

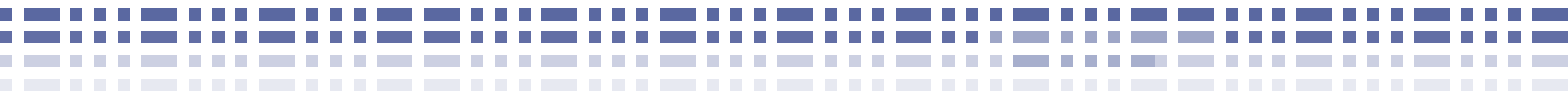
Corrie Hermann Symposium 30 maart 2019

Is geslacht een risicofactor voor het optreden van bijwerkingen?



Loes Visser, Ziekenhuisapotheker / Klinisch-epidemioloog

Inhoud



- Aanleiding voor het onderzoek
- ZonMw project
- Oorzaak van sekseverschillen
- Vervolgonderzoek: voorbeeld metoprolol

Aanleiding

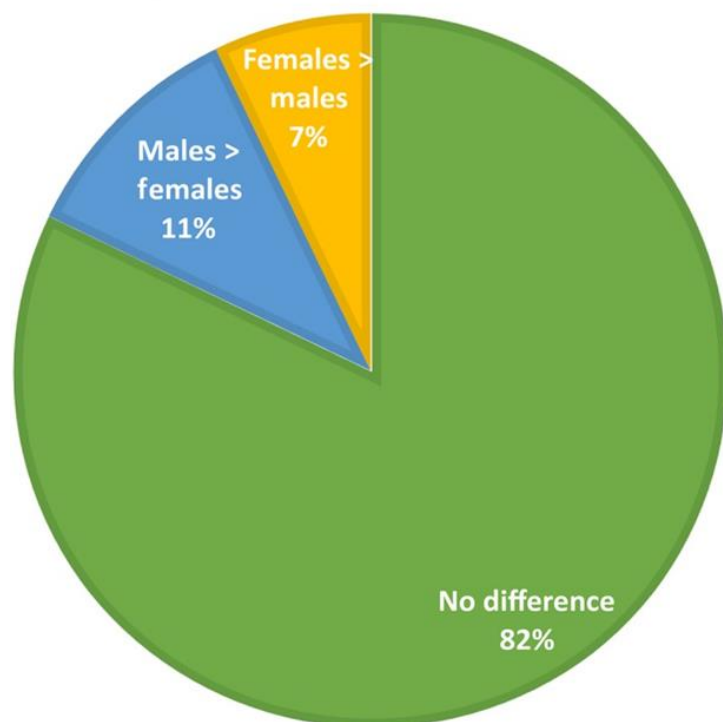
Drug Safety: Most Drugs Withdrawn in Recent Years Had Greater Health Risks for Women

Table 1: Prescription Drugs Withdrawn From the United States Market, Jan. 1, 1997 Through Dec. 31, 2000

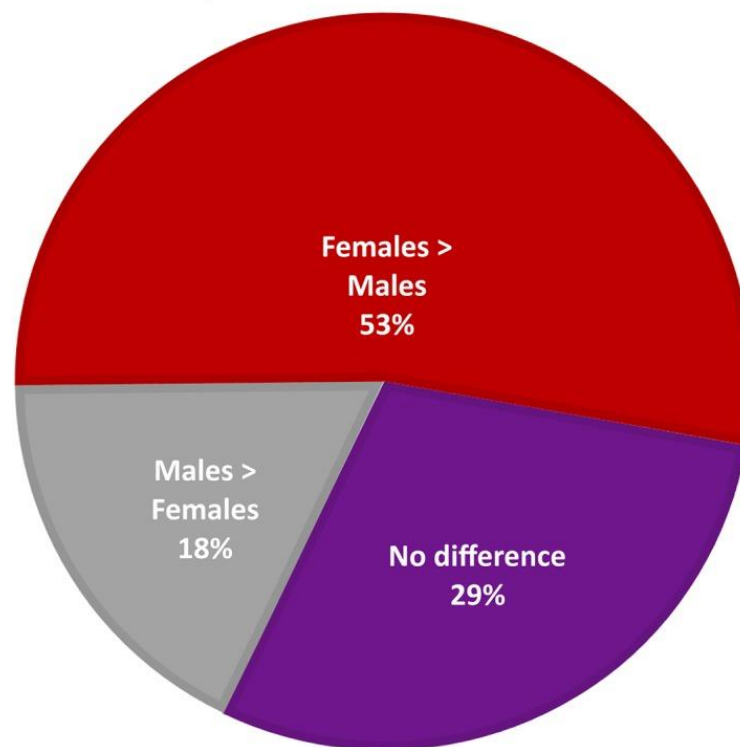
Drug	Type of Drug	Date Approved	Date Withdrawn	Primary Health Risk
Prescription Drugs With Evidence of Greater Health Risks in Women				
Pondimin (fenfluramine hydrochloride)	Appetite suppressant	6/14/1973	9/15/1997	Valvular heart disease
Redux (dexfenfluramine hydrochloride)	Appetite suppressant	4/29/1996	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

Aanleiding

QUALITATIVE EFFICACY ANALYSIS



QUALITATIVE SAFETY ANALYSIS



Dossieronderzoek van 137 veel gebruikte geneesmiddelen

Aanleiding

Table 6

Drugs acting on the cardiovascular system

Adverse reaction per drug type	Women (n)*	Men (n)*	RR (95% CI)†
Cardiac rhythm regulator (C01B)			
Heart dysrhythmia	49	52	0.79 (0.54, 1.17)
Cardiotonic glycosides (C01A)			
Unwanted drug effect	190	77	2.07 (1.59, 2.70)
Poisoning	291	101	2.42 (1.93, 3.03)
Coronary vasodilators (C01D)			
Syncope/collapse	128	170	0.63 (0.50, 0.79)
Saluretics and diuretics (C03A + C)			
Disorder kidney/ureter	57	48	1.00 (0.68, 1.47)
Hypo-osmolality/hyponatraemia	642	101	5.33 (4.32, 6.58)
Hypokalaemia	163	40	3.42 (2.41, 4.83)
Hypovolaemia	348	231	1.26 (1.07, 1.49)
Renal failure	57	34	1.41 (0.92, 2.15)

BJCP British Journal of Clinical Pharmacology

Sex-related differences in hospital admissions attributed to adverse drug reactions in the Netherlands

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Algemene gegevens / General Information

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Subsidieronde / Subsidy round	:	Gender en Gezondheid - Algemene onderzoeksrunde
Projecttitel / Project title	:	Sex as a risk factor for clinically relevant adverse drug reactions.
Projecttaal / Project language	:	Engels / English
Geplande startdatum / Planned start date	:	01-12-2017
Geplande duur / Planned duration	:	24 maanden / months
Datum indienen / Date of application	:	20-04-2017
Projecttype / Project type	:	Strategisch onderzoek / Strategic research
Vervolg eerder ZonMw-project / Continuation previously funded project ZonMw	:	Nee / No

