

# De waarde van “big data” om therapietrouw op populatie niveau te bestuderen

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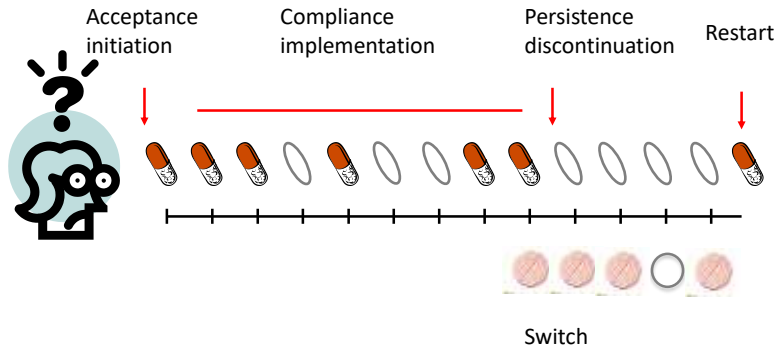
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## Wat aan bod komt

- Hoe kunnen we therapietrouw meten met 'big data'?
- Wie lopen er risico: selectie op basis van apotheekdata?
- Relatie therapietrouw - uitkomsten

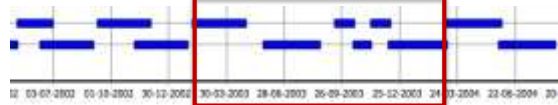


## Adherence phases



## Database with prescriptions: longitudinal data

Date	ATC	Quantity	Drug	Use	Strength
07-05-2002	C10AA01	56	zocor20mgtablet	1D1T	20
12-06-2002	C10AA01	84	zocor20mgtablet	1D1T	20
09-09-2002	C10AA01	84	zocor20mgtablet	1D1T	20
06-11-2002	C10AA01	84	zocor20mgtablet	1D1T	20
05-02-2003	C10AA01	84	zocor20mgtablet	1D1T	20
26-05-2003	C10AA01	90	simvastatine	1D1T	20
15-09-2003	C10AA07	30	crestora0mgtabletfilmomh	1D1T	10
13-10-2003	C10AA07	30	crestora0mgtabletfilmomh	1D1T	10
10-11-2003	C10AA07	30	crestora0mgtabletfilmomh	1D1T	10
08-12-2003	C10AA07	90	crestora0mgtabletfilmomh	1D1T	10
04-03-2004	C10AA07	90	crestora0mgtabletfilmomh	1D1T	10



Medication Possession Ratio (MPR):  
 $\Sigma$  supply of drug in period = 354/393 = 0.9



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## Same MPR, different pattern

Drug	MPR	1	2	3	4	5	6	7	8	9	10
A	0.5	Yellow	Yellow	Yellow	Yellow	Light Blue	Light Blue	Light Blue	Light Blue	Light Blue	Yellow
B	0.5	Light Blue	Light Blue	Green	Green	Green	Green	Green	Light Blue	Light Blue	Light Blue
C	0.5	Brown	Light Blue	Brown	Light Blue	Brown	Light Blue	Brown	Light Blue	Brown	Light Blue

- Evaluation period in relation to expected duration of prescriptions
- Data exploration and cleaning: expected duration/dosing of drugs, deal with overlapping prescriptions



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## Multiple drug regimen

Drug	1	2	3	4	5	6	7	8	9	10
A	Brown	Brown	Brown	Light Blue	Light Blue	Light Blue	Light Blue	Light Blue	Light Blue	Light Blue
B	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Light Blue	Yellow	Yellow	Yellow
C	Light Blue	Light Blue	Light Blue	Green	Green	Green	Light Blue	Green	Green	Light Blue

- Patient using 3 different antihypertensives
- Is the patient adherent?
  - Drug A: nonpersistence or switch to C
  - Drug B: noncompliance of drugs collected elsewhere
  - Drug C: see A & B, noncompliance or nonpersistence
- Define start, stop, switch, restart at class/drug level
- Adherence to at least 1, to all, average?

