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SYMPOSIUM

Farmacotherapeutische actualiteit 2023

Welkom!

het symposium zal dadelijk beginnen

Praktische info

✓ **Accreditatie**

- Ter plaatse:
  - o Zorg zeker dat je het **formulier** getekend hebt aan de receptie voor het eind van de dag
- Online:
  - o Je zal af en toe een **pop-up** zien verschijnen op het scherm, hier dien je steeds op te klikken. Aan de hand hiervan kunnen wij jouw aanwezigheid bevestigen.

Praktische info

✓ **Vragen**

- Ter plaatse:
  - Aan het eind van de presentatie
  - Tijdens de pauze
- Online:
  - Via de chat

Praktische info

- ✓ **Polls**
  - Online :
    de polls verschijnen op jouw scherm
  - In de zaal:
    we overlopen samen de resultaten

Programma

09u45 Introductie
09u50 Bruistabletten: een goede keuze?
10u20 Gerandomiseerd vs observationeel onderzoek: sterktes en zwaktes

10u50 Pauze
11u20 Nieuwigheden in de medicamenteuze behandeling van chronische nierinsufficiëntie
11u50 De rol van P-glycoproteïne (P-gp) bij geneesmiddeleninteracties

Sprekers

- ✓ Sarah Thooft MD
- ✓ Thierry Christiaens MD, PhD
- ✓ Joachim Vandenhoven MD
- ✓ Ann Van Ermen MPharmSc, PhD

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Farmacotherapeutische actualiteit 2023

Bruistabletten: een goede keuze?

Sarah Thooft MD

Quiz 1

Q1 : What is the main class of medicine (i.e. registered as a medicine) in effervescent form in Belgium?

a) Laxatives
b) Mucolytics and expectorants
c) Painkillers and anti-inflammatories
d) Vitamins

Feedback quiz 1

Q1 : What is the main class of medicine (i.e. registered as a medicine) in effervescent form in Belgium?

a) Laxatives
b) Mucolytics and expectorants
c) Painkillers and anti-inflammatories
d) Vitamins

Quiz 2

Q2 : What are the risks of effervescent forms?

a) Higher mortality from all causes
b) Higher risk of cardiovascular disease
c) An increase in blood pressure
d) All answers are correct

Feedback quiz 2

Q2 : What are the risks of effervescent forms?

a) Higher mortality from all causes
b) Higher risk of cardiovascular disease
c) An increase in blood pressure
d) All answers are correct

Quiz 3

Q3 : In which patients should particular attention be paid to the amount of sodium in medicines?

a) Patients on a strict low-salt diet
b) Adults on antibiotics
c) Children
d) Diabetics

Feedback quiz 3

Q3 : In which patients should particular attention be paid to the amount of sodium in medicines?

a) Patients on a strict low-salt diet
b) Adults on antibiotics
c) Children
d) Diabetics

Summary

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1. Introduction

1.1. Specialities in effervescent form in Belgium

Group	Proportion	Name (examples)	Sodium content	Amount of NaCl
Painkillers and anti-inflammatories	51%	*Dafalgan® eff. 1g*	565 mg	1 400 mg
		Sedergine 1g ®	460 mg	1 200 mg
		Aspirine 500®	250 mg	638 mg
		Brufen®	197 mg	491 mg
Vitamins and minerals	41%	*D-Vital Forte®*	10 mg	26 mg
		Steovit Forte®	96 mg	245 mg
		Upsa-C®	284 mg	724 mg
Mucolytics and expectorants	5%	*Acetylcystéine EG®*	145 mg	370 mg
		Lysomucil®	157 mg	401 mg
Laxative	3%	*Spagulax*	120 mg	306 mg

Folia mai 2023, Sodium dans les médicaments: risques cardiovasculaires, https://www.cbip.be/fr/articles/4084?folia=4079

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1. Introduction

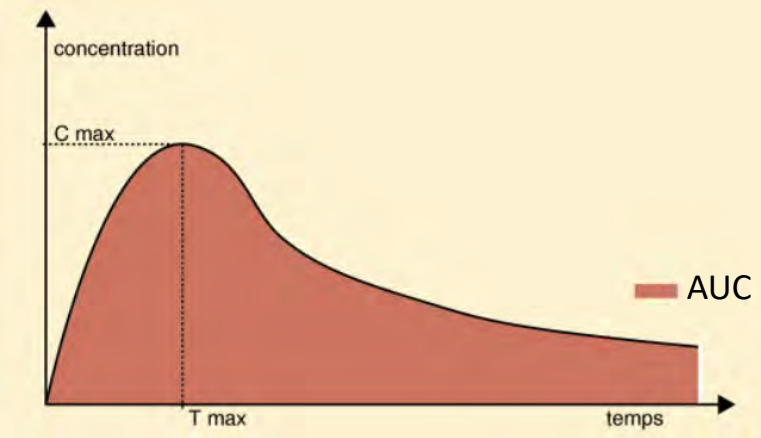
1.2. How does it work?

$$Na^+ + HCO_3^- + R\text{-}COOH \longrightarrow CO_2 + H_2O + RCOO^- + Na^+$$

In water, the carbonate or bicarbonate reacts with the acid to release carbon dioxide, which acts as a disintegrating agent for the tablet.

2. Advantages of effervescent forms

2.1. Pharmacokinetics



Bioavailability refers to the fraction of an administered dose that reaches the general circulation and the rate at which it does so.

It is characterised by three parameters :

- The **maximum concentration of the substance** (C_{max}) reached in the plasma;
- The **time** taken to reach it (T_{max});
- The **area under the curve** (AUC), which gives an idea of the total quantity reaching the general circulation.

Prescrire, C'est-à-dire ? Biodisponibilité, mai 2018, tome 38 (415) : page 349.

2. Advantages of effervescent forms

2.1. Pharmacokinetics

Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers (2000)

Table 1 The time to maximum serum concentration (t_{max}), the maximum serum concentration (C_{max}) and the area under the curve 0–3 h ($AUC_{0-3\ h}$) after a 1000-mg dose of paracetamol effervescent tablets (Pinex Brusetablett, Alpharma AS) compared with ordinary paracetamol tablets (Panodil, SmithKline Beecham). Values are given as mean with the 95% confidence interval

Parameter	Effervescent paracetamol	Ordinary paracetamol	*P* value
t_{max} (min)	27 (20–34)	45 (34–56)	0.004
C_{max} (μmol/l)	143 (104–158)	131 (118–168)	0.203
$AUC_{0-3\ h}$ ($\mu mol \cdot h \cdot l^{-1}$)	224 (195–253)	198 (171–225)	0.003

- ***Objective***: to compare the rate of absorption between ordinary paracetamol tablets and effervescent paracetamol tablets.
- ***Methods***: open randomised crossover study with 20 healthy volunteers. Given 1000 mg of either ordinary paracetamol or effervescent paracetamol with 3 weeks wash-out period.
- ***Limitations***:
  - Area under the curve only form 0 to 3h
  - Open study
  - Only 20 healthy volunteers, baseline characteristics not presented
  - Sponsorised

Rygnestad, T., Zahlsen, K., & Samdal, F. A. (2000). Absorption of effervescent paracetamol tablets relative to ordinary paracetamol tablets in healthy volunteers. European journal of clinical pharmacology, 56, 141-143

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2. Advantages of effervescent forms

