic screening for DM should be considered.[188–191]	IIa	B
	In women with a history of premature or stillbirth, periodic screening for hypertension and DM may be considered.[192,193]	IIb	B
	Assessment of CVD risk should be considered in men with ED.	IIa	C

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ED = erectile dysfunction; LV = left ventricular; OSA = obstructive sleep apnoea.

[a]Class of recommendation.

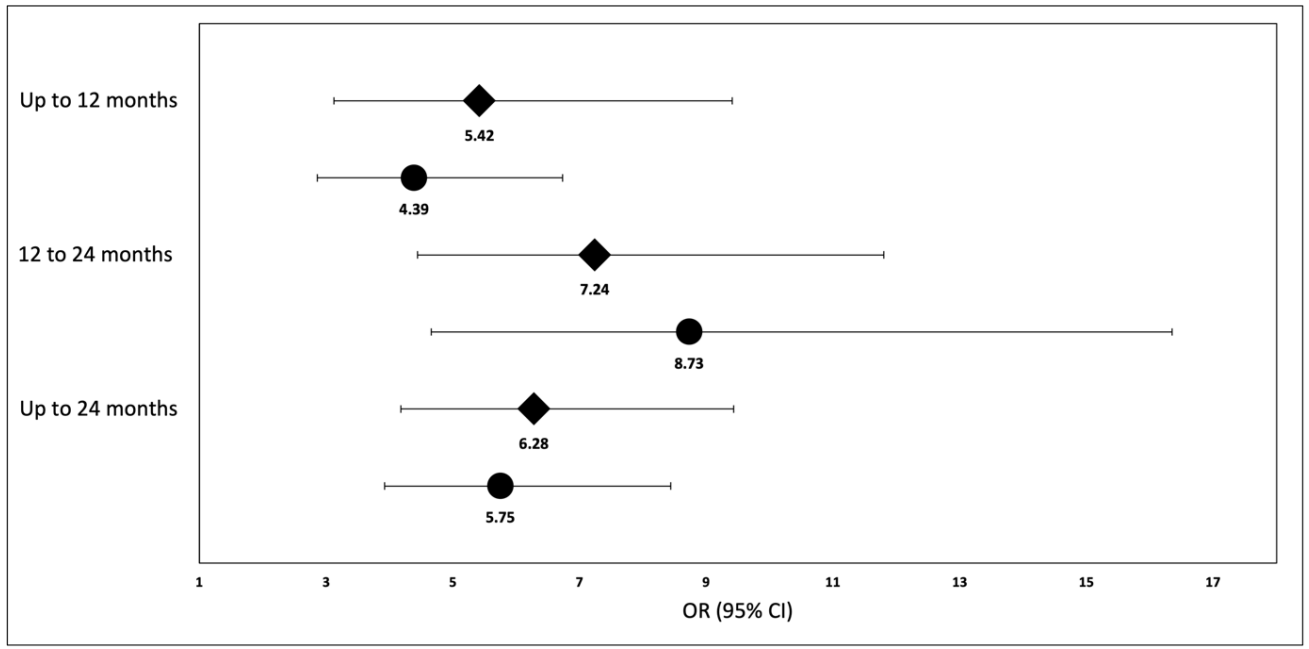
[b]Level of evidence.

PERIPARTUM AND LONG-TERM MATERNAL

CARDIOVASCULAR HEALTH AFTER PRE-ECLAMPSIA

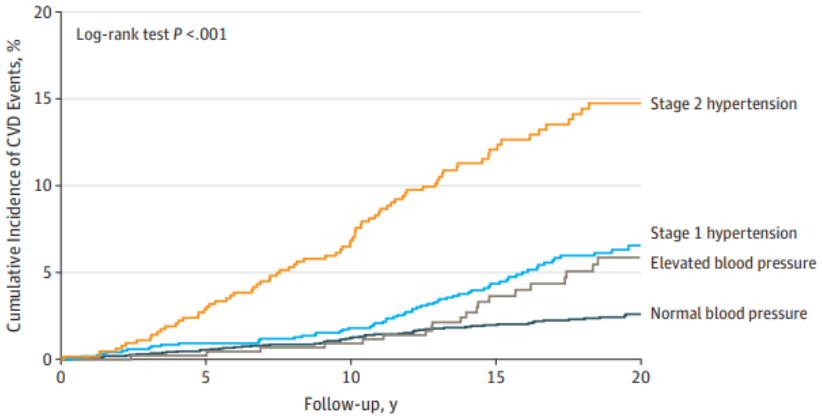
Veronica Giorgione[1]*, Gwyneth Jansen[2,3]*, Jamie Kitt[4]*,

Chahinda Ghossein-Doha[2,5], Paul Leeson[4], Basky Thilagalathan[1]



Giorgione… Ghossein-Doha et al, Hypertension 2023

MODIFIABLE RISK FACTOR

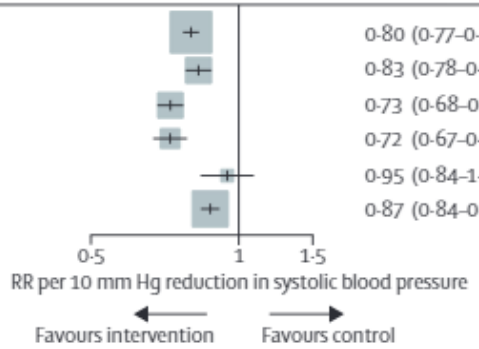


aHR 3.49 (95% CI 2.42-5.05)

aHR 1.75 (95% CI 1.22-2.53)
aHR 1.67 (95% CI 1.01-2.77)

N=4851
FU: 18.8 y

	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)



Yano, Reis et al. JAMA, 2018
Ettehad, Emdin et al. Lancet, 2016

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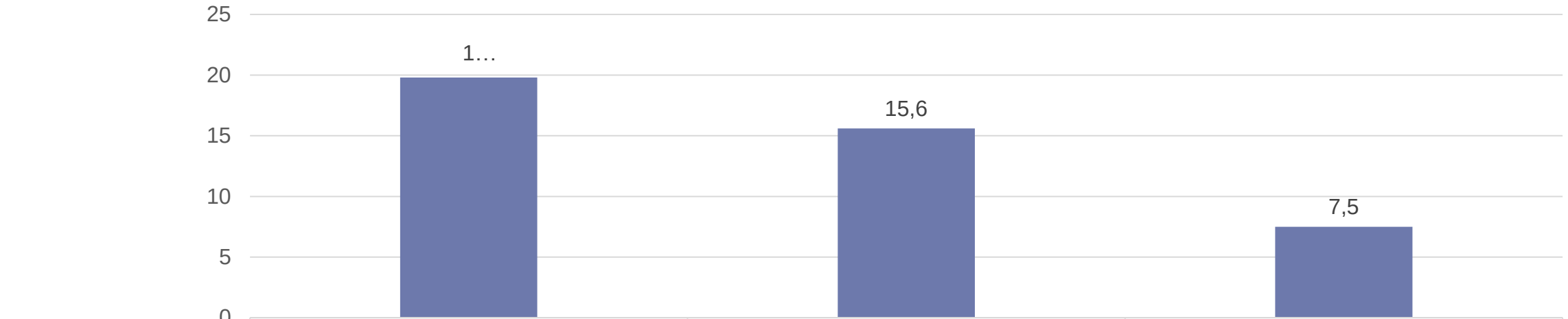
METABOOL SYNDROOM