***Kennisagenda
Gender en Gezondheid***

**ZonMw**

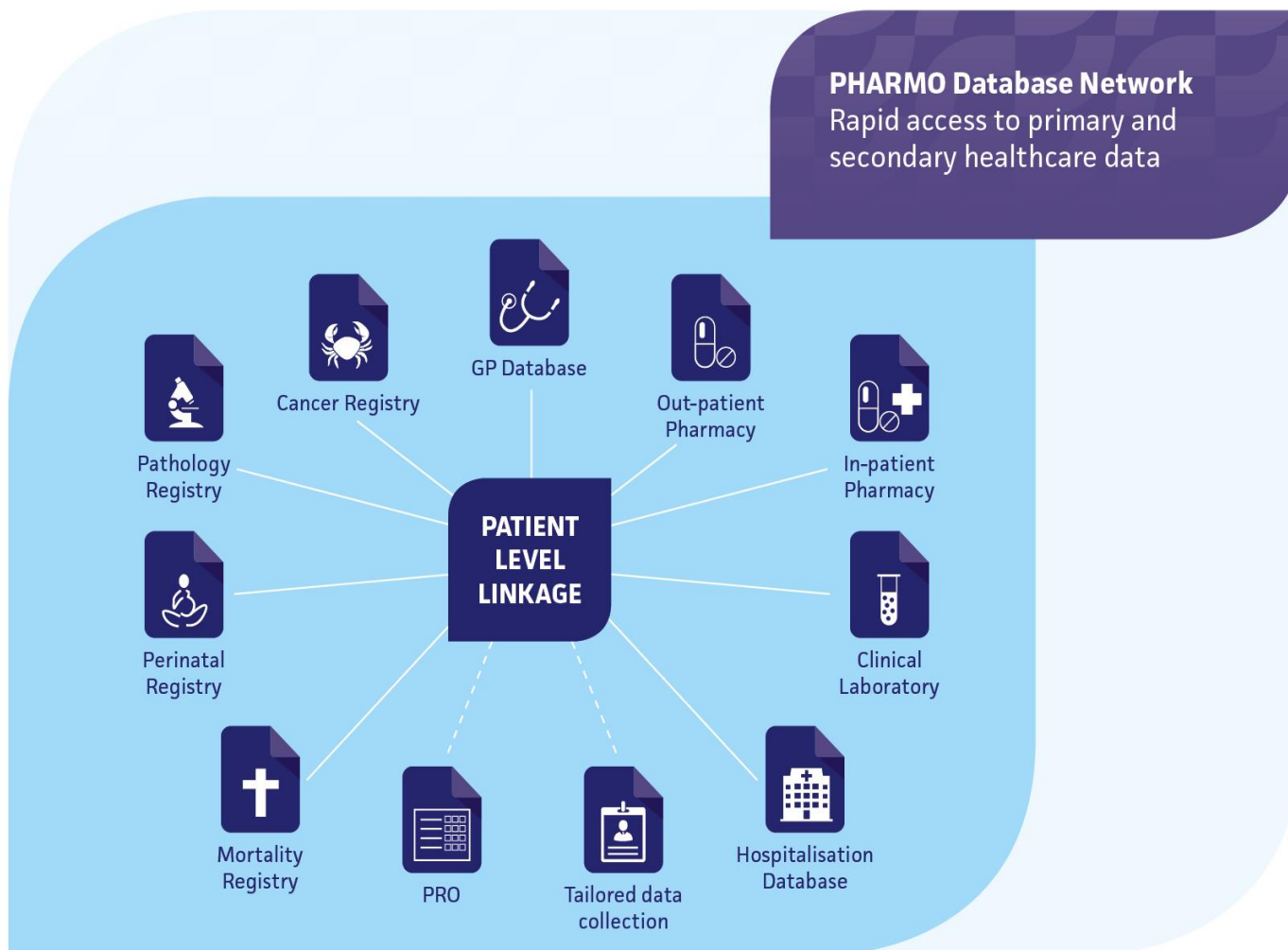
ZonMw project

■ Onderzoeksvraagstellingen:

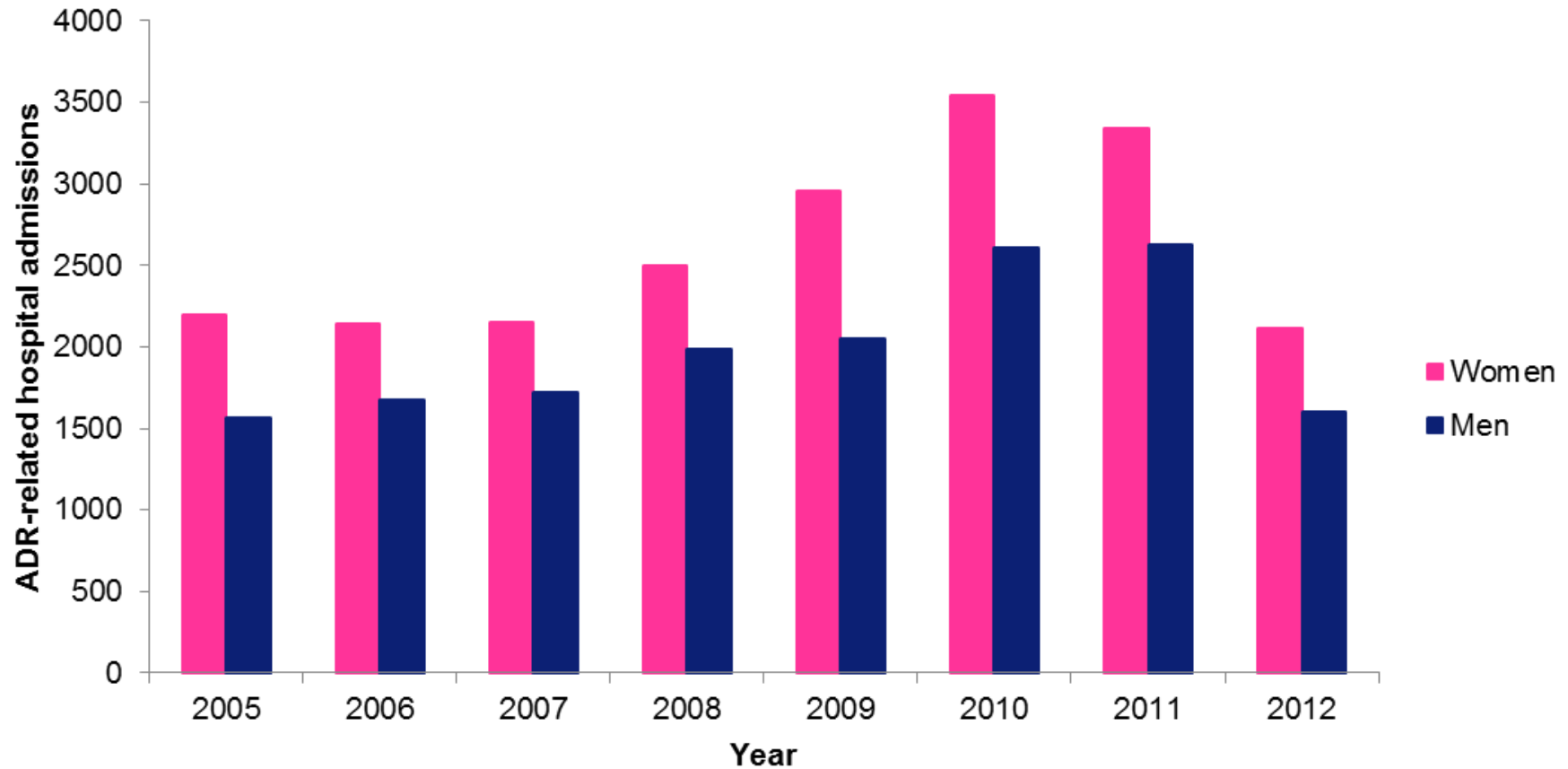
- Bij welke geneesmiddelgroepen bestaan er seksverschillen in bijwerking-gerelateerde ziekenhuisopname?
- Wat zijn, binnen deze groepen, de meest voorkomende bijwerkingen bij mannen en vrouwen?
- Is geslacht een risicofactor voor deze bijwerkingen?
- Is leeftijd een 'effect-modifier' voor het risico op een bijwerking?

PHARMO Database Network (NL)

PHARMO Database Network
Rapid access to primary and
secondary healthcare data



ZonMw project



ZonMw project

■ Top 20 geneesmiddelgroepen

E-code	Drug group	Women (N) ¹	Men (N) ¹	OR (95% CI) ²
E9447	Uric acid metabolism drugs	33	55	0.45 (0.29, 0.69)
E9422	Antilipemic and antiarteriosclerotic drugs	41	59	0.52 (0.35, 0.77)
E9424	Coronary vasodilators	117	163	0.53 (0.42, 0.68)
E9353	Salicylates	308	387	0.59 (0.51, 0.69)
E9342	Anticoagulants	2775	2855	0.72 (0.69, 0.76)
E9320	Adrenal cortical steroids	858	853	0.75 (0.68, 0.82)
E9413	Sympatholytics [antiadrenergics]	162	156	0.77 (0.62, 0.96)
E9420	Cardiac rhythm regulators	142	135	0.78 (0.62, 0.99)
E9426	Other antihypertensive agents	441	386	0.85 (0.74, 0.97)
E9356	Antirheumatics [antiphlogistics]	468	404	0.86 (0.75, 0.98)
E9354	Aromatic analgesics, not elsewhere classified	83	50	1.23 (0.87, 1.75)
E9330	Antiallergic and antiemetic drugs	75	42	1.33 (0.91, 1.93)
E9398	Other psychotropic agents	165	90	1.36 (1.05, 1.76)
E9421	Cardiotonic glycosides and drugs of similar action	261	133	1.46 (1.18, 1.80)
E9444	Other diuretics	1639	834	1.46 (1.34, 1.59)
E9390	Antidepressants	184	75	1.82 (1.39, 2.38)
E9433	Other cathartics, including intestinal atonia drugs	54	19	2.11 (1.25, 3.56)
E9443	Saluretics	773	244	2.35 (2.04, 2.72)
E9319	Other and unspecified anti-infectives	183	45	3.02 (2.18, 4.18)
E9324	Anterior pituitary hormones	61	6	7.55 (3.26, 17.46)