2.1. Pharmacodynamic

Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study (2000)

Table II Calculated Time to Onset of Analgesia and Time to Remedication

	Effervescent Acetaminophen, 1000 mg	Tablet Acetaminophen, 1000 mg	Effervescent Placebo	Tablet Placebo
Number of patients	60	60	62	60
Patients with onset, *n* (%)	42 (70.0)*	42 (70.0)+	12 (19.4)	9 (15.0)
Time to onset of analgesia (h)				
Median	0.34^A§ (20 minutes)	0.75° (45 minutes)	NE	NE
95% CI	[0.33-0.58]	[0.50-0.75]		
Time to meaningful pain relief (h)				
Median	0.75^Δ¶ (45 minutes)	1.00° (60 minutes)	NE	NE
95% CI	[0.50-1.00]	[1.00-1.13]		
Time to remedication (h)				
Median	2.11* (2 h: 07 min)	2.69+ (2 h: 41 min)	1.00	1.00
95% CI	[1.6-3.0]	[2.0-3.12]	[—]	[—]
Remedicated patients, *n* (%)	[illegible]*	44 (73.[illegible])*	62 (100)	56 (93.3)

Values are presented as mean ± standard deviation. NE, not estimable. Median time was not estimable since less than 50% of patients achieved an onset of analgesia and a meaningful pain relief.
*$p \leq 0.001$ versus effervescent placebo.
#$p \leq 0.01$ and +$p \leq 0.001$ versus tablet placebo.
Δ$p \leq 0.001$ versus effervescent placebo. Comparison based on survival distributions.
°$p \leq 0.001$ versus tablet placebo. Comparison based on survival distributions.
§$p = 0.0081$ and ¶$p = 0.0064$ versus tablet acetaminophen.

- ***Objectives***: to determine and compare, using the post-dental pain model and a stop-watch method, the time to onset of analgesia of two formulations of acetaminophen 1000 mg
- ***Methods***: randomized, double-blind and double dummy, placebo-controlled study.
- ***Limitations***:
  - Sponsorised

Møller, P. L., Nørholt, S. E., Ganry, H. E., Insuasty, J. H., Vincent, F. G., Skoglund, L. A., & Sindet-Pedersen, S. (2000). Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double-blind, randomized, placebo-controlled study. The Journal of Clinical Pharmacology, 40(4), 370-378.

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2. Advantages of effervescent forms

2.2. Other advantages

- ✓ Taste ?
  - o Citric acid
- ✓ Reduced risk of acute overdose
  - o Needs a lot of water to dissolve 6-8 tablets
  - o Nausea
- ✓ Easy to use in case of swallowing disorders

3. Risks associated with effervescent forms

3.1. Cardiovascular risks and mortality (2013)

Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study

Table 3 Odds ratios and 95% confidence intervals for composite cardiovascular outcome* and individual outcomes for sodium-containing formulations group compared with standard formulations group (OR=1)

	OR (95% CI)	
	Unadjusted	Adjusted†
Composite cardiovascular outcome*	1.13 (1.09 to 1.18)	1.16 (1.12 to 1.21)
Individual outcomes		
Incident non-fatal myocardial infarction	0.90 (0.85 to 0.96)	0.94 (0.88 to 1.00)
Incident non-fatal stroke	1.21 (1.15 to 1.28)	1.22 (1.16 to 1.29)
Vascular death	0.62 (0.31 to 1.24)	0.70 (0.31 to 1.59)
Hypertension	6.80 (6.41 to 7.21)	7.18 (6.74 to 7.65)
Heart failure	0.95 (0.91 to 1.00)	0.98 (0.93 to 1.04)
All cause mortality	1.30 (1.25 to 1.35)	1.28 (1.23 to 1.33)

*Incident non-fatal myocardial infarction, incident non-fatal stroke, and vascular death.

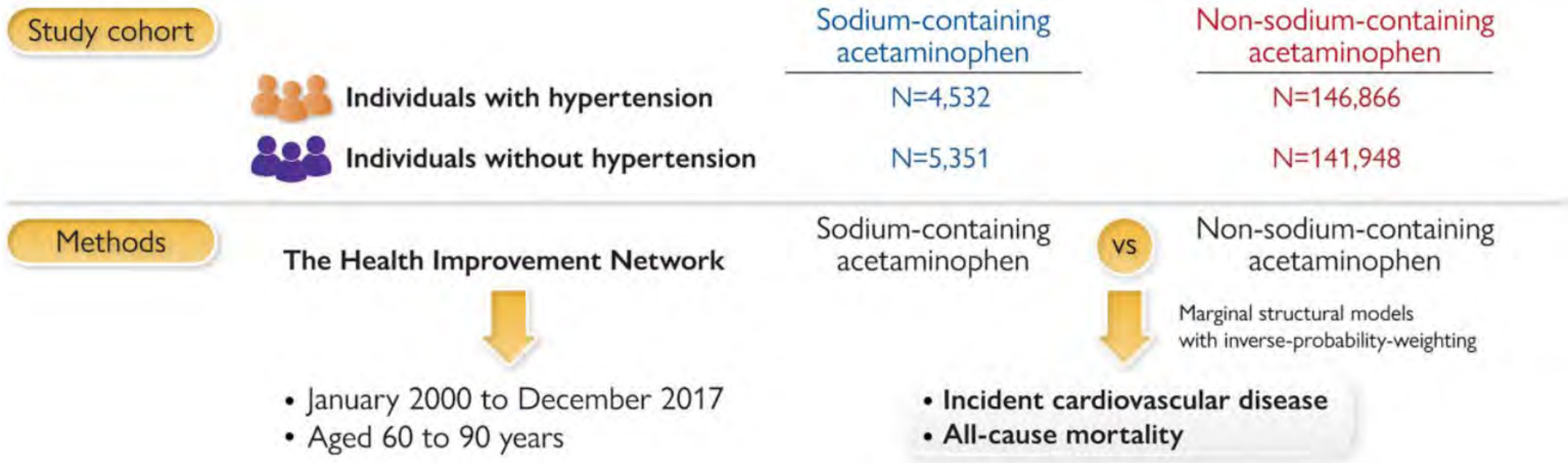
- ***Objective***: To determine whether patients taking formulations of drugs that contain sodium have a higher incidence of cardiovascular events compared with patients on non-sodium formulations of the same drugs.
- ***Methods***: case control study
- ***Limitations***:
  - Observational study ➔ confounding variables (sodium intake…)
  - No OTC drugs included

*George, J., Majeed, W., Mackenzie, I. S., MacDonald, T. M., & Wei, L. (**2013**). Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. Bmj, 347.*

3. Risks associated with effervescent forms

3.1. Cardiovascular risks and mortality (2022)

Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension



*Zeng, C., Rosenberg, L., Li, X., Djousse, L., Wei, J., Lei, G., & Zhang, Y. (**2022**). Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension. European Heart Journal, 43(18), 1743-1755.*