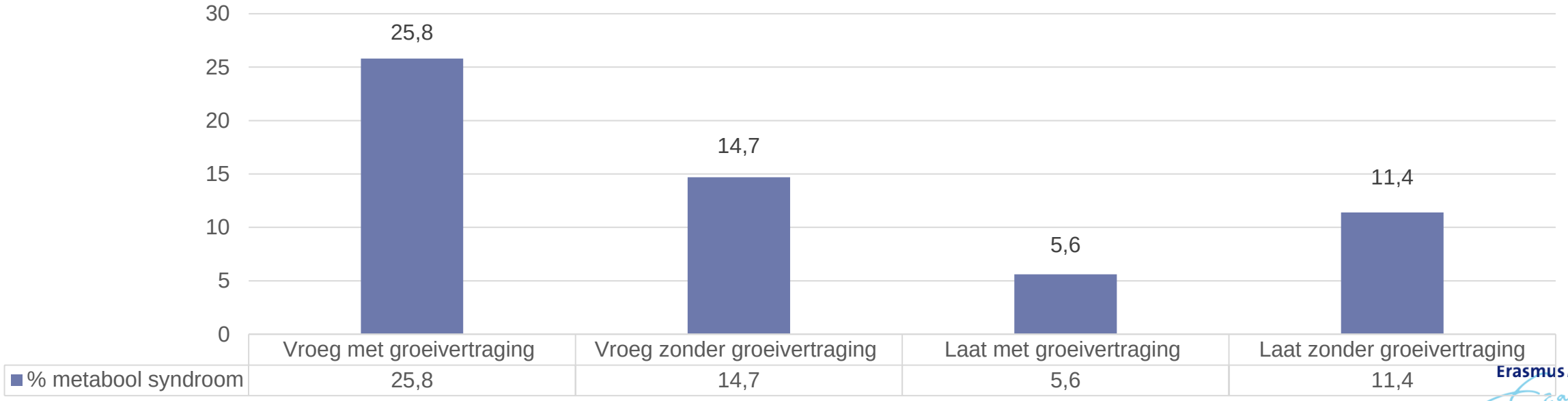
Is er verschil in het metabool syndroom na de zwangerschap tussen vrouwen met
1) pre-eclampsie; 2) groeivertraging van het kind; 3) allebei?



Hooijschuur, Ghossein-Doha; UOG, 2018

METABOOL SYNDROOM

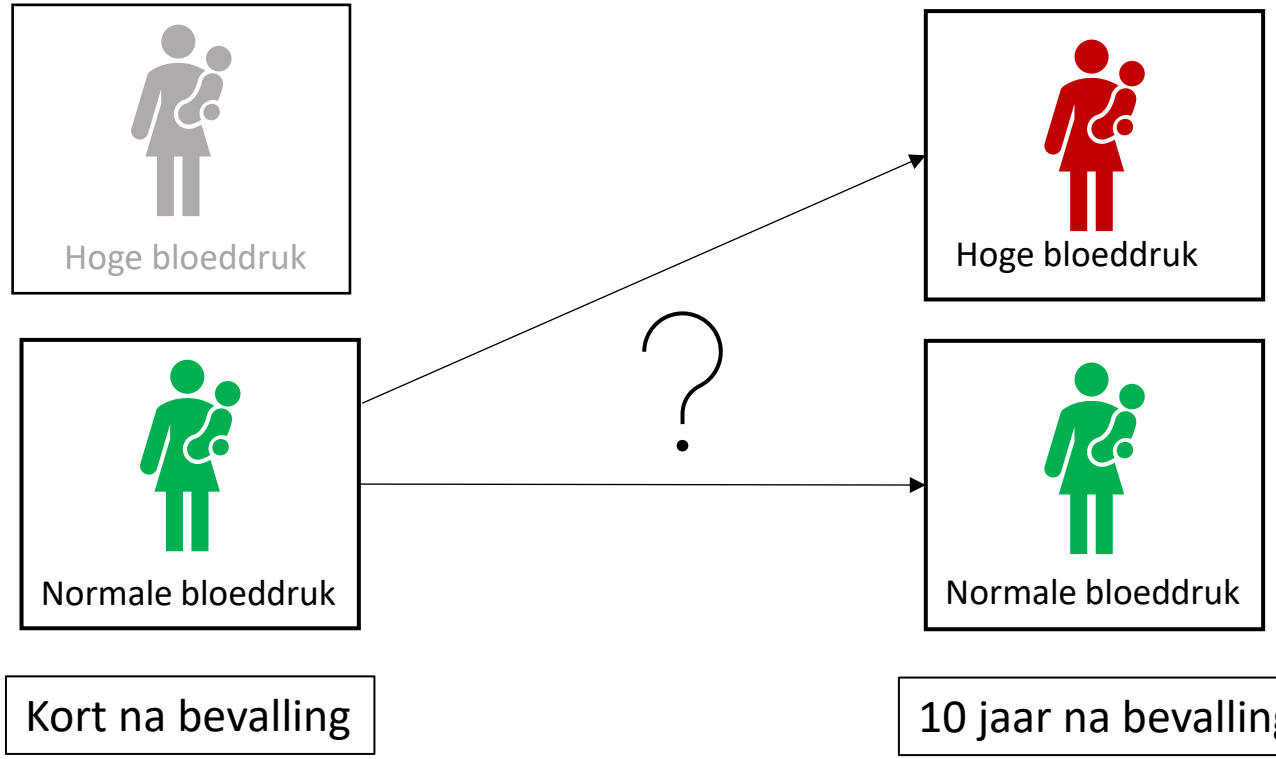
Maakt het moment dat pre-eclampsie optreedt in de zwangerschap in combinatie met wel of geen groeivertraging bij het kind uit in het voorkomen van het metabool syndroom na pre-eclampsie?



Hooijschuur, Ghossein-Doha; AJOG 2016

HOGE BLOEDDRUK NA PRE-ECLAMPSIE

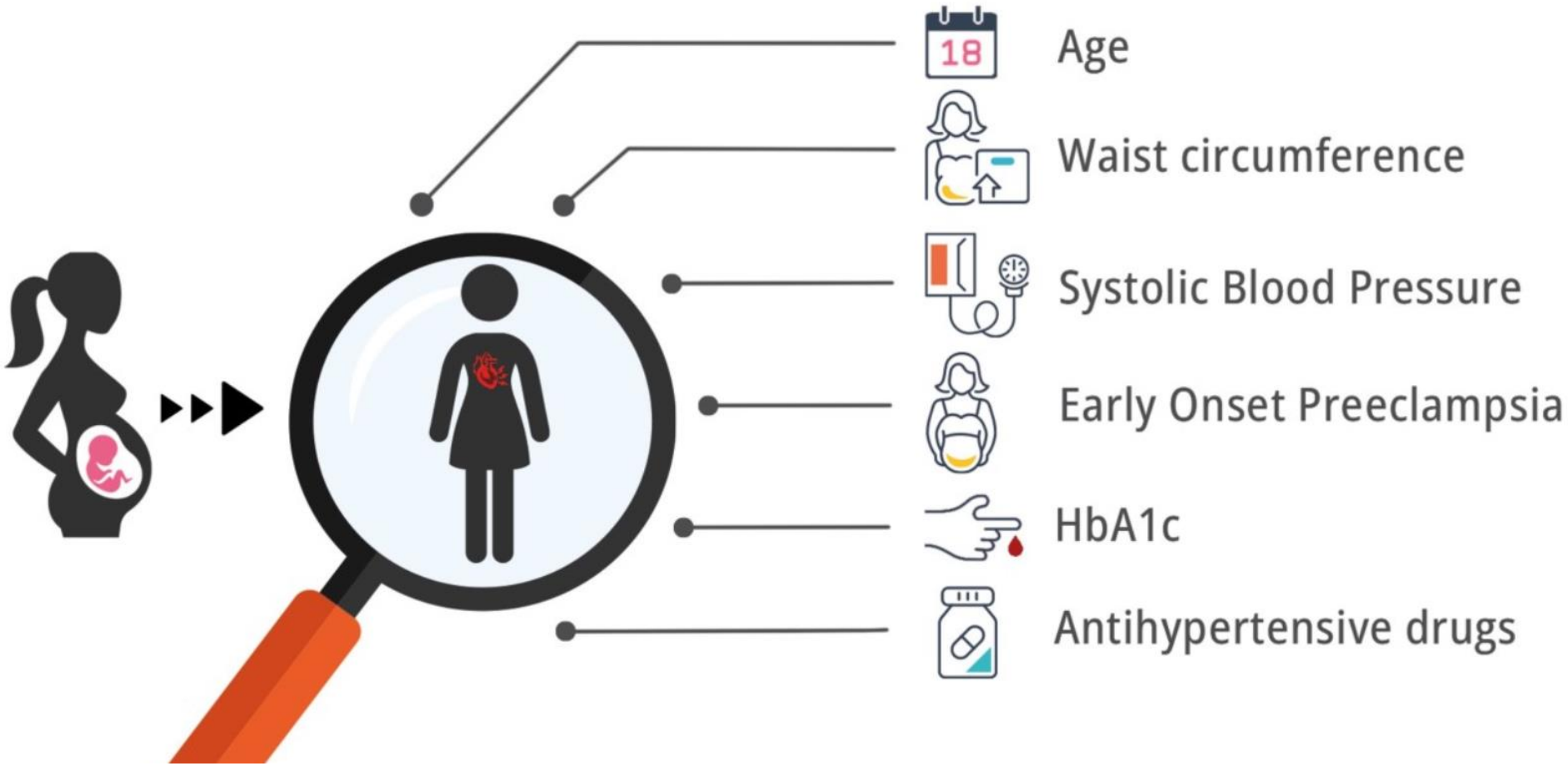
Kunnen we in vrouwen met pre-eclampsie het risico op hoge bloeddruk in de jaren na de bevalling voorspellen?