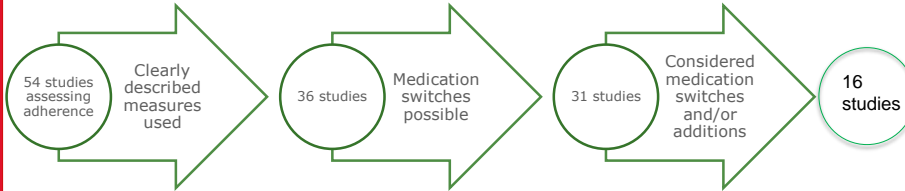


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## Systematic review multiple medication regimes for diabetes/cardiovascular drugs



- Not clear (18)
- Adherence to at least 1 drug (12)
- Adherence to both/all medication (16)
- Average adherence (19)

Alfian SD et al, J Clin Epidemiol 2019; ;108:44-53

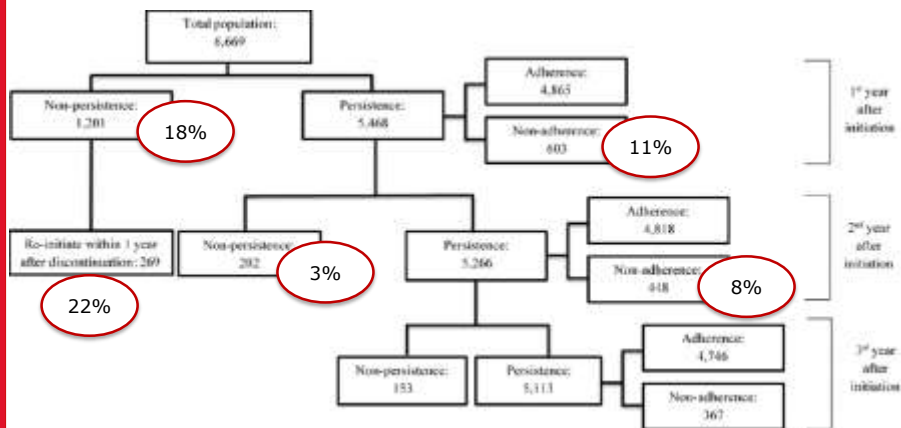


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## Diabetes patients initiating on antihypertensives



Alfian SD et al, PLoS One 2019, accepted



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## Selection of patients using pharmacy data?

	Non-adherence	Non-persistence	Re-initiation
Gender		+ (female)	
Age		+ (age > 80 yr)	
Type of prevention	+ (secondary prevention)		
Type of initial class	+ (diuretics compared to agents acting on renin-angiotensin system)	+ (diuretics, BB, CCB compared to agents acting on renin-angiotensin system)	
Duration of persistence			+ (longer duration of persistence)



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Bewust  
geprik  
voor  
u!
UMC initiatief

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### Bewust geprik voor u!

Op deze website vindt u achtergrondinformatie over de vaccinaties tegen griep.



Drie redenen om de grieprik te halen:

U heeft minder kans op griep  
U kunt het griepvirus niet overdragen aan patiënten  
U beschermt patiënten tegen de ernstige gevolgen van griep

Op deze website kunt u veelgestelde vragen en antwoorden lezen, informatie vinden over onderzoeken naar griep en uw kennis testen in een kennisquiz. De site is bedoeld voor medewerkers van UMC's. De informatie die u op de site vindt is ontwikkeld binnen het UMC Groningen en dus niet commercieel.

**De grieprik haart er gewoon bij. Haal daarom in 2009 drie keer een vaccinatie tegen griep!**



### Zoeken

 [zoek](#)

Deze website wordt ondersteund door!



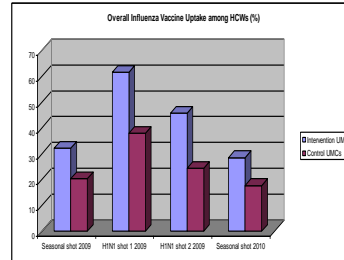

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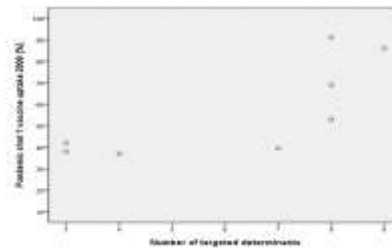
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socialmedia - contact - log in