¹ Number of admissions in the period 2005-2012

² Odds ratio of ADR-related hospitalizations with respect to total number of drug users (women: 12 265 630)

ZonMw project

■ Top 20 bijwerkingen

Main diagnose	Adverse reaction	Women (N) ¹	Men (N) ¹	OR (95% CI) ²
5997	Hematuria, unspecified	55	177	0.23 (0.17, 0.31)
4140	Coronary atherosclerosis	25	72	0.26 (0.16, 0.41)
7863	Hemoptysis	29	78	0.28 (0.18, 0.42)
53240	Chronic or unspecified duodenal ulcer with hemorrhage, without mention of obstruction	30	78	0.29 (0.19, 0.44)
4580	Orthostatic hypotension	35	60	0.43 (0.29, 0.66)
4321	Subdural hemorrhage	45	70	0.48 (0.33, 0.69)
2030	Multiple myeloma	44	66	0.50 (0.34, 0.73)
4589	Hypotension, unspecified	50	73	0.51 (0.35, 0.73)
20280	Other malignant lymphomas, unspecified site, extranodal and solid organ sites	37	52	0.53 (0.35, 0.81)
53140	Chronic or unspecified gastric ulcer with hemorrhage, without mention of obstruction	50	64	0.58 (0.40, 0.84)
1629	Malignant neoplasm of bronchus and lung, unspecified	86	106	0.60 (0.45, 0.80)
585	Chronic kidney disease (ckd)	50	61	0.61 (0.42, 0.88)
7840	Headache	52	21	1.84 (1.11, 3.05)
7870	Nausea and vomiting	800	318	1.87 (1.64, 2.13)
4151	Pulmonary embolism and infarction	131	50	1.95 (1.40, 2.69)
9721	Poisoning by cardiotonic glycosides and drugs of similar action	58	22	1.96 (1.20, 3.20)
49390	Asthma, unspecified type, unspecified	50	16	2.32 (1.32, 4.07)
2768	Hypopotassemia	151	41	2.73 (1.94, 3.86)
7331	Pathologic fracture	61	16	2.83 (1.63, 4.91)
2761	Hyposmolality and/or hyponatremia	605	114	3.94 (3.23, 4.81)

¹ Number of admissions in the period 2005-2012

² Odds ratio of ADR-related hospitalizations with respect to total number of drug users (women: 12,265,630 and men: 9,108,292) in the period 2005-2012.

ZonMw project

ATC-code	Drug group	Adverse reaction	Women (N) ¹	Men (N) ¹	OR (95% CI) ²	OR adj (95% CI) ³
J01C	Penicillins	Pneumonia, organism unspecified	51	33	1.19 (0.77, 1.85)	1.17 (0.76, 1.82)
J01C	Penicillins	Unspecified adverse effect of drug medicinal	64	39	1.27 (0.85, 1.89)	1.33 (0.89, 1.98)
H02A, H02B	Adrenal cortical steroids	Pneumonia, organism unspecified	51	84	0.43 (0.30, 0.61)	0.44 (0.31, 0.62)
H02A, H02B	Adrenal cortical steroids	Chronic airway obstruction, not elsewhere classified	79	62	0.90 (0.65, 1.26)	0.96 (0.69, 1.34)
A10	Insulins and antidiabetic agents	Other specified hypoglycemia	268	232	1.19 (1.00, 1.42)	0.99 (0.83, 1.19)
L	Antineoplastic and immunosuppressive drugs	Malignant neoplasm of bronchus and lung	58	76	0.49 (0.35, 0.68)	0.54 (0.38, 0.76)
L	Antineoplastic and immunosuppressive drugs	Myeloid leukemia acute	55	66	0.53 (0.37, 0.76)	0.52 (0.36, 0.74)
L	Antineoplastic and immunosuppressive drugs	Other specified aplastic anemias	115	126	0.58 (0.45, 0.75)	0.65 (0.50, 0.84)
L	Antineoplastic and immunosuppressive drugs	Pneumonia, organism unspecified	120	115	0.66 (0.51, 0.86)	0.77 (0.60, 1.00)
L	Antineoplastic and immunosuppressive drugs	Toxic gastroenteritis and colitis	119	112	0.68 (0.52, 0.87)	0.76 (0.58, 0.98)
L	Antineoplastic and immunosuppressive drugs	Other and unspecified noninfectious gastroenteritis and colitis	257	202	0.81 (0.67, 0.97)	0.93 (0.77, 1.12)
L	Antineoplastic and immunosuppressive drugs	Unspecified adverse effect	343	267	0.82 (0.70, 0.96)	0.87 (0.74, 1.02)
L	Antineoplastic and immunosuppressive drugs	Fever and other physiologic disturbances of temperature regulation	1522	1079	0.90 (0.83, 0.97)	0.93 (0.86, 1.01)
L	Antineoplastic and immunosuppressive drugs	Urinary tract infection	61	42	0.92 (0.62, 1.37)	1.07 (0.72, 1.59)
L	Antineoplastic and immunosuppressive drugs	Agranulocytosis	745	489	0.97 (0.86, 1.09)	1.00 (0.89, 1.12)
L	Antineoplastic and immunosuppressive drugs	Malaise and fatigue	380	241	1.00 (0.85, 1.18)	1.13 (0.96, 1.33)
L	Antineoplastic and immunosuppressive drugs	Volume depletion disorder	78	47	1.06 (0.73, 1.51)	1.20 (0.83, 1.72)
L	Antineoplastic and immunosuppressive drugs	Constipation	63	34	1.18 (0.78, 1.79)	1.20 (0.79, 1.82)
L	Antineoplastic and immunosuppressive drugs	Nausea and vomiting	568	240	1.50 (1.29, 1.75)	1.56 (1.34, 1.81)
B01	Anticoagulants	Hematuria	45	152	0.36 (0.26, 0.50)	0.28 (0.20, 0.40)
B01	Anticoagulants	Hemoptysis	22	63	0.42 (0.26, 0.69)	0.39 (0.24, 0.64)
B01	Anticoagulants	Subdural hemorrhage	38	61	0.76 (0.50, 1.13)	0.68 (0.45, 1.03)
B01	Anticoagulants	Epistaxis	85	87	1.19 (0.88, 1.60)	0.92 (0.68, 1.25)
B01	Anticoagulants	Intracerebral hemorrhage	118	117	1.22 (0.95, 1.58)	1.02 (0.78, 1.32)
B01	Anticoagulants	Hemorrhage of gastrointestinal tract unspecified	177	176	1.22 (0.99, 1.50)	0.97 (0.78, 1.20)
B01	Anticoagulants	Hemorrhage or hematoma complicating a procedure not elsewhere classified	64	62	1.25 (0.88, 1.78)	1.26 (0.88, 1.79)
B01	Anticoagulants	Hemorrhage of rectum and anus	54	50	1.31 (0.89, 1.93)	1.04 (0.70, 1.54)
B01	Anticoagulants	Blood in stool	111	100	1.35 (1.03, 1.77)	1.10 (0.83, 1.45)
B01	Anticoagulants	Hemorrhage unspecified	429	305	1.71 (1.47, 1.98)	1.45 (1.25, 1.68)
N02A	Other opiates and related narcotics	Constipation	157	135	0.71 (0.57, 0.90)	0.69 (0.55, 0.87)
N02A	Other opiates and related narcotics	Nausea and vomiting	58	18	1.98 (1.17, 3.36)	1.83 (1.07, 3.11)
N02BA	Salicylates	Hemorrhage of gastrointestinal tract unspecified	37	56	0.34 (0.22, 0.51)	0.38 (0.25, 0.57)
C01A	Cardiotonic glycosides and drugs of similar action	Poisoning by cardiotonic glycosides and drugs of similar action	55	21	2.33 (1.41, 3.85)	2.33 (1.41, 3.87)
C02AC	Other antihypertensive agents	Angioneurotic edema not elsewhere classified	50	51	0.58 (0.39, 0.85)	0.56 (0.37, 0.83)
C03A, C03EA	Saluretics	Hyposmolality and/or hyponatremia	178	21	4.85 (3.09, 7.63)	3.86 (2.45, 6.08)
C03C	Other diuretics	Heart failure unspecified	59	41	0.92 (0.62, 1.36)	0.87 (0.58, 1.30)
C03C	Other diuretics	Volume depletion disorder	127	81	1.00 (0.76, 1.32)	0.97 (0.73, 1.29)
C03C	Other diuretics	Pneumonia, organism unspecified	71	38	1.19 (0.80, 1.76)	1.11 (0.74, 1.65)
C03C	Other diuretics	Hyposmolality and/or hyponatremia	255	46	3.53 (2.58, 4.83)	3.43 (2.50, 4.71)
C03C	Other diuretics	Hypopotassemia	67	12	3.55 (1.92, 6.57)	3.53 (1.91, 6.55)
V08	Other drugs and medicinal substances	Unspecified adverse effect	65	34		

¹ Number of admissions in the period 2005-2012

² Odds ratio of ADR-related hospitalization with respect to the number of drug users in the period 2005-2012.