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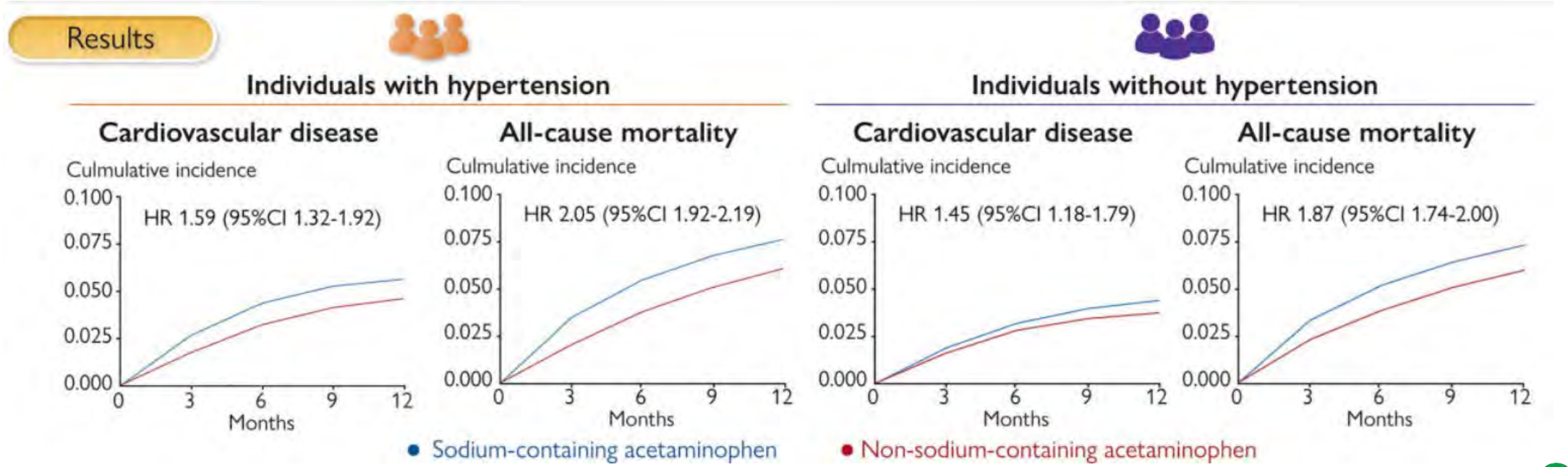

*Zeng, C., Rosenberg, L., Li, X., Djousse, L., Wei, J., Lei, G., & Zhang, Y. (**2022**). Sodium-containing acetaminophen and cardiovascular outcomes in individuals with and without hypertension. European Heart Journal, 43(18), 1743-1755.*

4. Clinical case

Jean-Pierre, aged 75, secondary cardiovascular prevention and rheumatological condition

- CV prevention : Asaflow ® 1x/day
- Cholesterol : Totalip® 10mg 1x/day
- Recent rheumatological condition : Medrol 4 mg®
- Calcium + vitamin D : Steovit® compr. efferv. Forte Orange
- Pain : Dafalgan® efferv. 1g 3x/day
- Cough : Lysomucil® efferv. 1x/day in the morning

4. Clinical case

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- Cough : Lysomucil® efferv. 1x/day in the morning

Médicaments	Teneur en sodium par comprimé	Teneur en NaCl par comprimé	Teneur en sel par jour
Asaflow®	/	/	/
Totalip®	10 mg	25,5 mg	25,5 mg
Medrol®	/	/	/
Steovit®	96.1 mg	245 mg	245 mg
Dafalgan®	565 mg	1400 mg	4200 mg
Lysomucil®	157 mg	401 mg	401 mg
			4,87g de sel par jour

5. Take home message

- ✓**In all patients**, and **particularly those suffering from hypertension**, it is certainly preferable to avoid medicines with a high sodium content, especially when several tablets are taken daily or when they must be taken for a long time.

- ✓In patients on a **strict low-salt diet**, effervescent forms must be avoided

Thank you for your attention!

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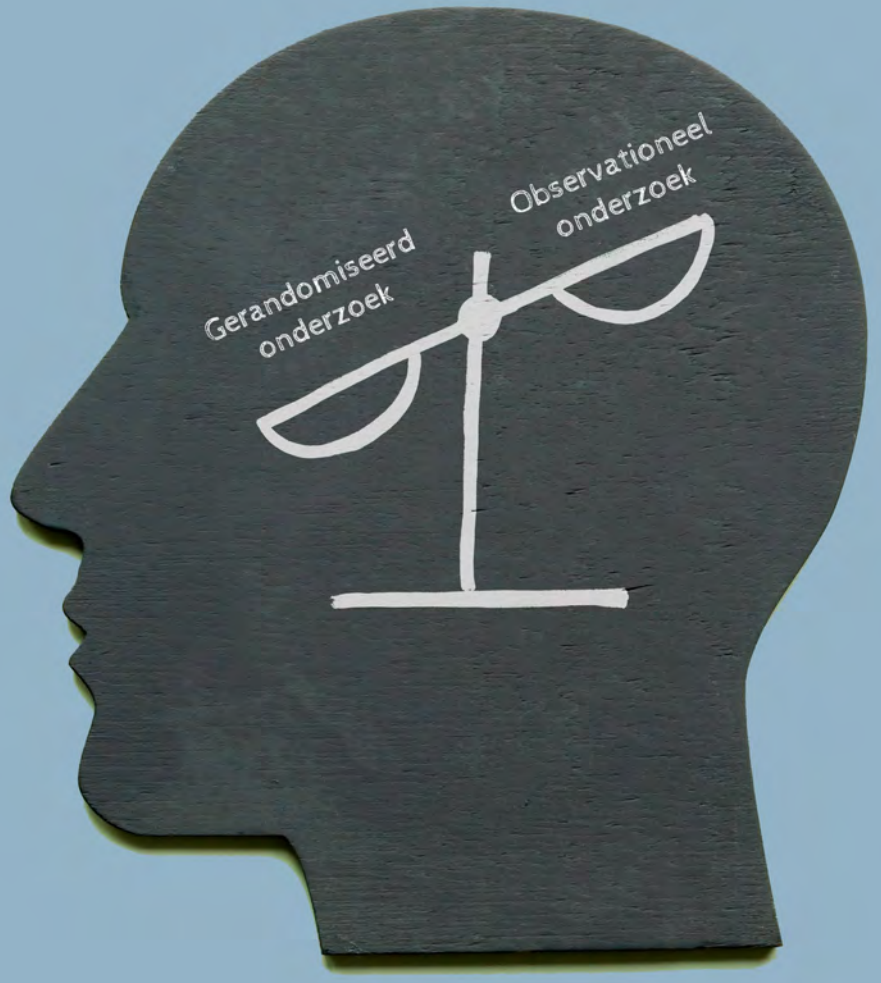
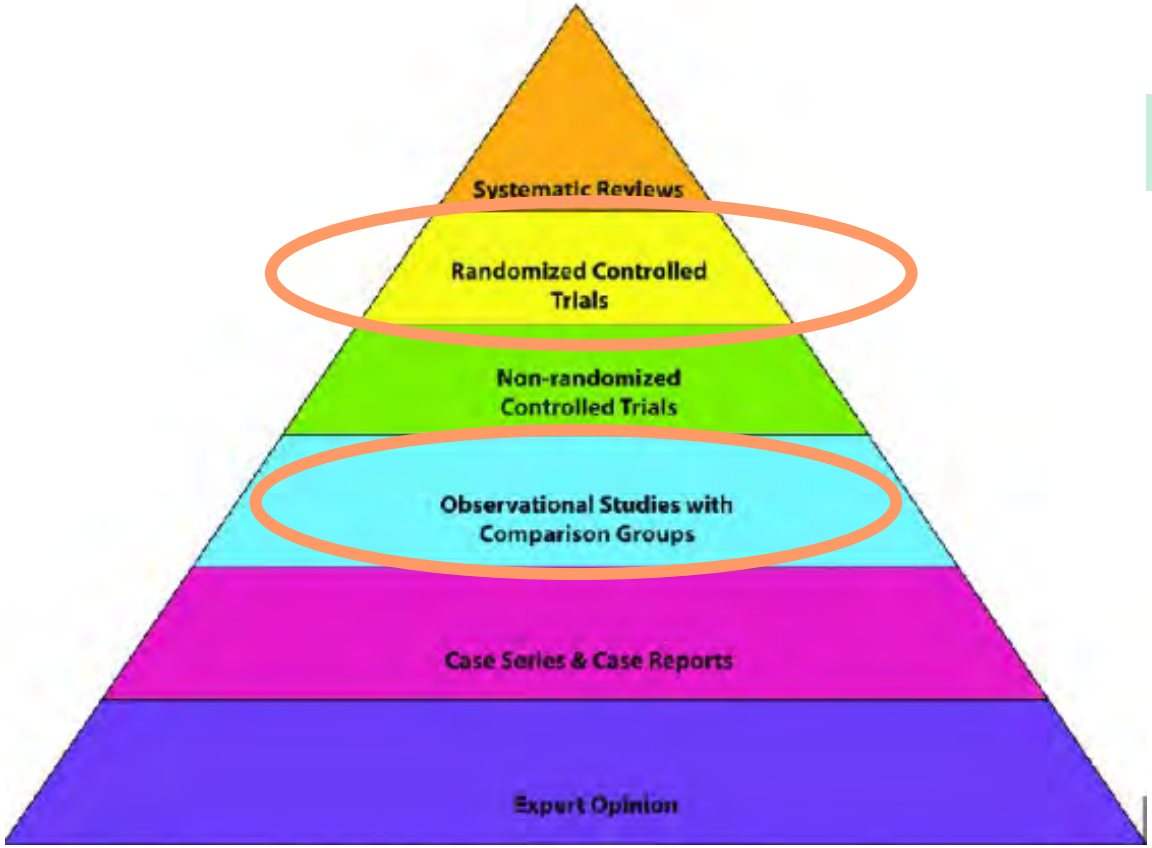
Farmacotherapeutische actualiteit 2023