### Grote Big Data trials: Pragmatische geclusterde gerandomiseerde gecontroleerde trial

	Intervention UMCs (n=3)	Control UMCs (n=3)	External UMCs (n=2)
<b>Year 2009</b>			
Mean no. of HCWs full time equivalents	865	575	654
Mean no. of clinic admissions	34,385	28,944	25,988
Mean HCW/patient ratio	8.23	8.20	6.25
Mean % of HCWs older than 40 years	37.8%	42.9%	42.1%
Mean % of female HCWs	88.1%	79.8%	88.9%



	Intervention UMCs Cont. HCWs (n=10416)	Control UMCs Cont. HCWs (n=10018)	PR (95% CI) P-value
<b>Outcomes</b>			
Patients on influenza during hospital admission	17.5%	7.2%	2.1 (2.0-2.2), P<0.001
Hospitalised with community acquired pneumonia	0%	2.7%	2.2 (0.0-19.6), P=0.42
Influenza and pneumonia during hospital admission	3.8%	8.7%	0.47 (0.3-0.6), P<0.001
Pneumonia during hospital admission	1.4%	4.9%	0.28 (0.21-0.38), P<0.001
Use of intensive care during hospital admission	5.5%	7.4%	0.7 (0.4-1.3), P=0.28
Mean duration of hospitalisation in days, (mean difference in days, 95% CI)	(13.2 (0.51))	(10.7 (0.44))	0.36 (1.1-0.3), P=0.38



Riphagen J, et al. Eurosurveillance, 2013



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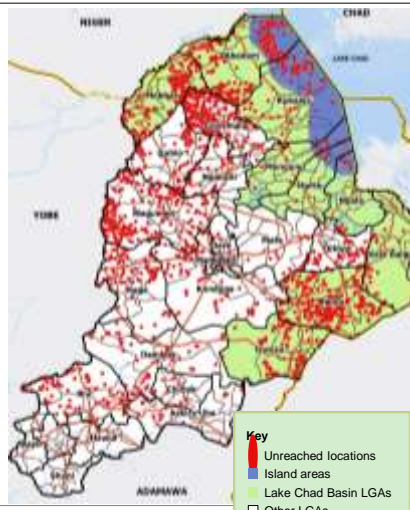


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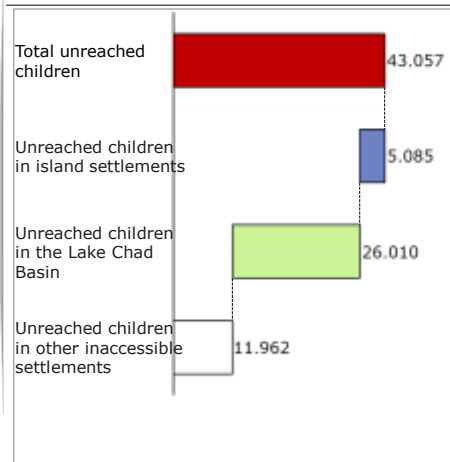
### UNREACHED POPULATION ANALYSIS – SPECIAL POPULATIONS: Borno state, Nigeria

**72% (31,095) of the 43,057 unreachable children are in the Lake Chad islands and other settlements in the Lake Chad Basin**

Map showing all unreachable locations highlighting special populations, as @ August 2019



Breakdown of unreachable U-5 children among all special populations as @ August 2019 (Number of children)



Source: Tally sheet summary, adjusted satellite imagery data v 7.7



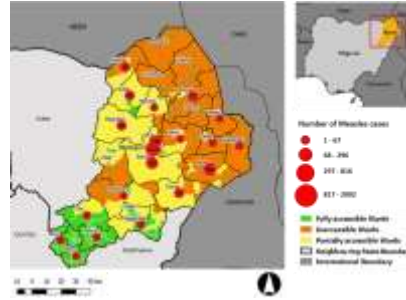
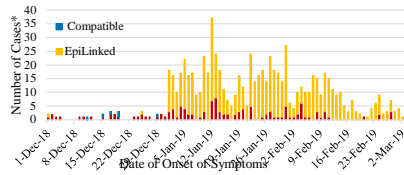
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## Epidemic curves of measles cases in security compromised areas, Borno state, Nigeria