³ Odds ratio of ADR-related hospitalization with respect to the number of drug users in the period 2005-2012. (adjusted for age)

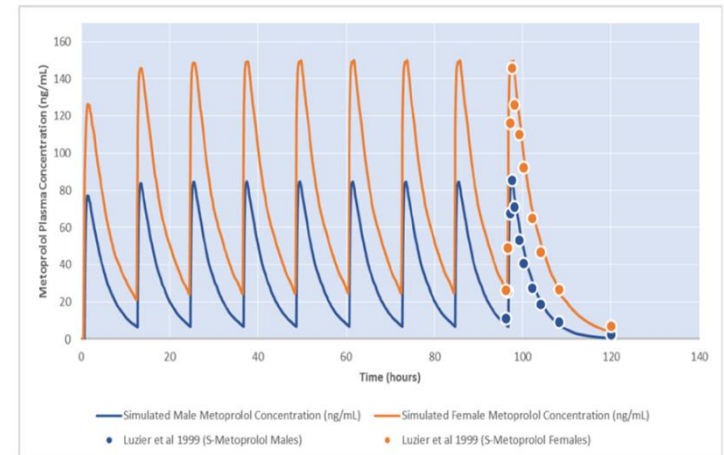
Mogelijke oorzaken

- Vrouwen worden relatief overgedoseerd
- Vrouwen reageren sterker
- Vrouwen gebruiken meer gnm
- Vrouwen vertonen ander gedrag

(BIJ) WERKING GENEESMIDDELEN SEKSESPECIFIEK.



Relatieve overdosering



Mogelijke oorzaken

- Vrouwen worden relatief overgedoseerd
- *Vrouwen reageren sterker*
- Vrouwen gebruiken meer gnm
- Vrouwen vertonen ander gedrag

(BIJ) WERKING GENEESMIDDELEN SEKSESPECIFIEK.



Sterkere respons

**ZOU ZE ZELF OOK
VINDEN DAT
HAAR HORMONEN
SOMS EEN BEETJE
OVERDRIJVEN**

Loesje



VS



+



VS



Mogelijke oorzaken

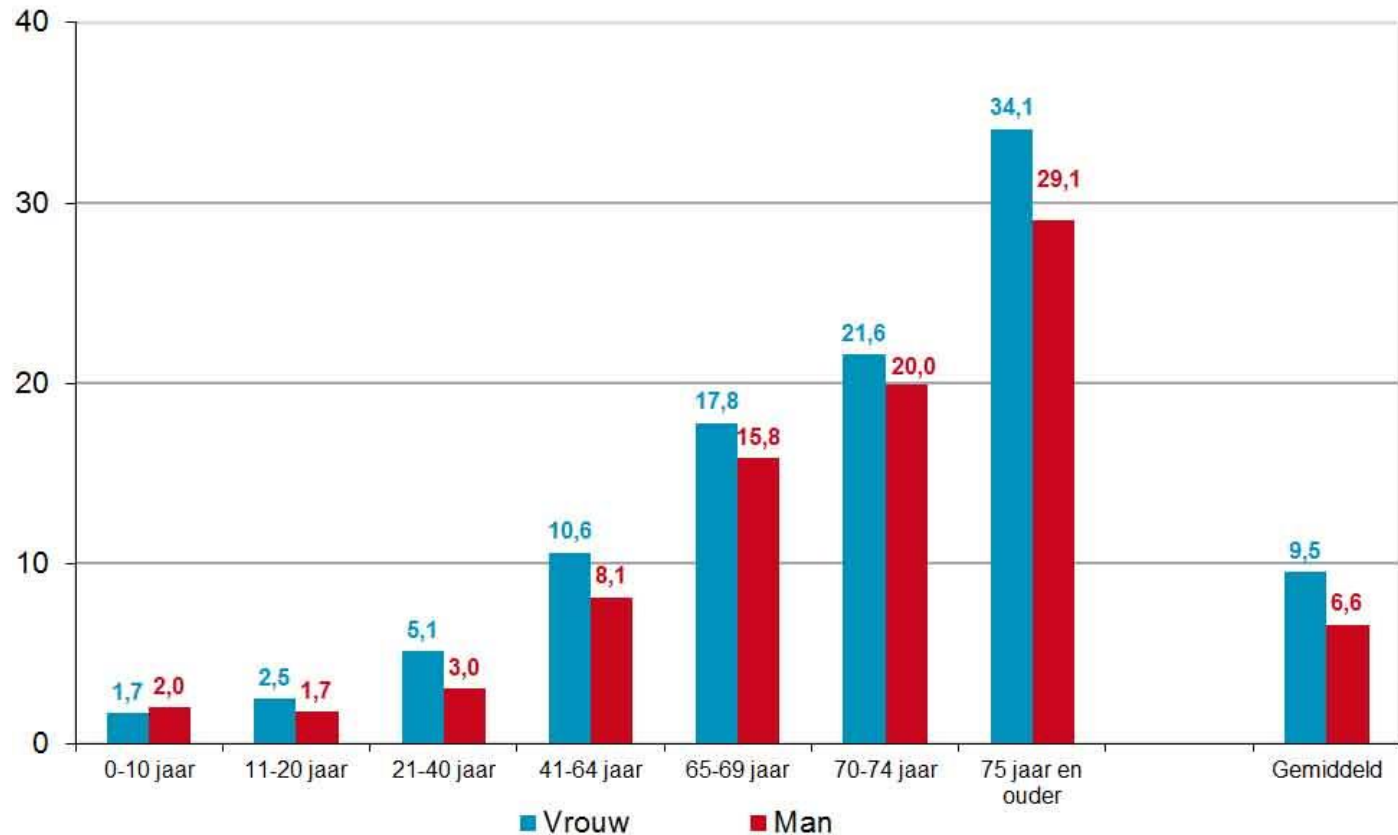
- Vrouwen worden relatief overgedoseerd
- Vrouwen reageren sterker
- *Vrouwen gebruiken meer gnm*
- Vrouwen vertonen ander gedrag

(BIJ) WERKING GENEESMIDDELEN SEKSESPECIFIEK.