Gerandomiseerd vs observationeel onderzoek: sterktes en zwaktes

Thierry Christiaens MD, PhD

RCT vs observationeel onderzoek: een hiërarchie...



Ja, maar....

RCT vs observationeel onderzoek

- **RCT: experimentele studie / interventiestudie** : de blootstelling wordt beïnvloed

  ('ideale situatie': geselecteerde patiënten, intensieve follow-up, frequente herbeoordelingen, enz.)

vs

- **Observationeel onderzoek**: de onderzoekers hebben geen invloed op de mate van blootstelling

Overzicht

- Waarom **RCT's** de gouden standaard zijn in klinisch onderzoek...
- ... en waarom RCT's ons niet alles vertellen wat we moeten weten

- Waarom het zo moeilijk is om een causaal verband vast te stellen op basis van een **observationeel onderzoek**
- ... en waarom observationele studies soms essentieel zijn ...

- ... en waarom we meer RCT's willen!

Waarom RCT's de gouden standaard zijn in klinisch onderzoek...

Hoe test je een (nieuw) geneesmiddel?

- Patiënten genezen ook zonder het geneesmiddel te slikken+ placebo-effect
  - Je moet patiënten die een geneesmiddel gebruiken, **vergelijken** met patiënten die géén geneesmiddel gebruiken
  - **Gecontroleerde klinische studie**

- De te vergelijken groepen moeten vergelijkbaar zijn.
  Het ENIGE VERSCHIL = een verschil in behandeling
  - randomisatie
  - **Gerandomiseerde gecontroleerde studie**

- Onderzoekers mogen niet bevooroordeeld zijn bij het beoordelen van resultaten
  - dubbele (driedubbele) blindering
  - **Gerandomiseerde, dubbelblinde, gecontroleerde klinische studie**

RCT's: de gouden standaard in klinisch onderzoek omdat

- Als de te vergelijken groepen in alle opzichten vergelijkbaar zijn, behalve wat de behandeling betreft ...
- ... dan is het verschil in uitkomst enkel toe te schrijven aan een verschil in behandeling
- **causaal verband** tussen blootstelling (geneesmiddel) en effect
  (in de studiepopulatie)

… en waarom RCT's ons niet alles vertellen wat we willen weten…

De RCT's...

- Moeilijke en zeer dure studies

  - Beperkte studieduur
  - Beperkt aantal deelnemers
  - Sterk geselecteerde deelnemers...

We willen weten…

… hoe dit geneesmiddel werkt in *real life*.

- RCT's: geselecteerde patiënten, ideale omstandigheden voor follow-up, beperkte duur
  - Waar zijn…
    - de vrouwen?
    - de ouderen?
    - de comorbiditeiten?
    - de zwangere vrouwen en vrouwen die borstvoeding geven?
    - de patiënten uit kansarme milieus?
  - Therapietrouw?
  - Werkzaamheid op lange termijn?

We willen weten…

… wat de effecten zijn van dit geneesmiddel op eindpunten die er voor de patiënt echt toe doen.

- **Intermediaire eindpunten** (surrogaateindpunten)
  - laten **kortere** studies toe …
    - Botdichtheid versus fractuurrisico?
    - Cholesterol versus cardiovasculair risico?
    - Oncologie: progressievrije overleving vs. totale overleving? Levenskwaliteit?
    - Alzheimer: vermindering van amyloïde plaques vs cognitieve verbetering

We willen weten…

… wat de effecten zijn van dit geneesmiddel op eindpunten die er voor de patiënt echt toe doen.

- **Intermediaire eindpunten** (surrogaateindpunten)
  - laten kortere studies toe …
  - … maar de kans is groot dat de winst wordt overschat (> 40%) *Ciani, BMJ 2022*
  - … en soms leiden ze tot grove fouten *(*bv fluoride en osteoporose…)

We willen weten…

… hoe veilig dit geneesmiddel is.

- RCT's laten niet toe **zeldzame** ongewenste effecten en/of **langetermijneffecten** te detecteren

We willen weten...

... of een bepaald geneesmiddel beter is dan de bestaande opties ...

... en niet of het beter is dan placebo.

(Nood aan vergelijkende studies!)

Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial

Ferrante, Lancet 2022

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Waarom is het zo moeilijk om een causaal verband vast te stellen op basis van een observationele studie...

Hoe test je een (nieuw) geneesmiddel?

- Patiënten genezen ook zonder het geneesmiddel te slikken + **placebo effect**
  - Je moet patiënten die een geneesmiddel gebruiken, **vergelijken** met patiënten die géén geneesmiddel gebruiken.
  - **Mogelijk in een observationele studie**

- De te vergelijken groepen moeten vergelijkbaar zijn.
  Het ENIGE VERSCHIL = verschil in behandeling.
  - **Dit is nooit het geval in een observationele studie!**
  - **Bekende (en onbekende?) confounders?**

- Onderzoekers mogen niet bevooroordeeld zijn bij het beoordelen van resultaten
  - Mogelijk in een observationele studie

Observationele studies

- Verschillende designs...
  - Retrospectieve/prospectieve cohortstudies
  - Case-control studies

- Gemakkelijker en goedkoper dan RCT's

- Door de betere beschikbaarheid van grote hoeveelheden data ('big data') kunnen grote databases worden onderzocht
  - *Electronic Health Records*
  - Administratieve databases
  - Registers ...