43,057 children < 5 years are trapped in security compromised areas of the state



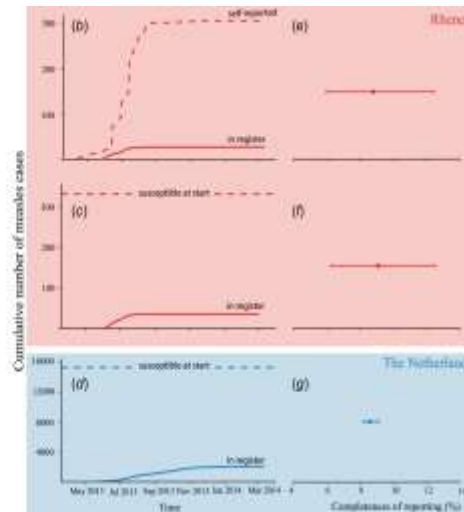
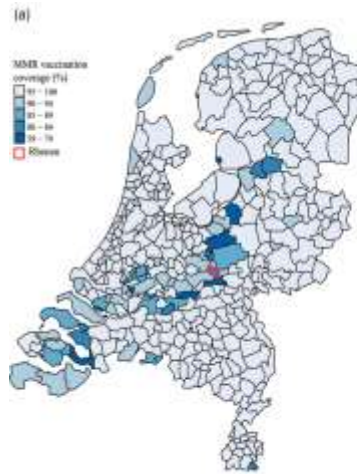
Anne Baptiste, thesis work 2019



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## Measles epidemic 2013-2014



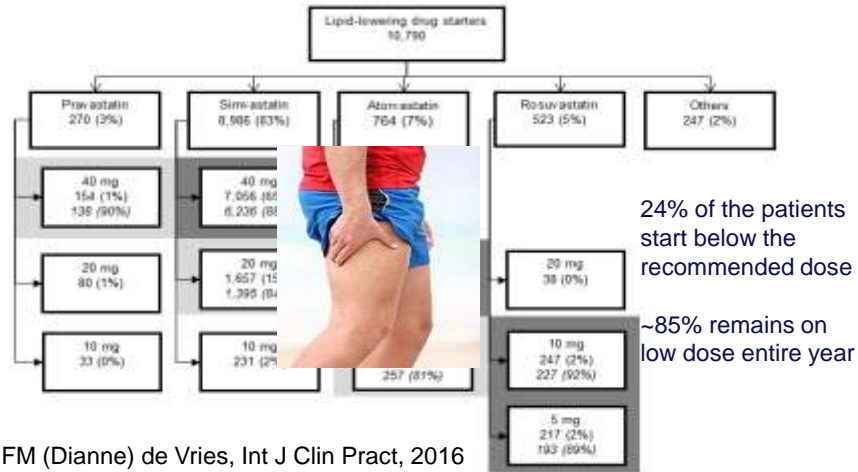
Woudenberg T, et al. Infect Epidemiol 2019



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## Statin use among Dutch diabetes type II patients (GIANTT data)



FM (Dianne) de Vries, Int J Clin Pract, 2016



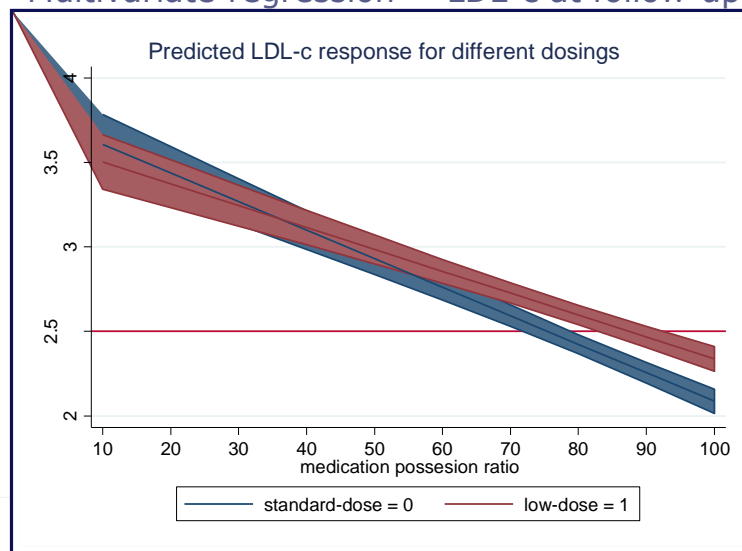
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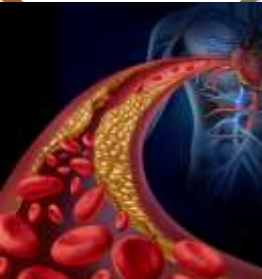
## Effect low vs. standard-dose