Met een model met 5 variabelen kan kort na de bevalling het risico op hoge bloeddruk 10 jaar later voorspeld worden

Hooijschuur…..;Ghossein-Doha; UOG; 2023

A Prediction Model Based on Easily Available Markers for Aberrant Cardiac Remodeling in Women after Pregnancy.



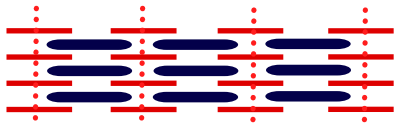
Mohseni…..; Ghossein-Doha; Hypertension; 2023

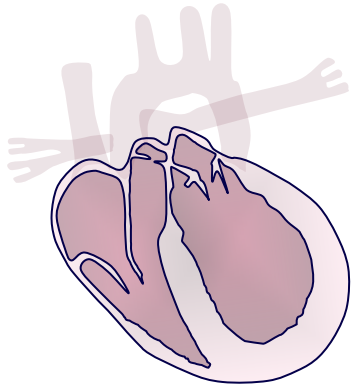
△ volume load ↑
pressure load ↓

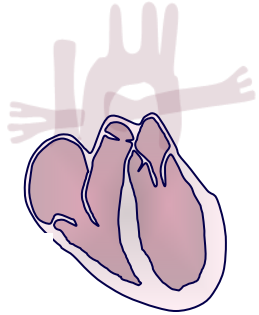
Normal Pregnancy
Sustained Aerobic exercise

△ LVM 28.3 (24%)
△ RWT 0.03 (10%)

Eccentric remodeling





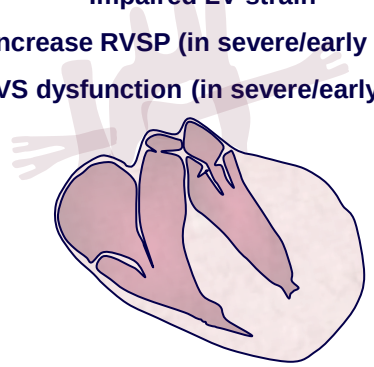


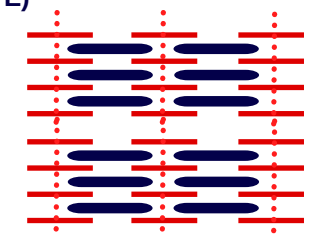
△ volume load ↓
pressure load ↑

Preeclampsia
Chronic hypertension

△ LVM 92.0 (95%)
△ RWT 0.14 (56%)

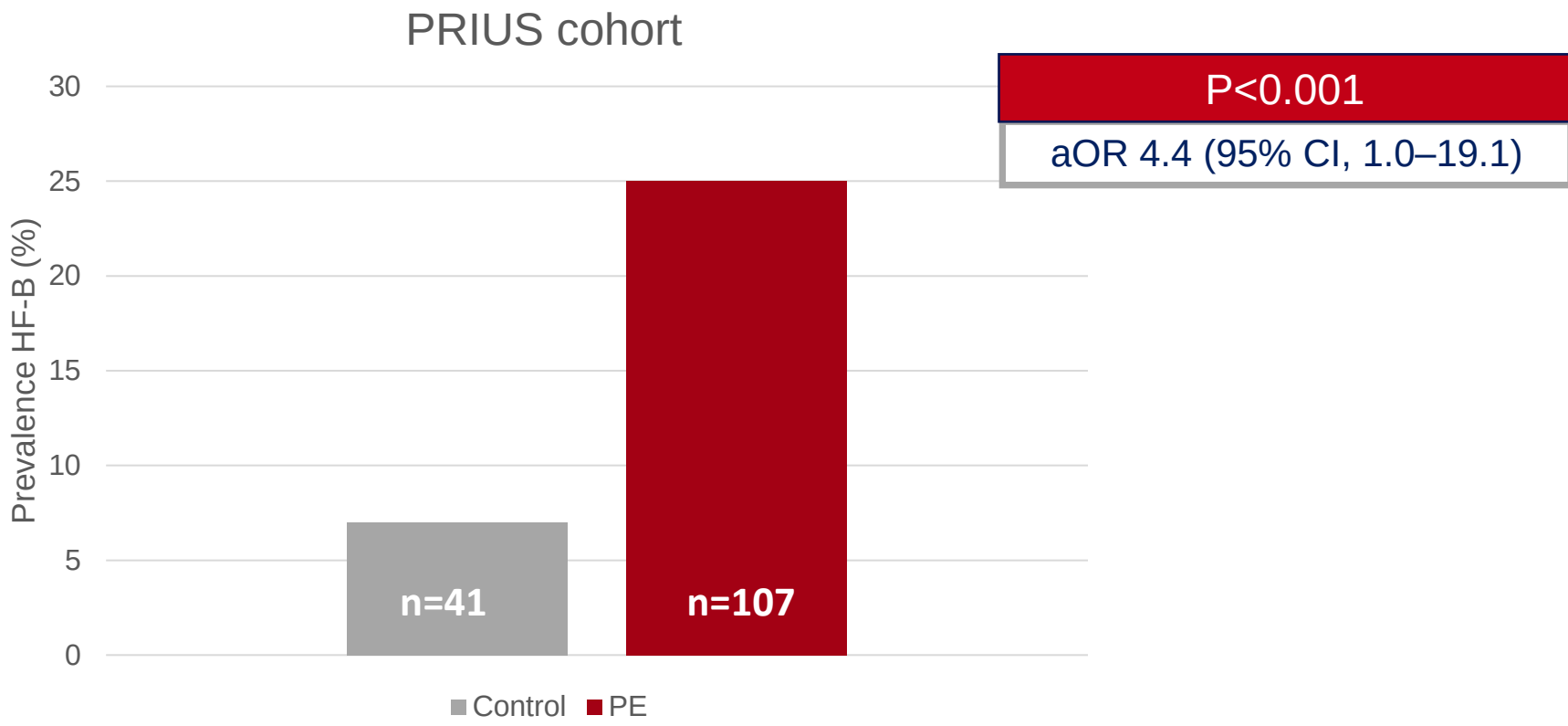
Concentric remodeling
Diastolic dysfunction
Impaired LV strain
Increase RVSP (in severe/early PE)
RVS dysfunction (in severe/early PE)