Meer geneesmiddelen

Aantal receptgeneesmiddelen per jaar



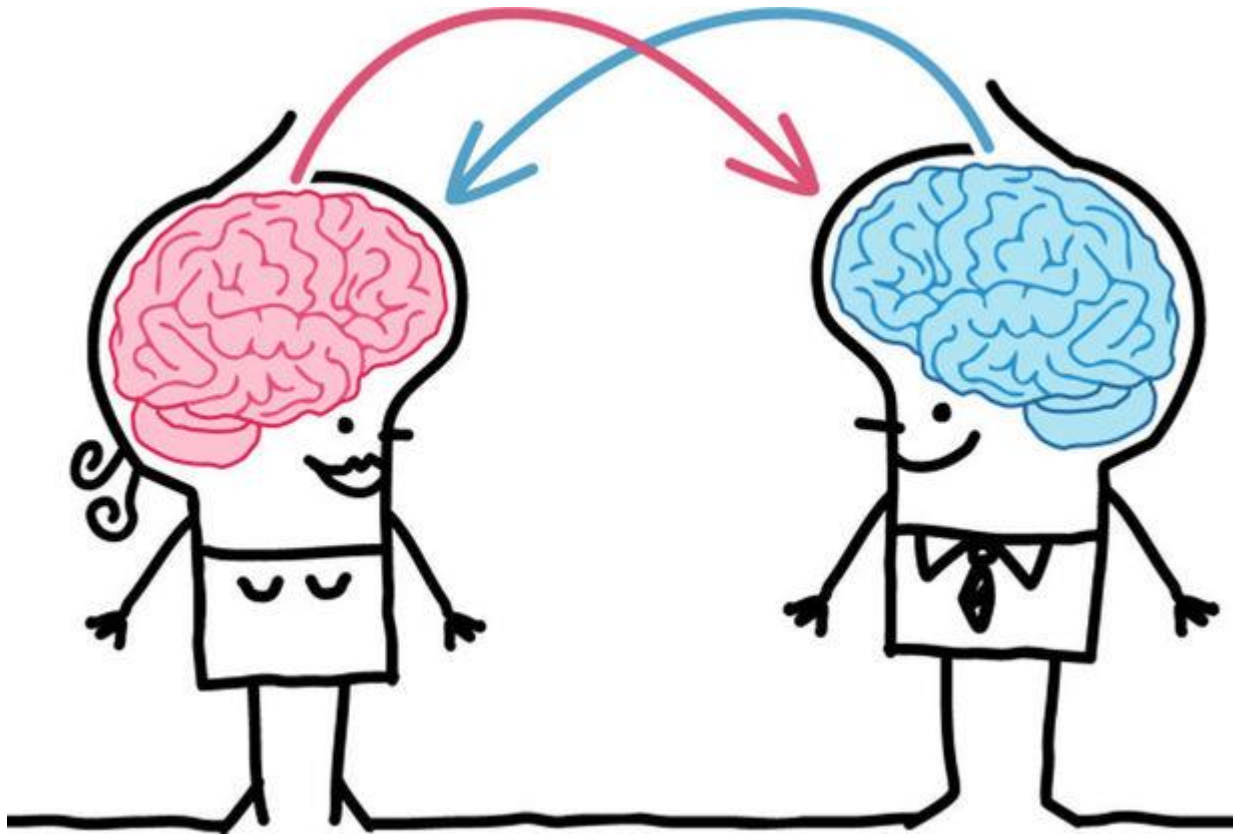
Mogelijke oorzaken

- Vrouwen worden relatief overgedoseerd
- Vrouwen reageren sterker
- Vrouwen gebruiken meer gnm
- *Vrouwen vertonen ander gedrag*

(BIJ) WERKING GENEESMIDDELEN SEKSESPECIFIEK.



Ander gezondheidsgedrag



Ander gezondheidsgedrag

Anna's hartinfarct werd haar fataal; artsen zagen haar atypische klachten voor stress symptomen aan.

Bij Willem was men op tijd; hij wees zijn arts op druk op de borst – en onderging een effectieve vroegtijdige interventie.

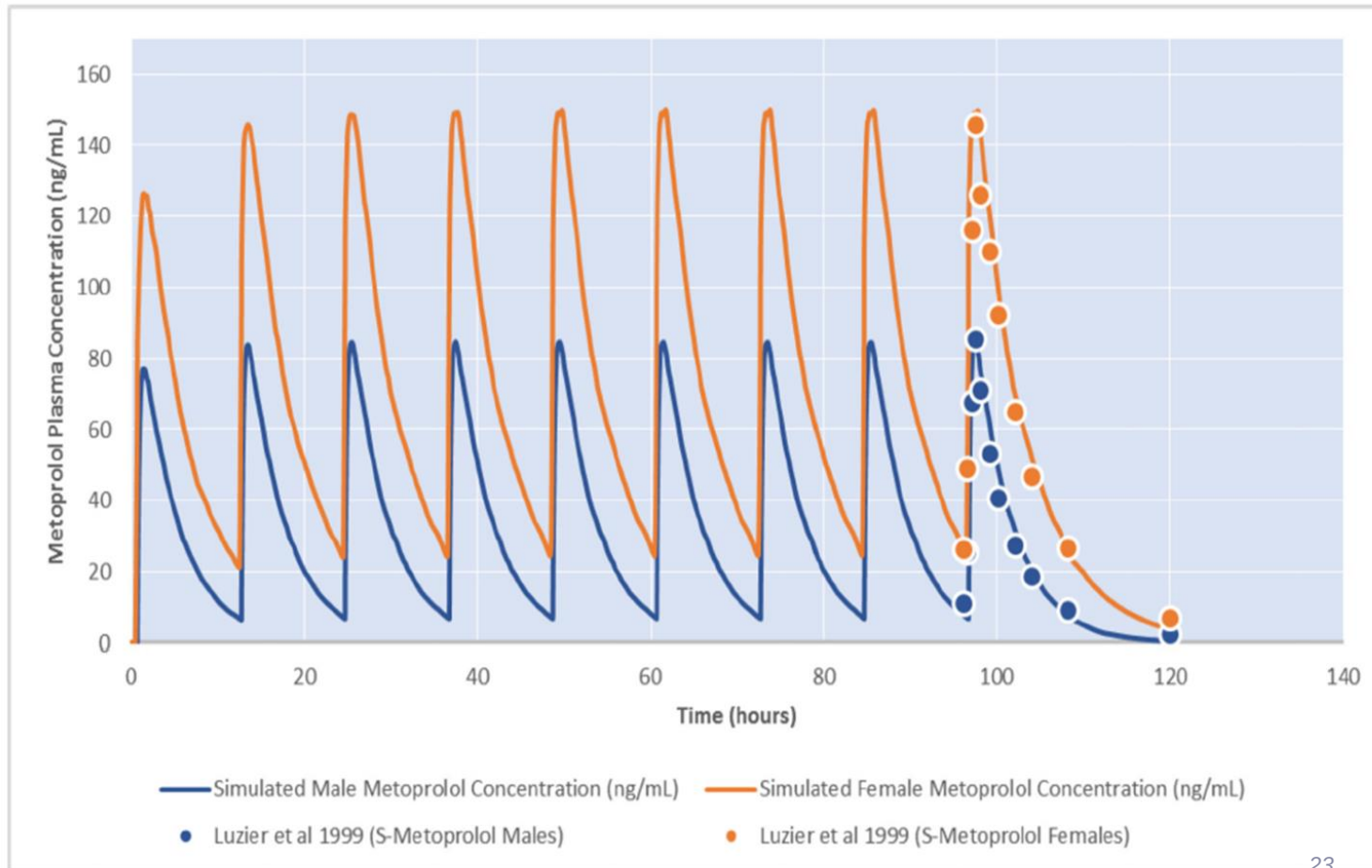
Gebrek aan kennis over en veronachtzaming van sekse- & gender verschillen in gezondheid

Sekse/gender indelen in '0' en '1' is veel te simpel

Toekomst ?

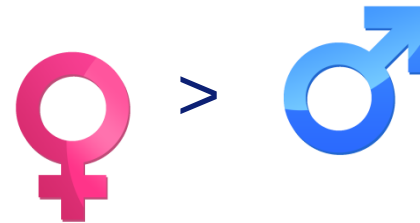


Voorbeeld sekseverschil: metoprolol

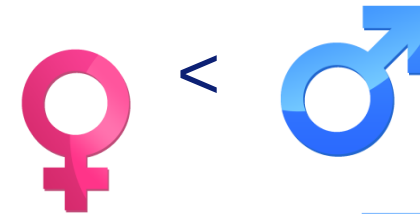


Voorbeeld: metoprolol

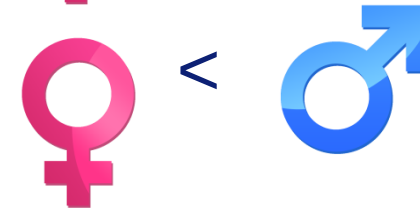
Absorptie



Distributie (V_D)



Metabolisme (CYP2D6)



Voorbeeld: metoprolol

- Richtlijnen: gelijke dosering



- Onderhoudsdosering: 100-200 mg per dag



nederlands huisartsen
genootschap



ESC

European Society
of Cardiology



AMERICAN
COLLEGE of
CARDIOLOGY

Voorbeeld: metoprolol

Onderzoeksvraagstellingen:

- Krijgen mannen en vrouwen dezelfde dosering voorgeschreven?
- Sekseverschil in kinetiek? Relatie dosis vs bloedspiegel?
- Sekseverschil in dynamiek? Relatie bloedspiegel vs hartslag?