Multivariate regression -- LDL-c at follow-up






# Sex disparities in statin prescriptions/effects

**PharmLines Initiative**

"Relevant variants in patients DNA can help in optimizing the choice of drugs and in finding the appropriate dose"

Approx. 80,000 participants



Rudolf de Boer & Eelko Hak



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Lisa Emmens, Sylvi Irawati, Eelko Hak, Rudolf de Boer

Data confidential, unpublished



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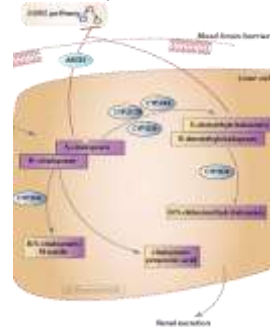
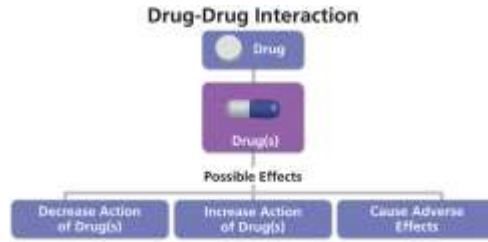


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## Drug-Drug-Interaction (DDI)

External factor ->

the presence of CYP modulators (CYP2C19/3A4/2D6 inhibitors/inducers).



<https://aidsinfo.nih.gov>

Muh. Akbar Bahar<sup>1</sup>, Pauline Lanting<sup>2</sup>, Jens H.J. Bos<sup>1</sup>, Rolf H. Sijmons<sup>2</sup>, Eelko Hak<sup>1</sup>, Bob Wilffert<sup>1</sup>



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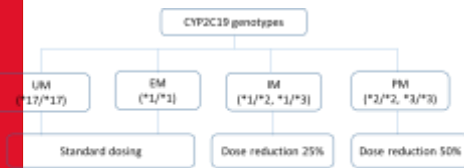
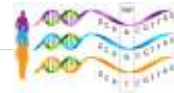
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## Drug-Gene-Interaction (DGI)

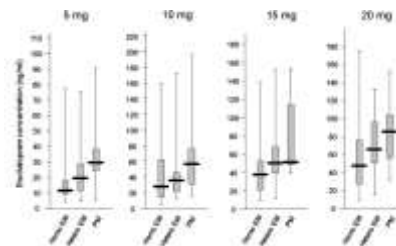


Internal factors ->

genetic polymorphisms -> SNP.



<https://kennisbank.knmp.nl/article/farmacogenetica/4195-4196-4197.html>



↑ (Es)citalopram = PM > IM > EM/NM > UM

Homo EM= EM/NM  
Hetero EM = IM

Tsuchimine, Shoko, et al., 2018



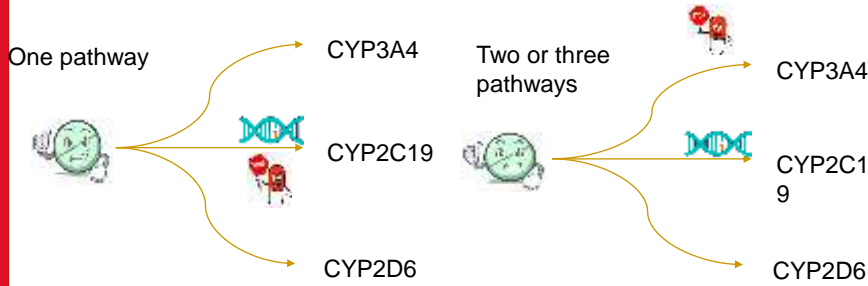
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**Drug-Drug-Gene-Interaction (DDGI)**

- Combination of the existing deviating alleles of CYP2C19/3A4/2D6 and the presence of a CYP2C19/3A4/2D6 modulator.