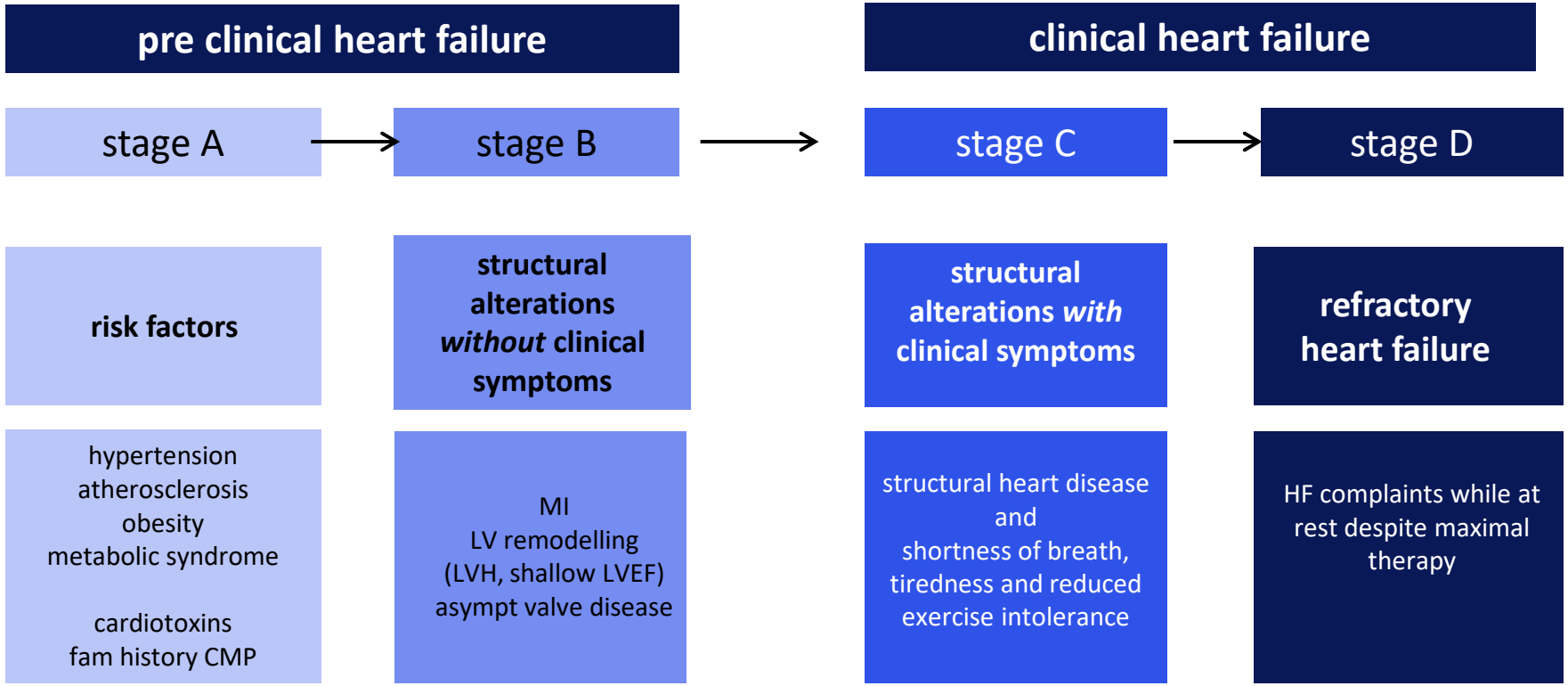
Ghossein-Doha JACC 2018

Prevalence HF B



Ghossein-Doha et al; UOG 2016

Stages of Heart Failure



1 † 5

Jessup et al. Circulation 2009

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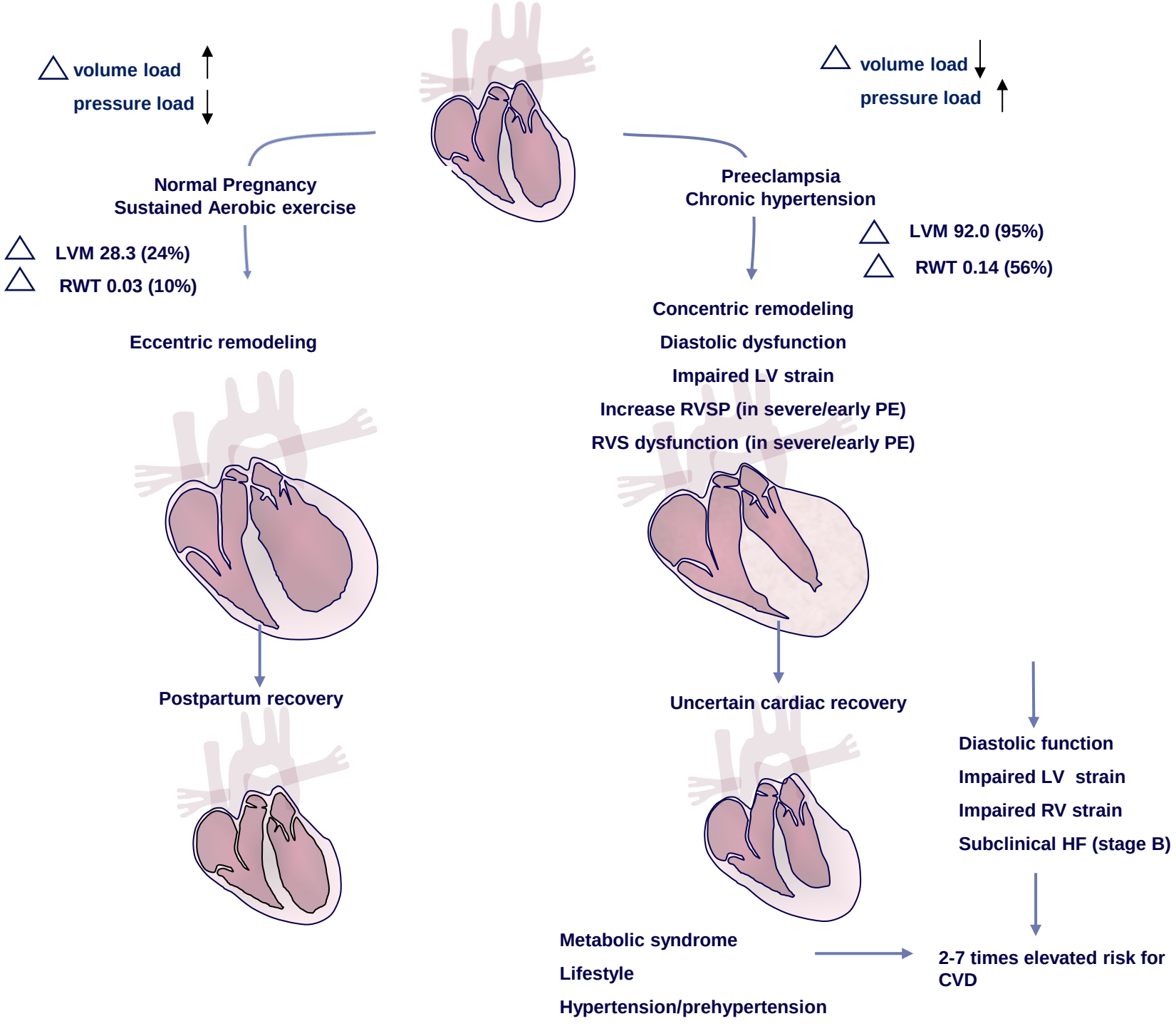