Observationele studies…

- **Vergelijkbaarheid** van **onderzoeksgroepen** moeilijk te garanderen

  - Confounders (onbekend)

  - Het schijnbaar causaal verband tussen blootstelling (geneesmiddel) en uitkomst kan worden verklaard door een andere factor

Een causaal verband vaststellen op basis van observationeel onderzoek: niet zo vanzelfsprekend...

Paracetamol in het eerste levensjaar → Astma rond 6-7 jaar

Lancet. 2008 Sep 20;372(9643):1039-48. doi: 10.1016/S0140-6736(08)61445-2.

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme

Een causaal verband vaststellen op basis van een observationele studie: niet zo vanzelfsprekend...

Paracetamol in het eerste levensjaar → Astma rond 6-7 jaar

Koorts in het eerste levensjaar

Lancet. 2008 Sep 20;372(9643):1039-48. doi: 10.1016/S0140-6736(08)61445-2.

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme

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Observationeel onderzoek…

- **Vergelijkbaarheid** van **onderzoeksgroepen** moeilijk te garanderen

- **Gevoeligheid voor bias** (selectiebias, informatiebias)

Informatiebias

Paracetamol in het eerste levensjaar

→ Astma rond 6-7 jaar

Beoordeeld door **retrospectieve vragenlijst** bij ouders

Lancet. 2008 Sep 20;372(9643):1039-48. doi: 10.1016/S0140-6736(08)61445-2.

Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6–7 years: analysis from Phase Three of the ISAAC programme

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+/- **50 soorten bias** … (niet alleen observationele studies…)

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Observationeel onderzoek…

- **Vergelijkbaarheid van onderzoeksgroepen** moeilijk te garanderen
- **Gevoeligheid voor bias** (selectiebias, informatiebias)

- Het vaststellen van een **causaal verband** is niet zo vanzelfsprekend…

- Ontwikkeling van epidemiologische / statistische methodes om de vergelijkbaarheid te verbeteren / corrigeren voor confounding
  bv. *propensity score matching*

- **Resultaten van observationele studies = SIGNAAL (≠ causaliteit)**
  - Meerdere vergelijkbare signalen in verschillende populaties ➔ waarschijnlijker!

… en waarom observationele studies soms onmisbaar zijn …

We willen weten…

… hoe veilig dit geneesmiddel is.

- Geneesmiddelenbewaking
- Farmaco-epidemiologie
- Case-control studies

- Observationele studies laten toe zeldzame en/of laattijdige ongewenste effecten te onderzoeken

- Noodzakelijk wanneer RCT onmogelijk/onaanvaardbaar is:
  Bv bij zwangerschap en borstvoeding

Case-control studie naar zeldzame ongewenste effecten

- Benfluorex (Mediator®) en hartkleplijden in Frankrijk (en dexfenfluramine in België)
- Valproïnezuur (Depakine®) tijdens de zwangerschap en autisme bij kinderen
- Chinolonen en aorta-aneurysma
- Glitazonen en blaaskanker

We willen weten…

… hoe dit geneesmiddel werkt in *real-life*.

(>< ideale settings in RCT)

› Eur J Cancer. 2021 Sep;155:136-144. doi: 10.1016/j.ejca.2021.07.001. Epub 2021 Aug 6.

Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

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‘Real-world evidence’?

Eur J Cancer. 2021 Sep;155:136-144. doi: 10.1016/j.ejca.2021.07.001. Epub 2021 Aug 6.

Real-world outcomes associated with new cancer medicines approved by the Food and Drug Administration and European Medicines Agency: A retrospective cohort study

- Vergelijking van resultaten van RCT's met resultaten van observationele studies (N=263) per indicatie
- 63% van de observationele studies rapporteerde een slechtere overleving dan de overeenkomstige RCT's
- 78% van de onderzoeken: methodologisch zeer zwak…
- Het waren de methodologisch zwakste studies die een hogere overleving toonden dan de overeenkomstige RCT's.

We willen weten...

... hoe dit geneesmiddel werkt in *real-life*.

- Big data: het voorbeeld van administratieve databases

Welke astmapatiënten komen in aanmerking voor tweedelijnsbehandeling

- Omalizumab (Xolair®): tweedelijnsbehandeling voor astmapatiënten die niet onder controle zijn met een correct uitgevoerde ICS+LABA therapie

- Analyse van de behandelingen (ICS+LABA) die de astmapatiënten kregen in het jaar vóór het starten van omalizumab

- Op basis van terugbetalingsgegevens *(beschrijvende studie)*

Administratieve databases

Omalizumab (Xolair®): geïndiceerd als tweedelijnsbehandeling bij astmapatiënten die niet onder controle zijn

> ERJ Open Res. 2019 Nov 25;5(4):00253-2018. doi: 10.1183/23120541.00253-2018. eCollection 2019 Oct.

Real-life effectiveness of omalizumab in difficult-to-treat *versus* severe asthma: a national cohort study in Belgium

Results: Between 2010 and 2016, omalizumab treatment was initiated in 2068 patients with asthma; only 24% fulfilled the eligibility criteria, mainly due to nonadherence to high-dose ICSs + LABAs. The

In tijden van big data...
Voorbeeld: administratieve databases (terugbetaling...)

Pluspunten

- Benutten van bestaande gegevens
- Zeer grote omvang, volledige populatie, geen selectiebias, follow-up in de tijd
- Beschrijvende analyses
  - Therapietrouw, behandelingsduur
  - Profiel patiënt, leeftijd, geslacht
  - Plaatsbepaling van een geneesmiddel binnen de behandelstrategie, comedicatie, enz.
  - ...

Minpunten

- Geen klinische gegevens
- Beperkte informatie
- De noodzaak van proxy's

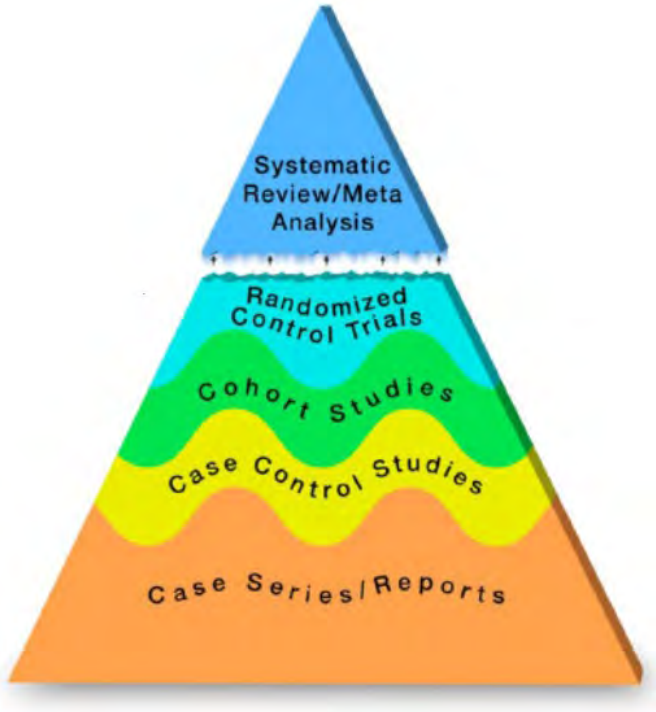
- Moeilijke **analyses**

RCT vs observationeel onderzoek: een hiërarchie?