**PharmLines Initiative**

"Relevant variants in patients DNA can help in optimizing the choice of drugs and in finding the appropriate dose"



Utrecht: [pharmlines.nl](http://pharmlines.nl) Groningen: [www.umcg.nl](http://www.umcg.nl)

**Outcomes (switching + dose reduction)**

Variables (n Yes, %)	Switch or Dose red (n= 31)	aOR (95%CI)	P value	Variables (n Yes, %)	Switch or Dose red (n= 31)	aOR (95%CI)	P value
<b>CYP2C19 &amp; CYP3A4 phenotypes</b>				<b>CYP modulator*</b>			
<b>CYP2C19 phenotypes*</b>				No inhibitor/inducer of CYP2C19/3A4/2D6			
CYP2C19 NM	12 (38.7)	Ref.		CYP2C19 inhibitor alone	4 (12.9)	2.36 (0.67-8.32)	0.18
CYP2C19 IM	18 (58.1)	3.16 (1.41-7.09)	0.01	CYP3A4 inhibitor alone	0 (0)	NA	
CYP2C19 PM	1 (3.2)	0.545 (0.07-4.52)	0.57	CYP2D6 inhibitor alone	0 (0)	NA	
CYP2C19 UM	0 (0)	NA		<b>Combined exposures^a</b>			
<b>CYP3A4 phenotypes**</b>				No exposures			
CYP3A4 NM	23 (74.2)			CYP2C19 NM + CYP3A4 NM + No CYP Modulator			
CYP3A4 IM	8 (25.8)	1.37 (0.55-3.39)	0.50	7 (22.6)			
CYP3A4 PM	0 (0)	NA		<b>DDI</b>			
<b>Phenotypes combination***</b>				CYP2C19 NM + CYP3A4 NM + Yes CYP Modulator			
CYP2C19 NM + CYP3A4 NM	9 (29)	Ref.		2 (6.5)			
CYP2C19 IM/PM + CYP3A4 NM	14 (45.2)	2.35 (0.96-5.76)	0.06	<b>DGI</b>			
CYP2C19 IM/PM + CYP3A4 IM/PM	5 (16.1)	3.46 (1.02-11.75)	0.05	CYP2C19 IM/PM + CYP3A4 NM + No CYP Modulator			
CYP2C19 NM + CYP3A4 IM/PM	3 (9.7)	1.11 (0.28-4.43)	0.88	13 (41.9)			
CYP2C19 UM + CYP3A4 NM/IM	0 (0)	NA		5 (16.1)			
				CYP2C19 NM + CYP3A4 IM/PM + No CYP Modulator			
				2 (6.5)			
				CYP2C19 NM + CYP3A4 IM/PM + No CYP Modulator			
				0 (0)			
				CYP2C19 UM + CYP3A4 NM/IM + No CYP Modulator			
				0 (0)			
				<b>DDGI</b>			
				2 (6.5)			

Adjusted for: \*CYP3A4 phenotypes, CYP modulator & N of co-prescriptions; \*\*CYP2C19 phenotypes, CYP modulator & N of co-prescriptions; \*\*\*CYP modulator & N of co-prescriptions; <sup>a</sup>CYP2C19 & CYP3A4 phenotypes, & N of co-prescriptions; <sup>b</sup>N of co-prescriptions.

**Akbar Bahar, promotie February 4, 2020 om 11 uur precies**



## SAMENGEVAT: een uitgebreid kleurenpalet

Therapietrouw meten en patiënten selecteren met 'big data' vraagt:

- heldere definities van starten, stoppen, switch, herstart
- kennis van te verwachten voorschrijf/aflever patronen/ruis in data
- aandacht voor gebruik meerdere middelen bij 1 indicatie
- onderscheid tussen onregelmatig gebruik en stoppen

Invloed therapietrouw op uitkomsten is afhankelijk van:

- geneesmiddel
- setting
- gedrag van de patiënt
- aanwezigheid comedicaatie
- genetische profiel

*“Je gaat het pas zien als je het door hebt.”*

*Johan Cruijff*

Contact: [e.hak@rug.nl](mailto:e.hak@rug.nl) en [p.denig@umcg.nl](mailto:p.denig@umcg.nl)



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