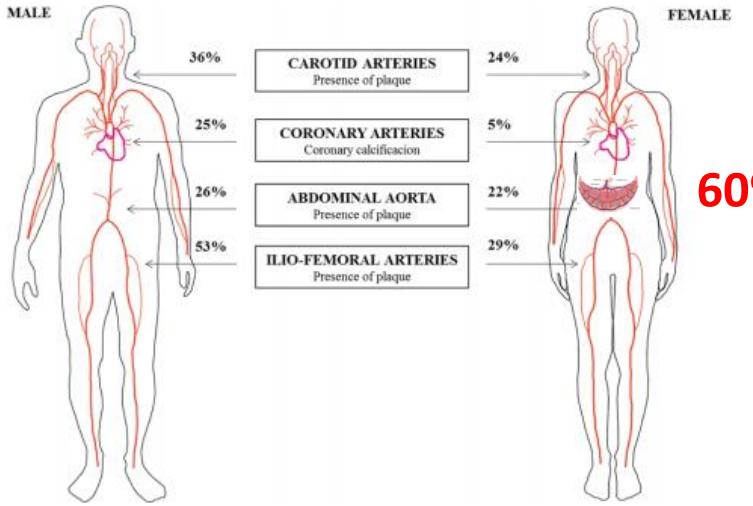
Ghossein-Doha JACC 2018

Meer vaatlijden na zwangerschapsvergiftiging

Meer verkalkte vaten

Vaker vet-opstapeling aan binnenbekleding van vaten

Vaker schade aan kleinste bloedvaatjes



60% vetophoping in placenta vaatjes

Maastricht UMC+

Leticia Fernández-Friera et al; Circulation, 2014
Steevens D, Placenta, 2014

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Early gestational age at preeclampsia onset is associated with subclinical atherosclerosis 12 years after delivery

MARTIN CHRISTENSEN[1,2], CAMILLA SKOVHUS KRONBORG[3], RASMUS KIRKESKOV CARLSEN[4], NIKOLAJ ELDRUP[5] & ULLA BRETH KNUDSEN[2,6]

Table 4. Multivariate regressions between main outcome measures and pregnancy exposure (normotensive, late-onset or early-onset preeclampsia) adjusted for age and time since delivery.

Outcome measure	Variable	Odds ratio	*p*-value
Carotid plaque presence	Pregnancy exposure		
	Normotensive	Reference	–
	Late-onset	0.47 (0.03; 7.26)	0.59
	Early-onset	6.40 (0.74; 55.49)	0.09
	Late-onset	Reference	–
	Early-onset	13.72 (1.02; 184.07)	<0.05

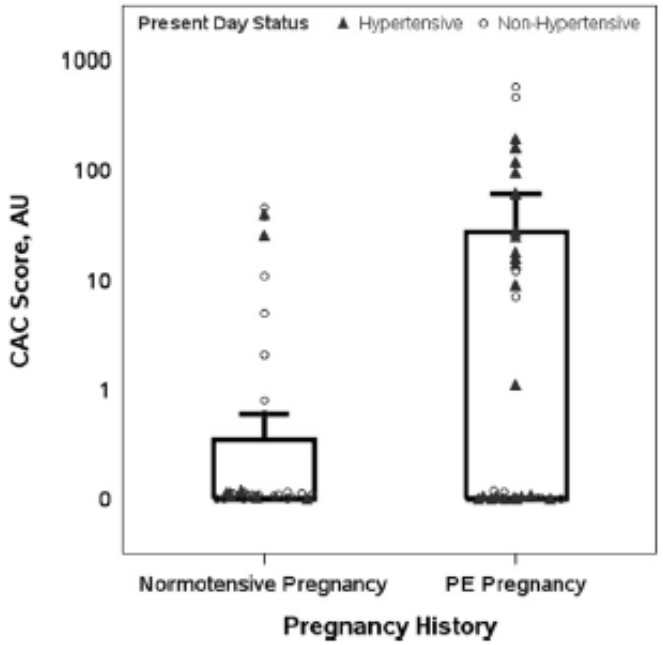
Christensen, AOG, 2018

A history of preeclampsia is associated with a risk for coronary artery calcification 3 decades later

Wendy M. White, MD; Michelle M. Mielke, PhD; Philip A. Araoz, MD; Brian D. Lahr, MS; Kent R. Bailey, PhD; Muthuvel Jayachandran, PhD; Virginia M. Miller, PhD; Vesna D. Garovic, MD

FIGURE

Distribution of coronary artery calcification (CAC) scores in subjects with and without history of preeclampsia (PE) stratified by present day hypertension



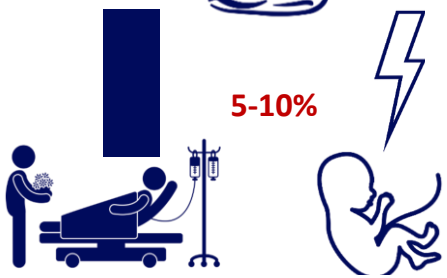
	Normotensive pregnancy N=40	PE N=40	P-value
CAC (Mean, AU)	4.3 (11.7)	54.1 (126.3)	0.007
Frequency of CAC >0	10 (25%)	19 (49%)	0.029
Frequency of CAC score >50 AU	0 (0%)	9 (23%)	0.001

TAKE HOME MESSAGE

- Klassieke risico factoren zijn (minstens) net zo belangrijk voor vrouwen
- Vrouw specifieke risicofactoren
  - Obstetrisch
  - Niet obstetrisch
- Zwangerschap spiegel voor de gezondheid van de vrouw

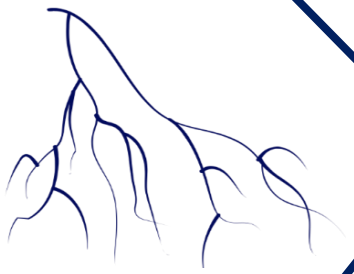
PEARLS studie

30% meer ciculerend volume
40% dikkere hartspier



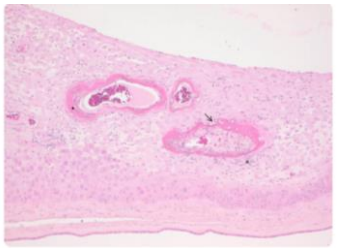
5-10%

8 x
IHD



Hypertensie
Hoger perifere vasculaire resistentie
Laag plasma volume
Hogere LDL

40-60%



Ghossein-Doha et al.; Hypertension 2015
Moe et al 2018, Hypertension
Stevens, AJOG, 2014, AJOG, 2015

TROMBOSE, INFARCT, BLOEDING

Maastricht UMC+

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PEARLS studie

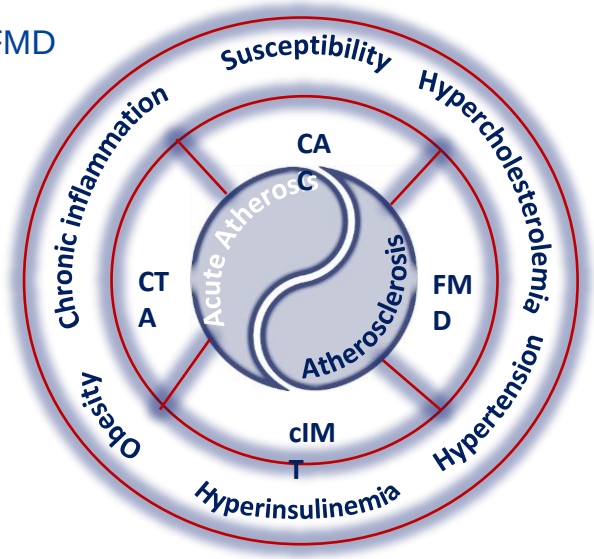
Hypothese: Acute atherose weerspiegelt subklinisch systemische atherosclerose