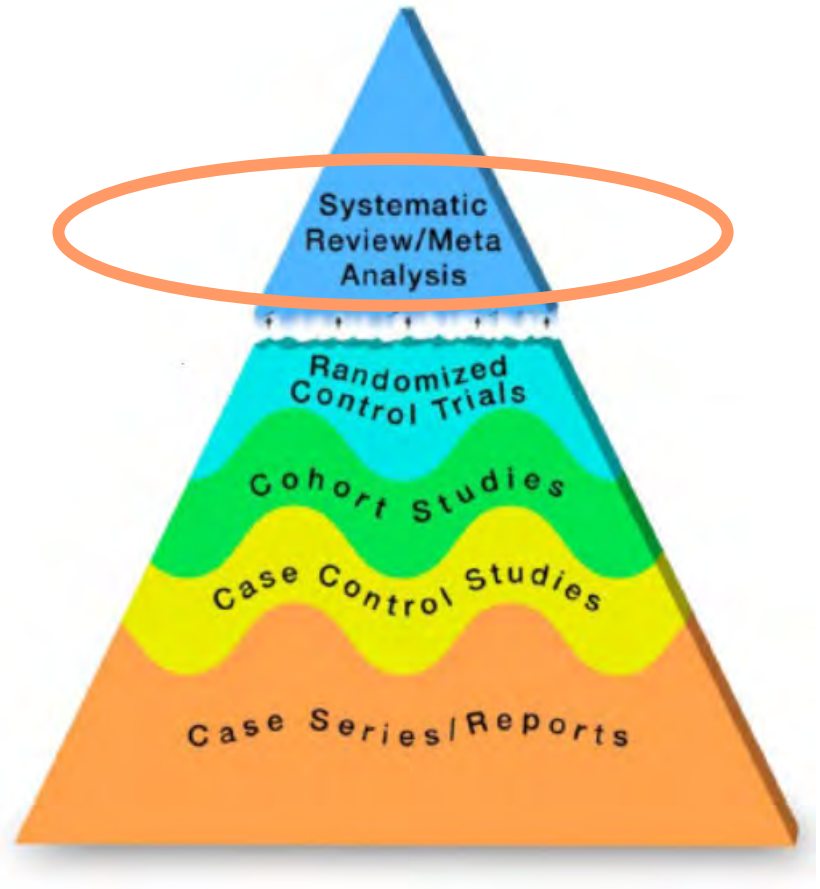
RCT:
een design dat *in principe* superieur is

Ja, maar....

Een **goede observationele studie** is beter dan een **slechte RCT**



RCT vs observationeel onderzoek: een hiërarchie?



Voorbeeld
Cochrane Reviews

Maar **meta-analyse** is niet superieur als het om een meta-analyse gaat van methodologisch zwakke studies!

… waarom we meer (en betere) RCT's nodig hebben…

Moeten we de toegang van patiënten tot "innovatieve" geneesmiddelen versnellen?

- Versnelde toegang, een argument dat (door de industrie) gebruikt wordt om een product sneller op de markt te kunnen brengen
  - … ten koste van de kwaliteit van de evidentie

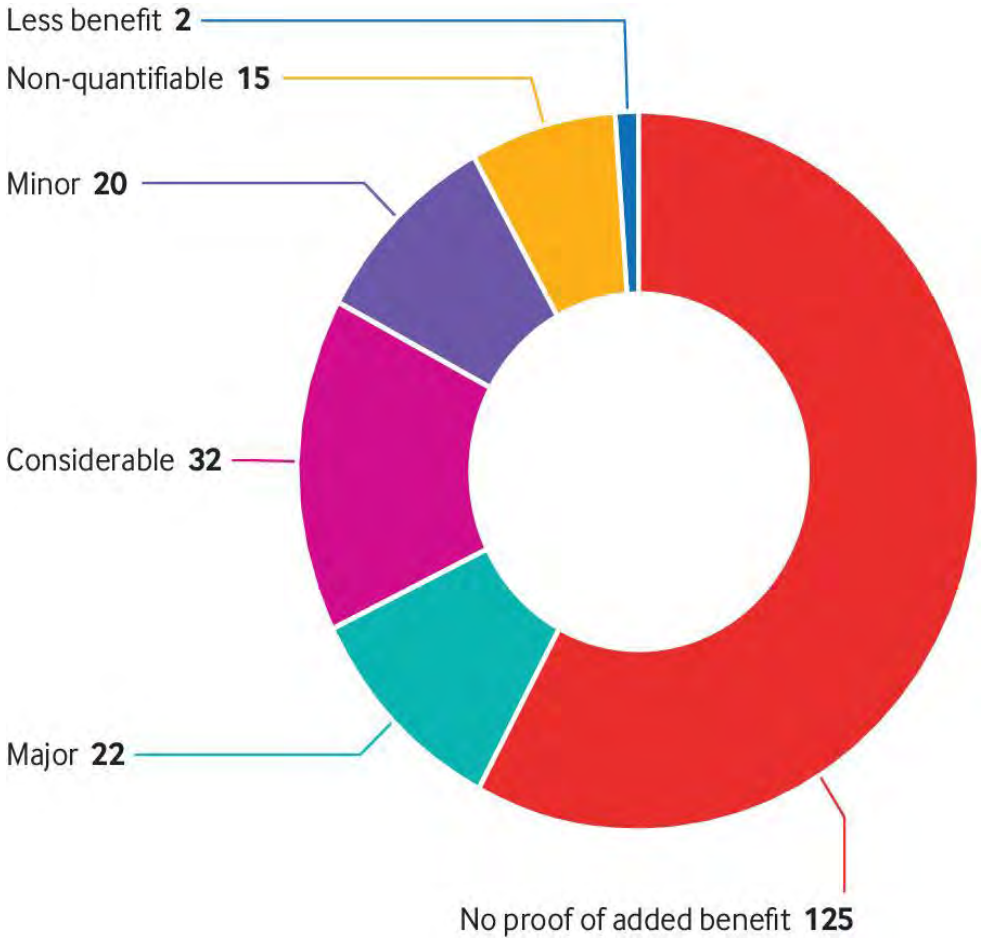
- 'Verschuiving' van het genereren van evidentie naar post-marketing studies, '*real world evidence*' retoriek

Boyle & al, Eur J Cancer, 2021

Illusie van de evidentie die verkregen wordt na commercialisering

- Sommigen stellen dat beperkte informatie op het moment van commercialisering de prijs is voor snellere toegang tot innovatie...
- Dit argument impliceert dat post-marketing onderzoek zal toelaten de winst voor de patiënt te bevestigen...
- ... maar een bekend probleem met post-marketingstudies is dat ze vaak ... *nooit uitgevoerd worden*.