Beschikbare data:

- IPCI - prescriptiedatabase huisartsen – 1,8 M pat
- Rotterdam Study – aflevergegevens apotheken – 15.000 pat
- Rotterdam Study - random sample 2000 pat met bloedmonster
93 metoprolol gebruikers met ECG ten tijde van bloedspiegel

Voorbeeld: metoprolol

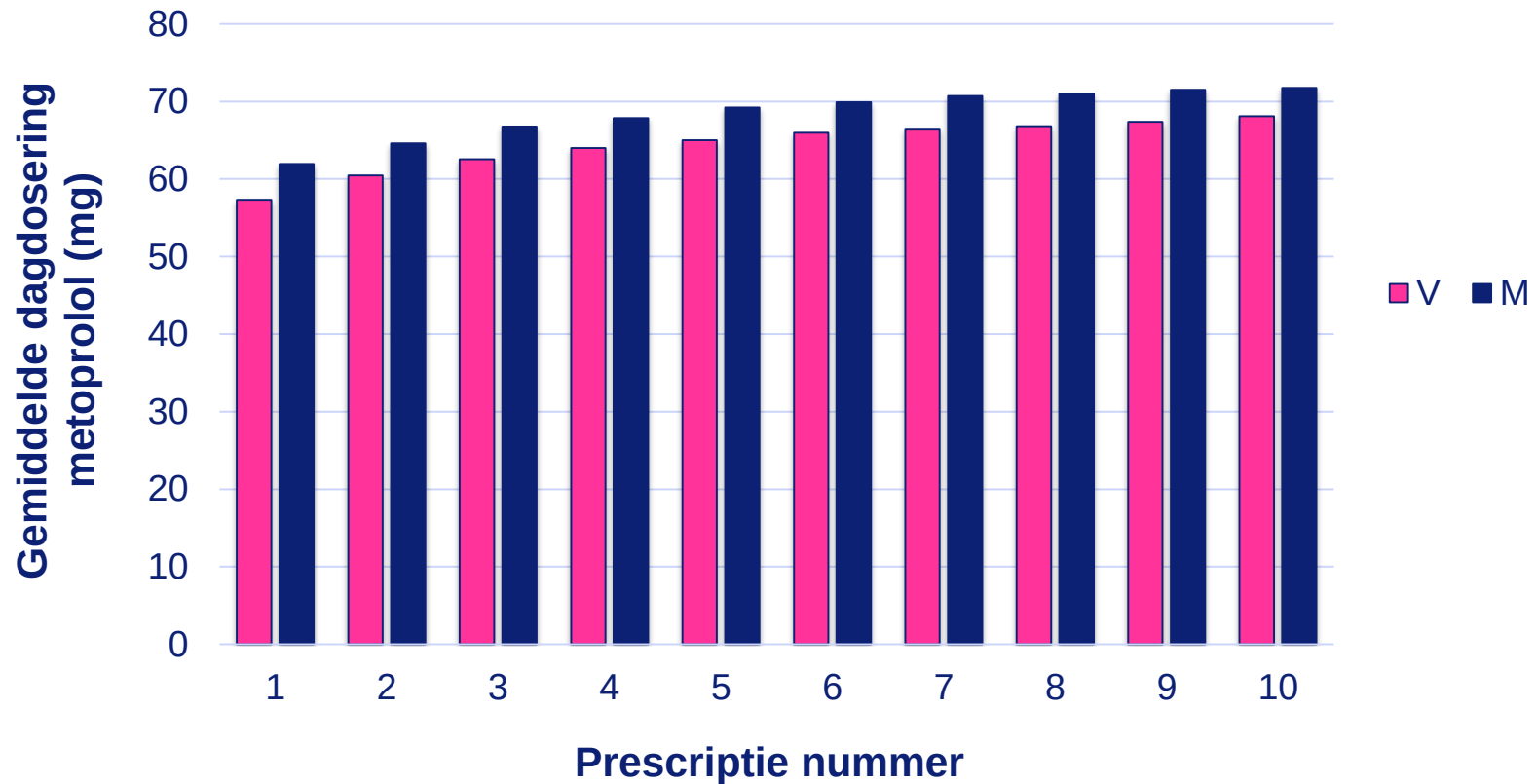
Gemiddelde dagelijkse **startdoser**ing metoprolol in:

- IPCI - prescriptiedatabase huisartsen
- Rotterdam Study – aflevergegevens apotheken