Studiedesign: Prospectieve cohort

Studiepopulaties: PE (n=184) vs controle (n=62)

Inclusie: Bij bevalling placenta onderzoeken

Follow up: 1 jaar later: CTA, MetS, cIMT, FMD



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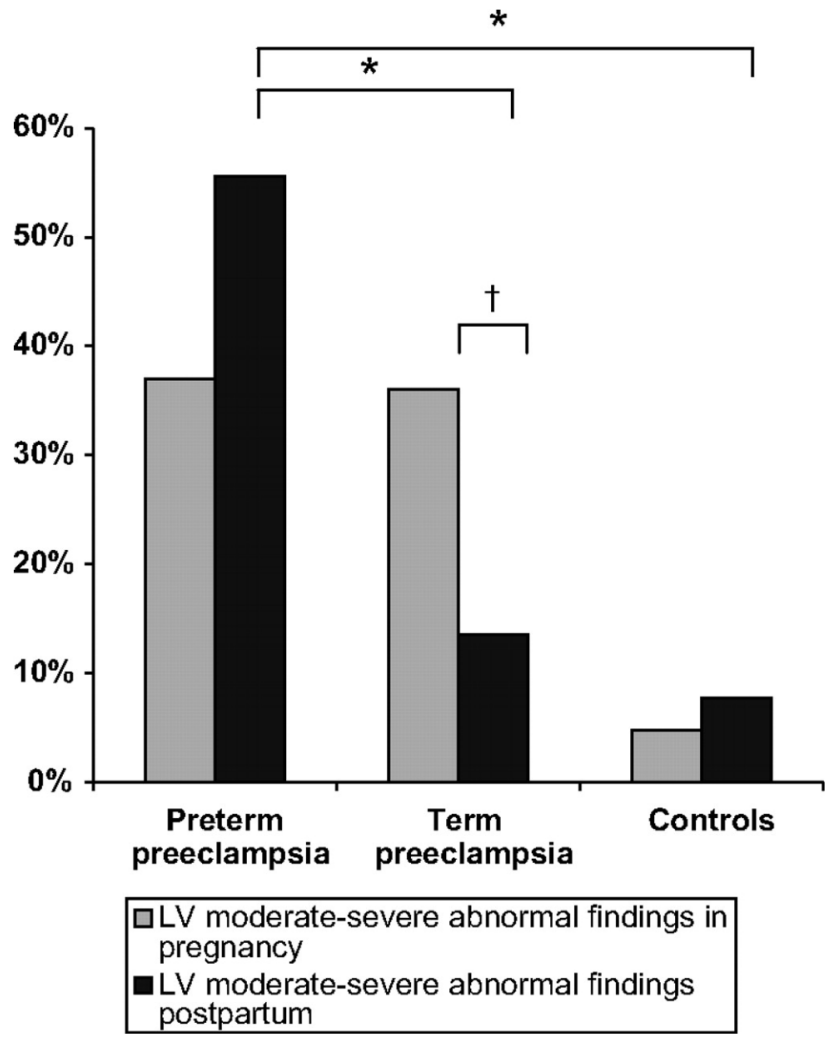
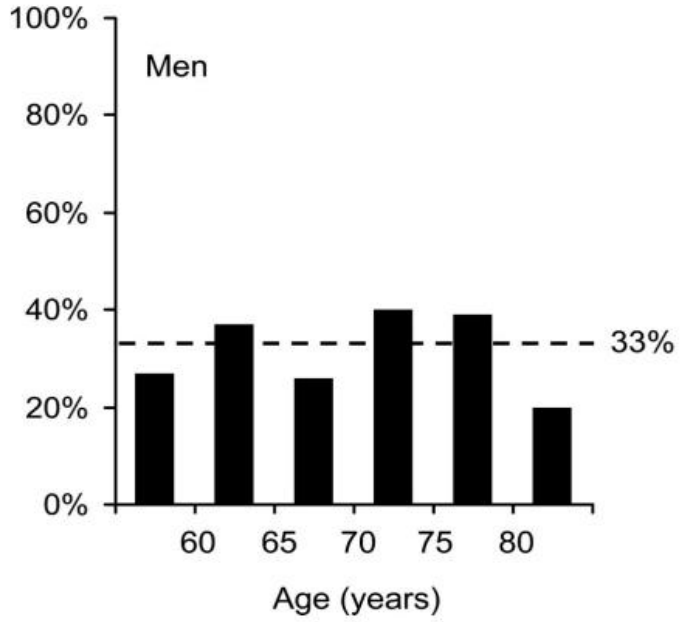
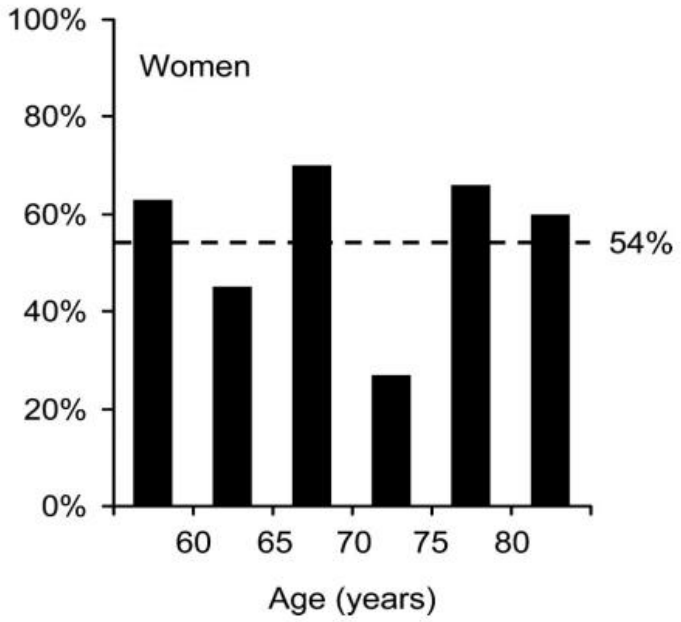
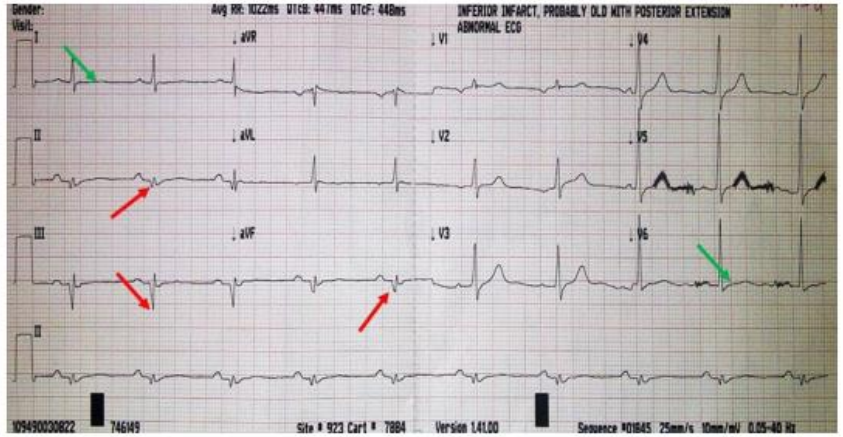