Nieuwe geneesmiddelen: ‘innovatie’ vs ‘bewezen therapeutische meerwaarde’



Onafhankelijke evaluatie van de meerwaarde van nieuwe geneesmiddelen in Duitsland, 2011-2017

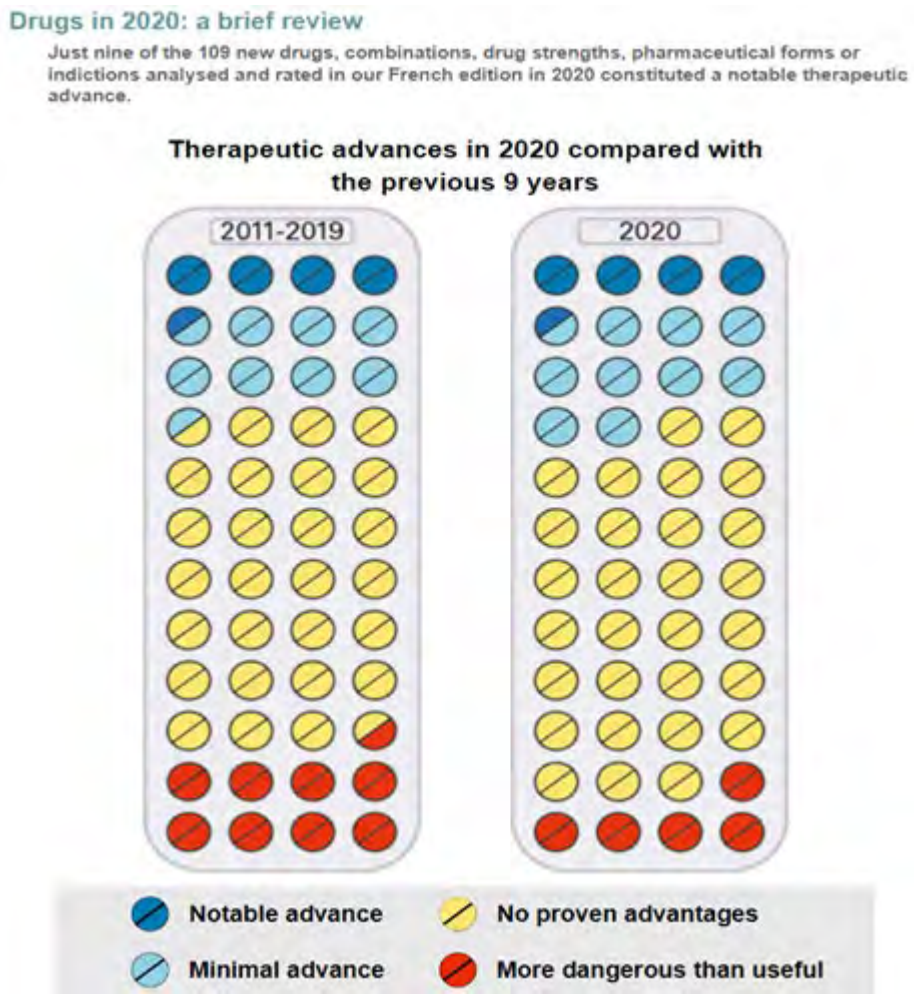
“Bewijs": statistisch significant voordeel op voor de patient relevante eindpunten, RCT of zeer groot effect in een niet-gerandomiseerd onderzoek.

Wieseler & al, BMJ 2019

Nieuwe geneesmiddelen: ‘innovatie’ vs ‘bewezen therapeutische meerwaarde’

Prescrire INTERNATIONAL
A critical eye on new drugs authorised in Europe

Prescrire ratings 2020



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Samengevat (1/3)...

- RCT's zijn en blijven de **gouden standaard** in klinisch onderzoek
  ... maar ze kunnen niet al onze vragen beantwoorden

- We hebben **meer - en betere - RCT's nodig**
  - Representatiever voor de doelpopulatie (vrouwen, ouderen, eerstelijn, ...)
  - Eindpunten die er toe doen voor de patiënt
  - *Comparative effectiveness*
  - Gefinancierd door **onafhankelijke** fondsen...

Cochrane Database of Systematic Reviews February 2017
Industry sponsorship and research outcome
A. Lundh, J. Lexchin, B. Mintzes, J.Schroll, L.Bero.
https://doi.org/10.1002/14651858.MR000033.pub3
34% more favourable conclusions in sponsored trials

Samengevat (2/3)…

- Observationele studies zijn nuttig als aanvulling (niet ter vervanging) - en soms is die aanvulling essentieel.
  - Zeker om de **veiligheid van het geneesmiddel** te beoordelen (ongewenste of laattijdige effecten) + zwangerschap & borstvoeding
  - Om de **werkzaamheid in *real-life* omstandigheden** te analyseren
  - Meerdere signalen = waarschijnlijker

- Elk type onderzoek kent methodologische beperkingen: een goed observationeel onderzoek is beter dan een slechte RCT.

- *Real-world data*: als aanvulling, niet ter vervanging

ANALYSIS

Check for updates

1 Institute for Quality and Efficiency in Health Care (IQWiG), Cologne, Germany

2 Belgian Health Care Knowledge Centre (KCE), Brussels, Belgium

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http://dx.doi.org/10.1136/bmj-2022-073100

Published: 2 March 2023

Replacing RCTs with real world data for regulatory decision making: a self-fulfilling prophecy?

Real world data are advocated as an alternative approach to RCTs for closing knowledge gaps on drugs, but **Beate Wieseler and colleagues** argue that this approach is the wrong remedy for current challenges in drug development

Beate Wieseler,[1] Mattias Neyt,[2] Thomas Kaiser,[1] Frank Hulstaert,[2] Jürgen Windeler[1]

BMJ: first published as 10.1136/bmj-20

BCFi CBiP

Samengevat (3/3)...

- De retoriek van versnelde toegang tot innovatie en het belang van *'real world data'* bij het genereren van evidentie …
  - gaat momenteel ten koste van de evidentie … en dus ten koste van patiënten.
  - er is nog veel onzekerheid over de risico/batenverhouding van nieuwe geneesmiddelen

- Het is belangrijk dat we blijven vasthouden aan hoge normen voor het bewijs als voorwaarde voor markttoelating van nieuwe geneesmiddelen + vergelijkend onderzoek


The End

Blijf ondertussen bijleren via het BCFI Auditorium:

- Meer dan 30 **gratis** e-learnings
- **Met accreditatie**
- **Interactief & praktijkgericht**
- Gebaseerd op **evidentie**

Pauze

het symposium zal opnieuw beginnen om 11u20

BCFi

SYMPOSIUM

Farmacotherapeutische actualiteit 2023

Nieuwigheden in de medicamenteuze behandeling van chronische nierziekte

Joachim Vandenhoven MD

Recent developments in drug therapy for chronic kidney disease (CKD)

- ✓Joachim Vandenhoven, MD, BCFI employee
  - ✓No conflicts of interest
- ✓Catherine Veys, MD, CBIP employee
  - ✓No conflicts of interest

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CBiP

Recent developments in drug therapy for chronic kidney disease (CKD)

- ✓Focus on pharmacotherapy, and more specific on new drug options

- ✓Medicines for chronic kidney disease: a practical guide (NPS Medicinewise (https://www.nps.org.au/news/medicines-for-chronic-kidney-disease-a-practical-guide)

- ✓Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (https://kdigo.org/guidelines)

Definition and staging of CKD

- ✓Case: Albert
  - ✓64 years old, in good health
  - ✓Hypertension (145/90 mmHg)
  - ✓Dyslipidaemia
  - ✓No other cardiovascular diseases, no diabetes

  - ✓eGFR: 71 ml/min/1,73m², UACR 26 mg/g

  - ✓Drugs:
    - ✓Chloortalidon 50 mg ½ /d
    - ✓Simvastatine 40 mg 1/d

Poll: Definition and staging of CKD

- ✓Case: Albert
  - ✓eGFR: 71 ml/min/1,73m², UACR 26 mg/g

- ✓Poll: Does this patient have CKD?
  A. Yes, he has decreased GFR (< 90 ml/min/1,73m²).
  B. No, his GFR is still above 60 ml/min/1,73m².
  C. No, he has mildly decreased GFR, but his UACR is still below 30 mg/g and he has no other signs of kidney damage.
  D. Yes, he has microalbuminuria.