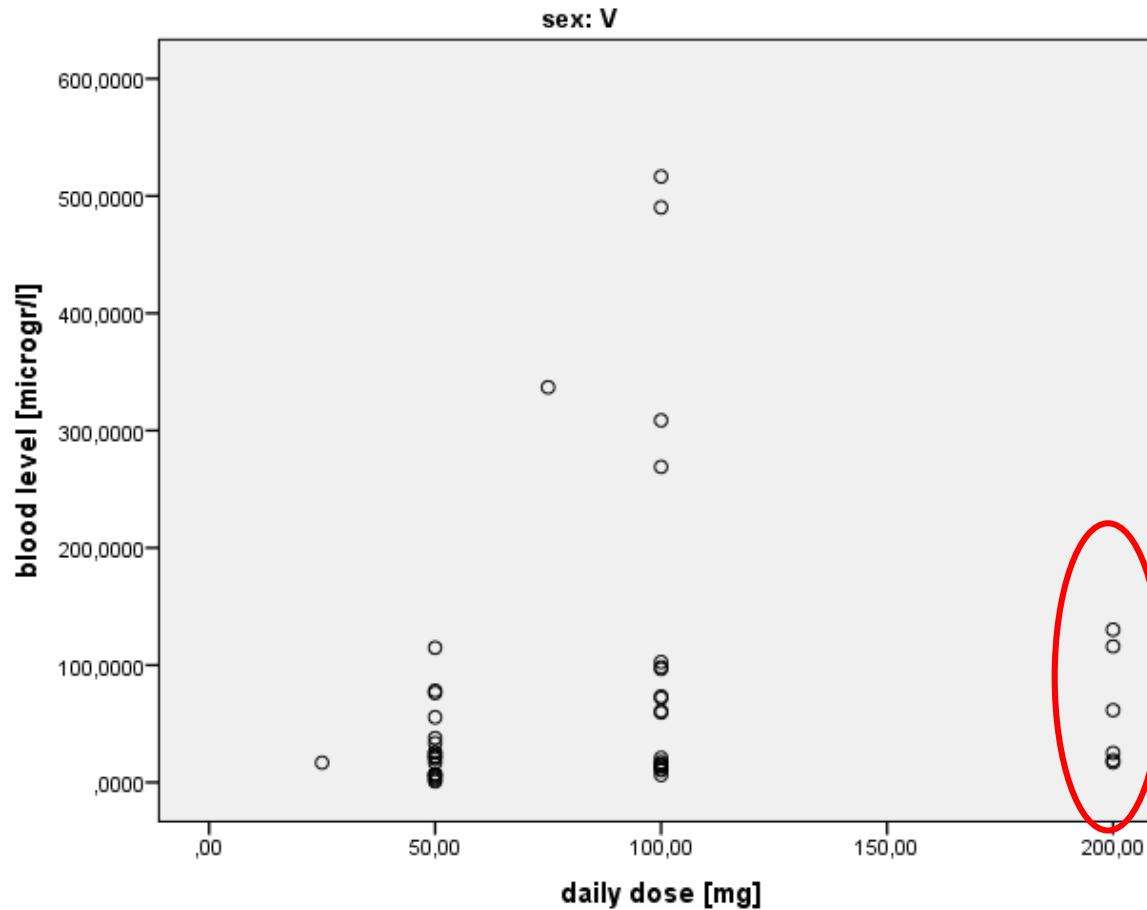
Mean daily starting dose of metoprolol

		
RS	61.1 mg	65.9 mg
IPCI	57.3 mg	62.0 mg

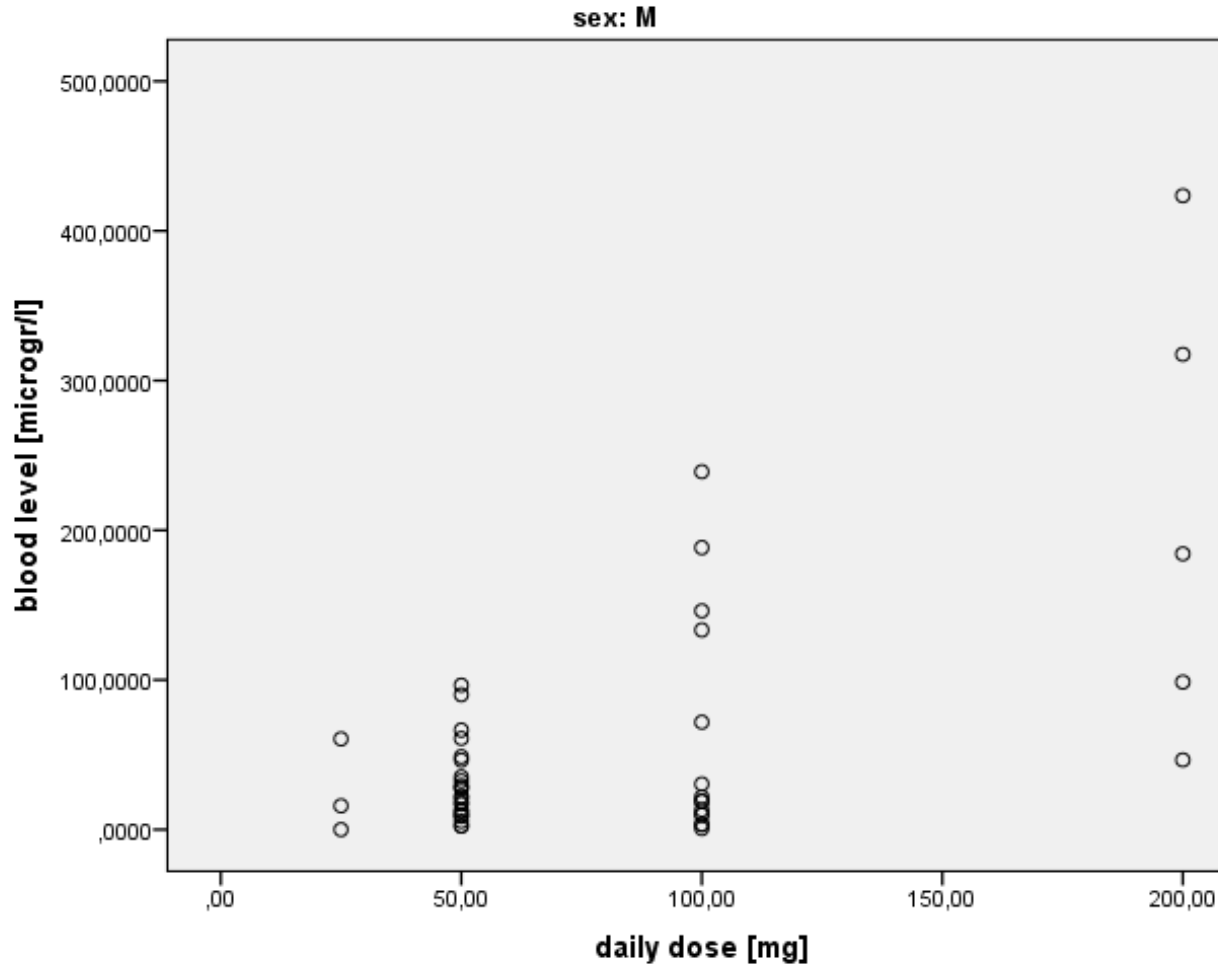
Voorbeeld: metoprolol



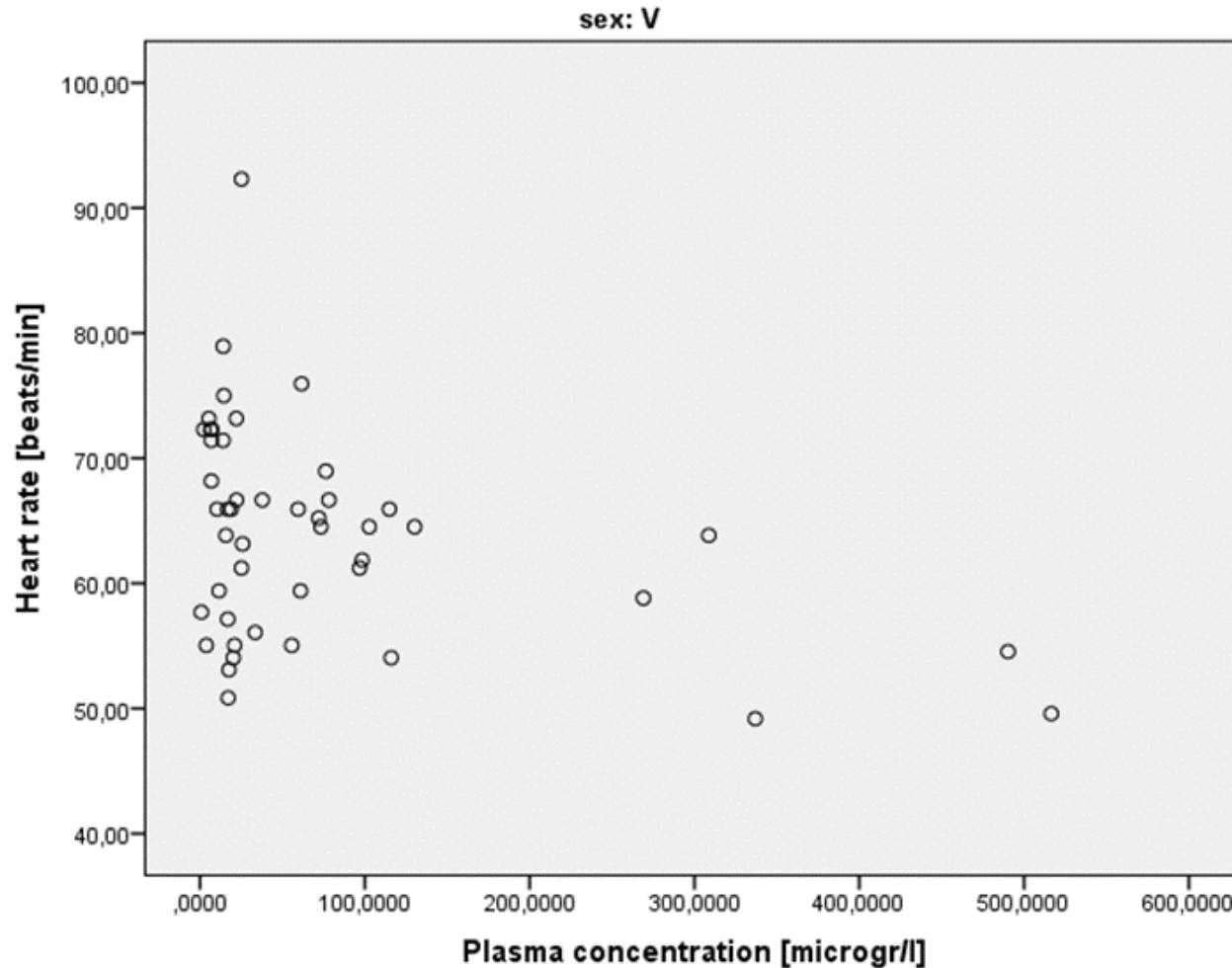
Relatie dosis - bloedspiegel



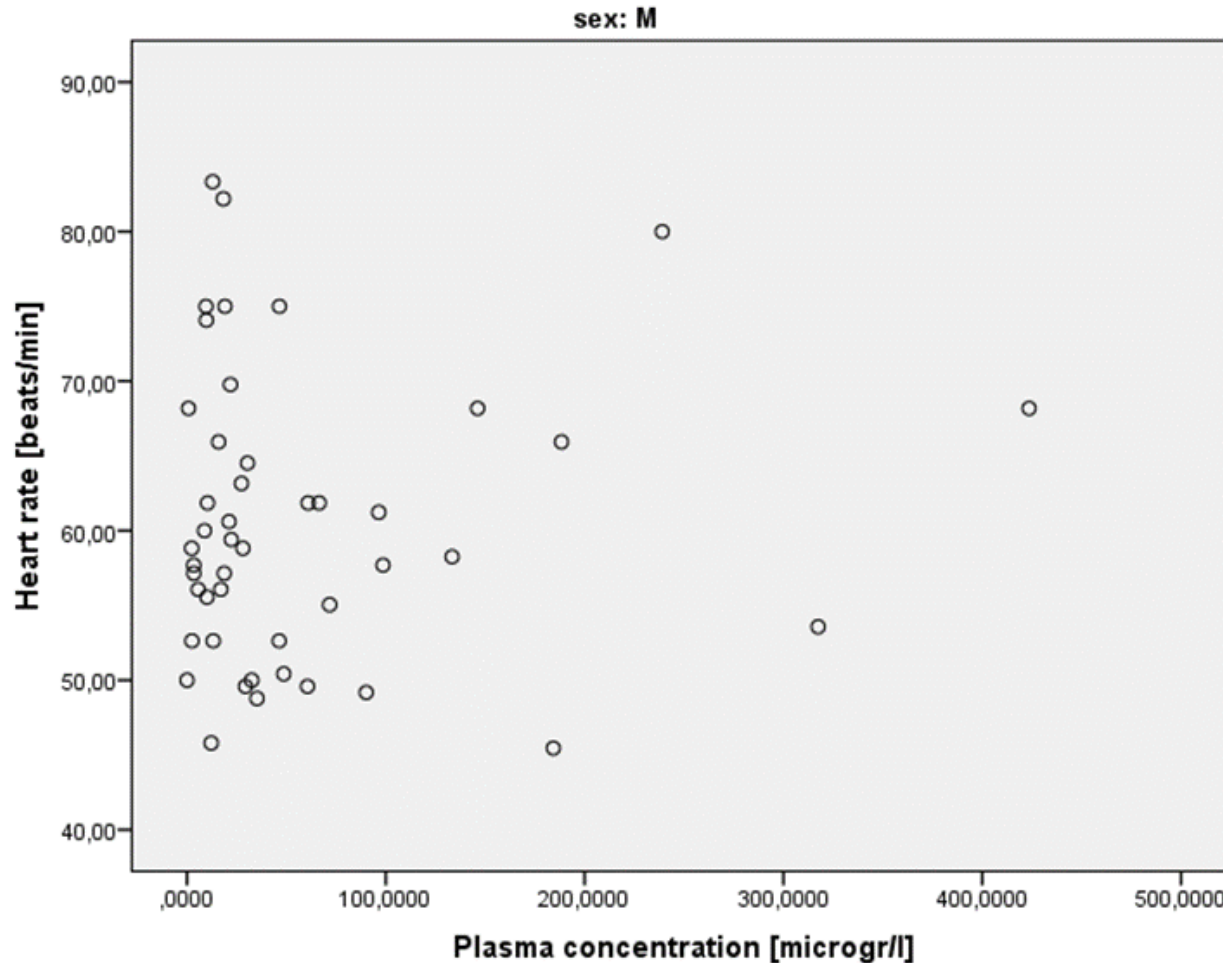
Relatie dosis - bloedspiegel



Relatie bloedspiegel - hartslag



Relatie bloedspiegel - hartslag



Relatie bloedspiegel - hartslag

Coefficients^{a,b}

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	42,755	25,412		1,682	,100	-8,645	94,155
	Age at baseline	,219	,251	,148	,871	,389	-,289	,727
	BMI at baseline	,012	,556	,003	,021	,983	-1,113	1,137
	Time between blood sample and ECG [sec]	,000	,000	,075	,471	,640	,000	,001
	Diabetes	-6,608	7,411	-,142	-,892	,378	-21,599	8,382
	Plasma concentration [microgr/l]	,011	,019	,103	,592	,557	-,028	,051

a. sex = M

b. Dependent Variable: Heart rate [beats/min]



Coefficients^{a,b}

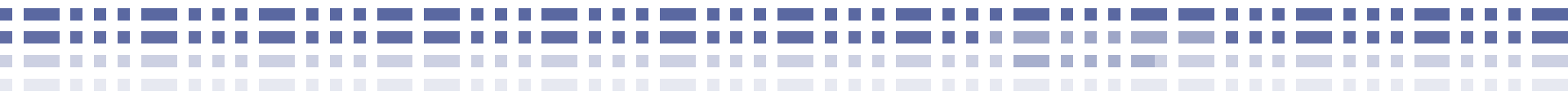
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95,0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	72,930	15,312		4,763	,000	41,959	103,901
	Age at baseline	,005	,160	,004	,028	,977	-,318	,327
	BMI at baseline	-,172	,317	-,084	-,544	,589	-,813	,468