Melchiorre, Hypertension 2011

STILLE INFARCTEN







De Torbal Eur Heart J 2006, van der Ende Int J Cardiol 2017

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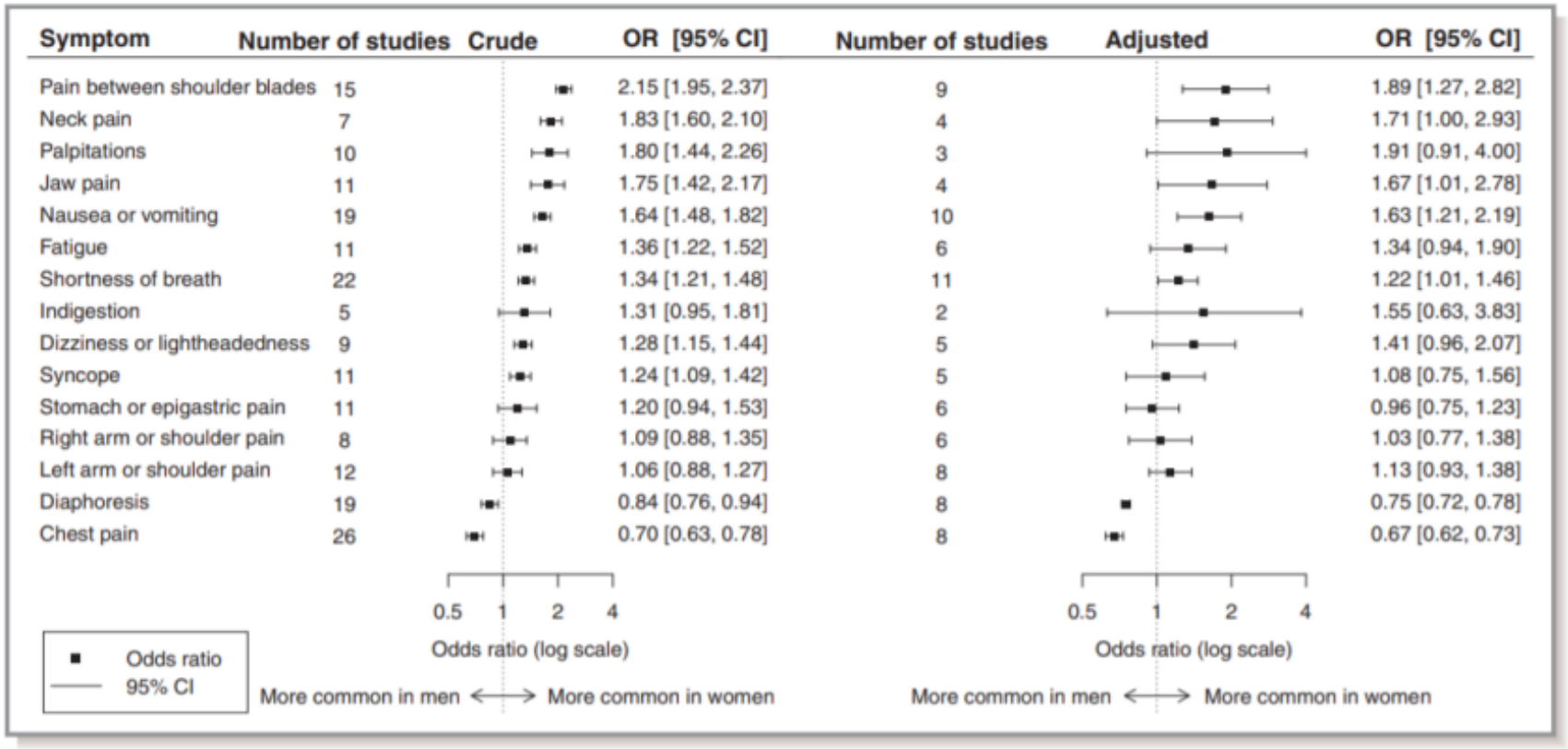
SYMPTOMEN BIJ VROUWEN



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WEINIG VROUWEN IN STUDIES

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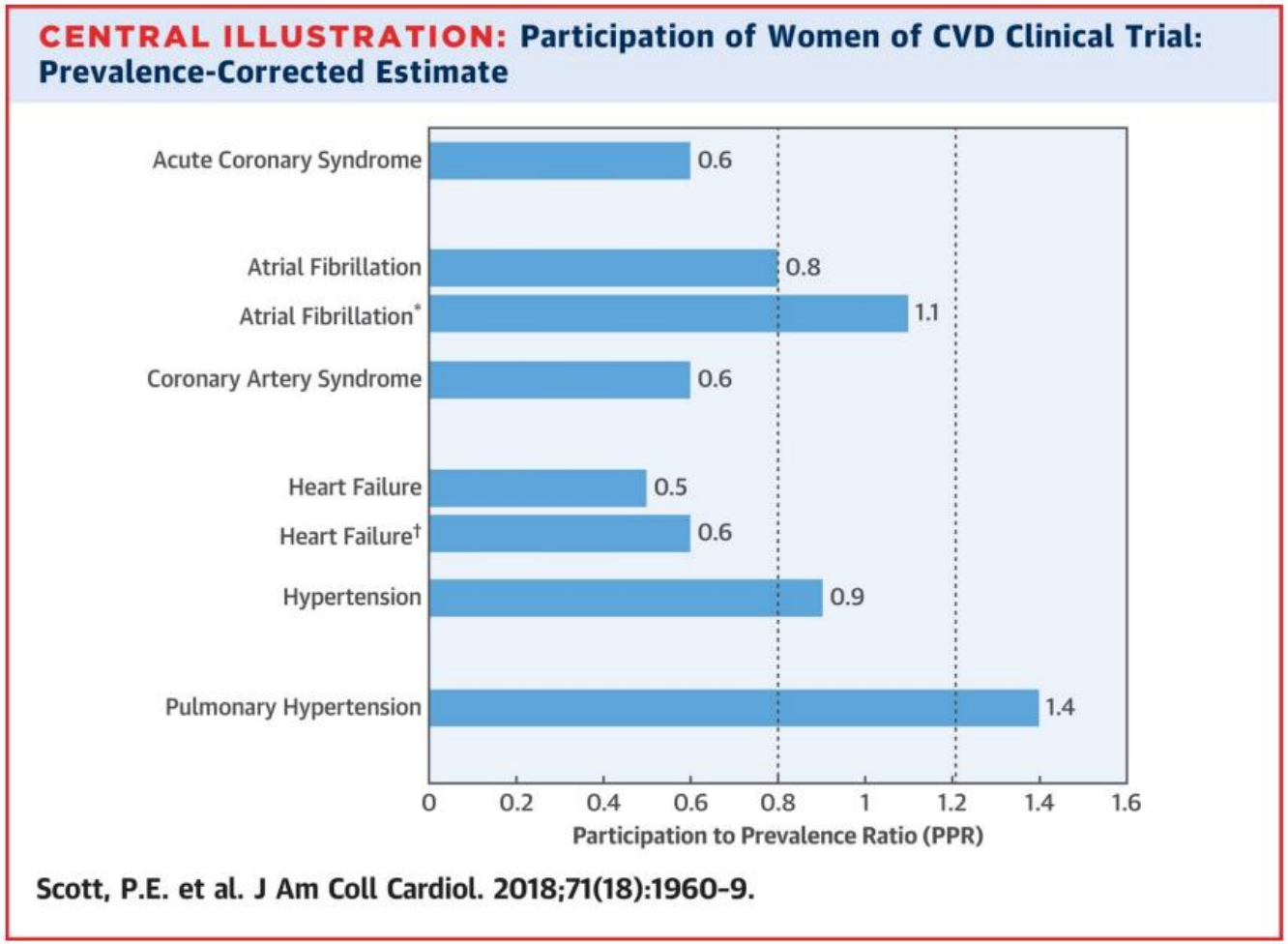
DE HELFT VAN WAT JE ZOU VERWACHTEN BIJ CORONAIRLIJDEN EN HARTFALEN



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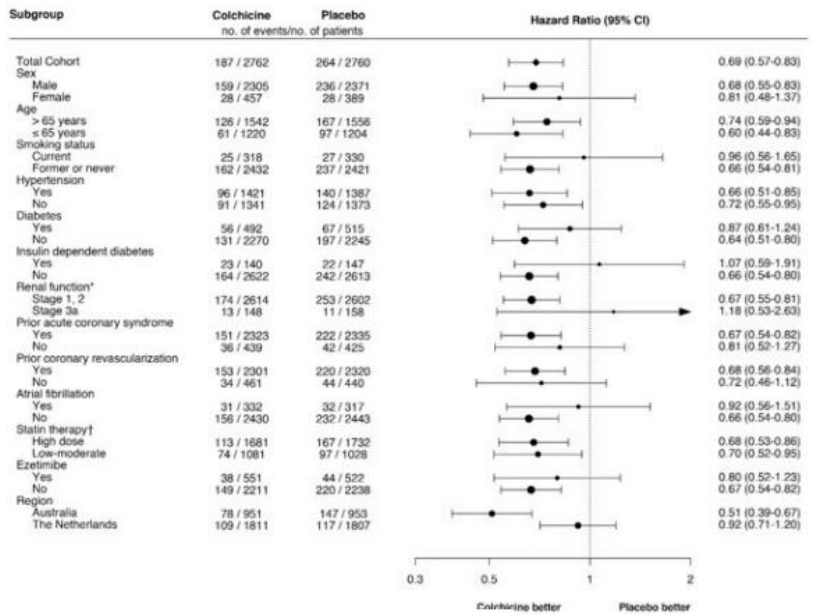
COLCHICINE

Colchicine

Table 1. Characteristics of the Trial Patients at Baseline.*

Characteristic	Colchicine (N=2762)	Placebo (N=2760)
Age — yr	65.8±8.4	65.9±8.7
Female sex — no. (%)	457 (16.5)	389 (14.1)
Country — no. (%)		
Australia	951 (34.4)	953 (34.5)
The Netherlands	1811 (65.6)	1807 (65.5)
Current smoker — no. (%)†	318 (11.5)	330 (12.0)
Hypertension — no. (%)	1421 (51.4)	1387 (50.3)
Diabetes — no. (%)		
Patients receiving any treatment for diabetes	492 (17.8)	515 (18.7)
Patients dependent on insulin	140 (5.1)	147 (5.3)
Renal function — no. (%)‡		
Stage 1 or 2	2614 (94.6)	2602 (94.3)
Stage 3a	148 (5.4)	158 (5.7)
Prior acute coronary syndrome — no. (%)	2323 (84.1)	2335 (84.6)



CONCLUSIONS

In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Health Medical Research Council of Australia and others; LoDoCo2 Australian New Zealand Clinical Trials Registry number, ACTRN12614000093684.)

Erasmus MC

HISTORIE

- DES dochters (1941)
- Thalidomide of softenon
- Tussen 1977-1993: FDA vrouwen mogen niet participeren aan vroege fases van onderzoek

VROUWEN HEBBEN VAKER BIJWERKINGEN

Bijwerkingen worden in studies naar HF medicatie slechts in 9% apart gerapporteerd voor mannen en vrouwen.

Drug	Type of Drug	Date Approved	Date Withdrawn	Primary Health Risk
Prescription Drugs With Evidence of Greater Health Risks in Women				
Pondimin (fenfluramine hydrochloride)	Appetite suppressant	6/14/1973	9/15/1997	Valvular heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant	4/29/1996	9/15/1997	Valvular heart disease
Seldane[a] (terfenadine)	Antihistamine	5/8/1985	2/27/1998	Torsades de Pointes (potentially fatal irregular heartbeat)
Posicor (mibefradil dihydrochloride)	Cardiovascular	6/20/1997	6/8/1998	Lowered heart rate in elderly women and adverse interactions with 26 other drugs
Hismanal (astemizole)	Antihistamine	12/19/1988	6/18/1999	Torsades de Pointes
Rezulin (troglitazone)	Diabetic	1/29/1997	3/21/2000	Liver failure
Propulsid[b] (cisapride monohydrate)	Gastrointestinal	7/29/1993	7/14/2000	Torsades de Pointes
Lotronex (alosetron hydrochloride)	Gastrointestinal	2/9/2000	11/28/2000	Ischemic colitis (intestinal inflammation due to lack of blood flow)
Prescription Drugs Without Evidence of Greater Health Risks in Women				
Raxar (grepafloxacin hydrochloride)	Antibiotic	11/6/1997	11/1/1999	Torsades de Pointes
Duract (bromfenac sodium)	Analgesic and anesthetic	7/15/1997	6/22/1998	Liver failure

HARTFALEN STUDIES

Women across all trials was 25.2% (11.5–51.6). Fewer than half of the studies reported sexspecific efficacy data (11/23, 48%), and only 2 studies (9%) presented sex-specific information about ADRs

Table. Overview of the Trials Included in the Systematic Review

Drug Class	Drug	Acronym	No.	Women, %	Average Age, y	Sex-Specific Adverse Events	Sex-Specific Efficacy	Inclusion: EF≤40%
ACEI	Enalapril	CONSENSUS	253	29.5	71	No	No	Not mentioned
		SOLVD Treatment	2569	19.7	61	Yes*	No	Yes
		SOLVD Prevention	4228	11.5	59	Yes*	No	Yes
	Lisinopril	ATLAS	3164	20.5	64	No	Yes	Yes
MRA	Eplerenone	EMPHASIS-HF	2747	22.3	69	No	No	Yes
		J-EMPHASIS-HF	221	20.4	69	No	No	Yes
		EPHESUS	6632	29.0	64	No	No	Yes
	Spironolactone	RALES	1663	27.0	65	No	No	Yes
		TOPCAT	3445	51.6	69	No	Yes	No (EF≥45%)
β-Blocker	Bucindolol	BEST	2708	22.0	60	No	No	Yes
	Carvedilol	COPERNICUS	2279	20.5	63	No	No	Yes
		US Carvedilol Heart Failure Study	1094	23.4	58	No	Yes	Yes
	Metoprolol	MERIT-HF	3991	22.5	64	Yes	Yes	Yes
	Nevibilol	SENIORS	2128	36.9	76	No	Yes	Yes
	Bisoprolol	CIBIS II	2647	19.5	61	No	Yes	Yes
ARB	Candesartan	CHARM-Alternative	2028	31.9	67	No	No	Yes
		CHARM-Overall	7599	31.6	66	No	No	No
	Losartan high	HEAAL	3834	29.5	66	No	Yes	Yes
	Valsartan	Val-HeFT	5010	20.1	63	No	No	Yes
Digitalis glycoside	Digoxin	DIG	6800	22.4	63	No	Yes	No (EF≤45%)
If channel inhibitor	Ivabradine	SHIFT	6505	23.5	60	No	Yes	Yes
		BEAUTIFUL	10 917	17.0	65	No	Yes	Yes
		SIGNIFY	19 102	27.6	65	No	Yes	No (EF≥40%)

WAT WETEN WE VAN VERSCHILLEN

Vaker voorkomend in mannen	Vaker voorkomend in vrouwen
Obstructief vaatlijden	**Niet obstructief vaatlijden**
HFrEF	HFpEF
Brugada syndroom	Takotsubo cardiomyopathy
Hartstilstand bij sporten	SCAD
Ernstige genetische cardiomyopathy	**Spasme/CMD**
	Beroerte
	Ruptuur AA