	Time between blood sample and ECG [sec]	,000	,000	-,221	-1,429	,161	-,001	,000
	Diabetes	1,514	4,811	,046	,315	,755	-8,217	11,245
	Plasma concentration [microgr/l]	-,027	,011	-,367	-2,442	,019	-,049	-,005

a. sex = V

b. Dependent Variable: Heart rate [beats/min]



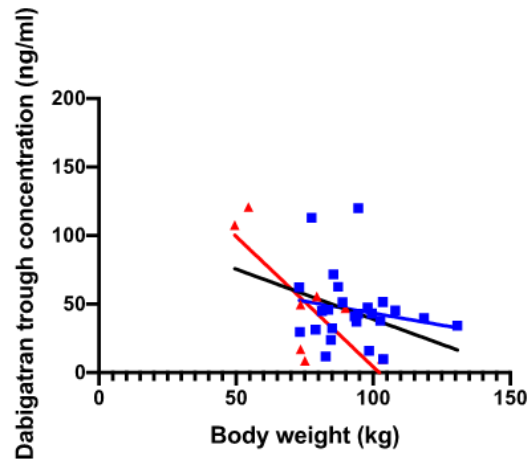
Voorlopige conclusies metoprolol



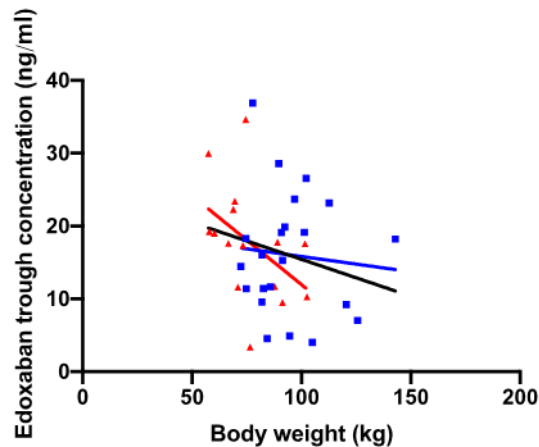
- Artsen schrijven een lagere dosering metoprolol voor aan vrouwen
- Mannen en vrouwen krijgen lagere doseringen dan aanbevolen in de verschillende behandelrichtlijnen
- Bij mannen een duidelijker verband tussen dosis en bloedspiegel
- Effect van metoprolol op de hartslag is groter bij vrouwen
- Nog aantal onzekerheden (n pat, oude bloedmonsters, etc.)

Voorbeeld: DOACs

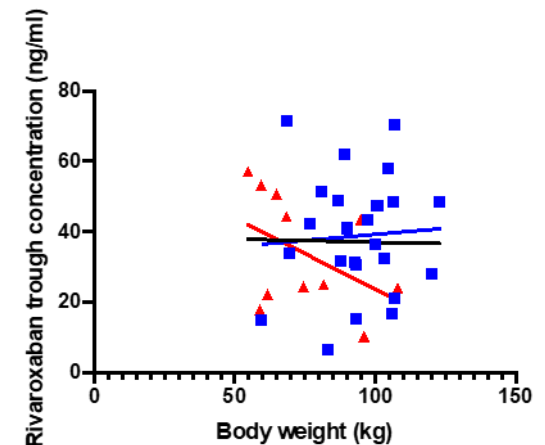
Dabigatran



Edoxaban



Rivaroxaban

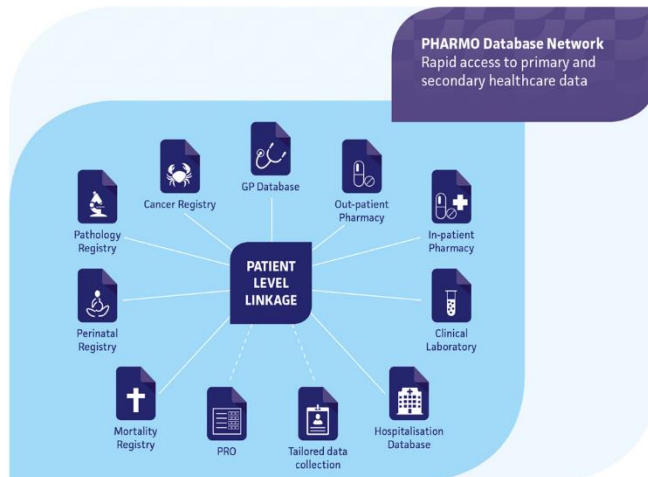


Relatie tussen lichaamsgewicht en dalspiegel is anders voor mannen en vrouwen!

2 disciplines nodig

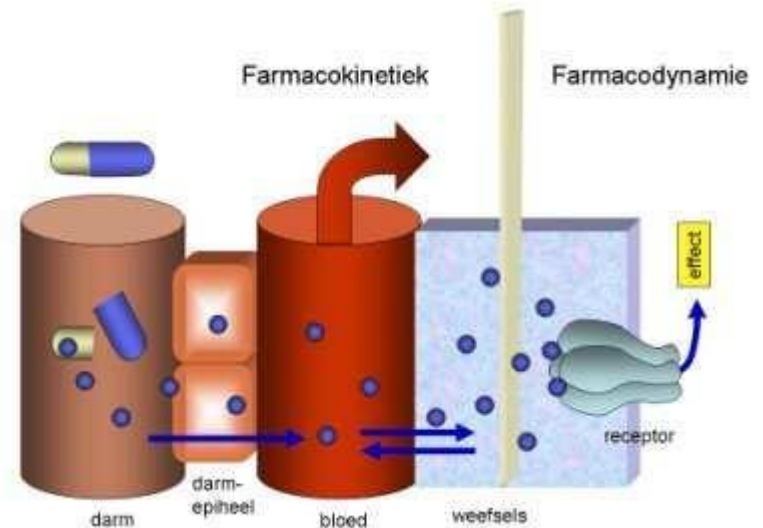
Farmaco-epidemiologie

Houdt zich bezig met de studie van het gebruik en het effect van geneesmiddelen onder grote aantallen mensen



Klinische farmacologie

Bestudeert de wisselwerking tussen een geneesmiddel en het lichaam



Personalized medicine

Traditional Medicine