Definition and staging of CKD

- ✓KDIGO definition of CKD:
  - ✓abnormalities in kidney structure or function
    - ✓kidney structure:
      - ✓ Albuminuria > 30 mg/24u or > 30 mg/g creatinine
      - ✓ Other abnormalities in urine sediment, in kidney biopsy or on imaging
      - ✓ History of kidney transplant
    - ✓kidney function:
      - ✓ GFR < 60 ml/min/1,73m²
  - ✓present for more than 3 months
  - ✓with implications for health
      - ✓ Drug toxicity, adverse events of interventions for prevention or treatment
      - ✓ Elevated cardiovascular risk, metabolic and endocrine complications

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Definition and staging of CKD

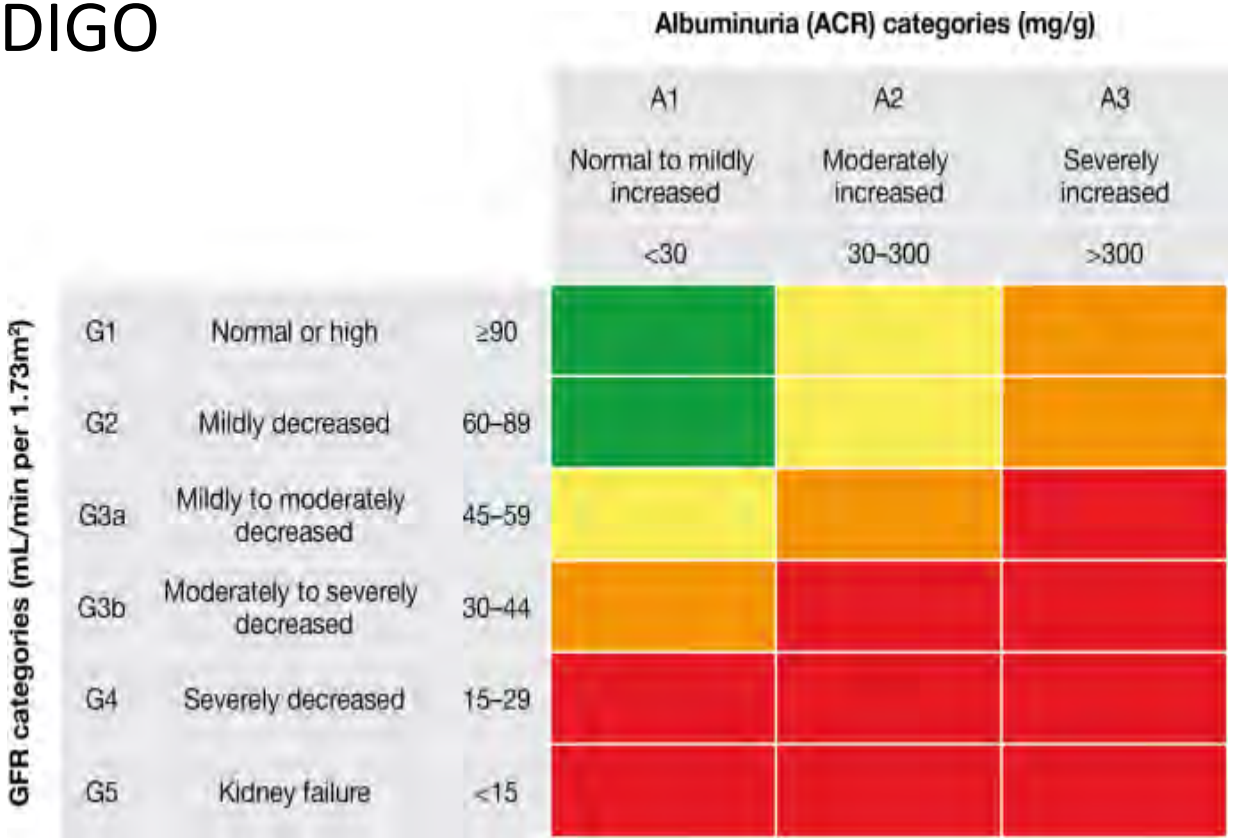
- ✓KDIGO proposes to stage CKD on the base of:
  - ✓**C**ause
  - ✓**G**FR
  - ✓**A**lbuminuria

GFR categories (GFR in ml/min/1,73m²)		
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	< 15	Kidney failure

Albuminuria categories (UACR in mg/g creat)		
A1	<30	Normal to mildly increased
A2	30-300	Moderately increased
A3	>300	Severely increased

Definition and staging of CKD

KDIGO



Risk of CKD progression, kidney failure, acute kidney injury and CV and all cause mortality:

- Green: low (no CKD if no other markers of kidney disease)
- Yellow: moderately incrased
- Orange: high
- Red: very high

Feedback poll: Definition and staging of CKD

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  - D. Yes, he has microalbuminuria.

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Management of CKD

- ✓Goals
  - ✓Treat underlying kidney disease and comorbid conditions
  - ✓Delay progression of CKD
  - ✓Avoid acute kidney injury

- ✓Rationale:
  - ✓High cost of therapy in end stage renal disease
  - ✓Risk factor for cardiovascular disease (also for decreased physical condition and cognitive functioning)
  - ✓Higher risk for drug adverse events and complications during interventions and procedures

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Pharmacotherapy for CKD

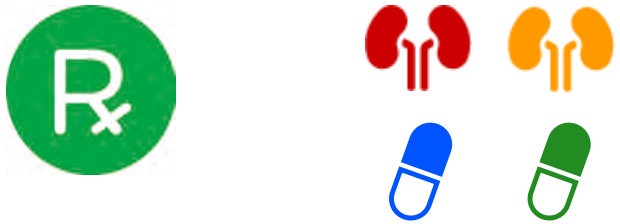
- ✓Treating underlying and comorbid conditions
- ✓Adapt drug posologies and avoid nephrotoxic drugs
- ✓Sick day rules to avoid acute kidney injury
- ✓**Specific drugs to delay progression of CKD**

- ✓Whole patient approach
- ✓Not everything at once, focus on the long term

Pharmacotherapy for CKD

- ✓Treating underlying and comorbid conditions
  - ✓Hypertension
  - ✓Diabetes
  - ✓Dyslipidaemia/high cardiovascular risk
  - ✓Glomerulonephritis, systemic disease with effects on kidneys

- ✓Adapt drug posologies to decreased kidney function and avoid nephrotoxic medication



Pharmacotherapy for CKD

- ✓Sick day rules to prevent acute kidney injury:
  - ✓Decrease dose or stop temporarily specific drugs during episodes (<24h) with high risk for dehydration (heat, fever, vomiting, diarrhea):
    - **S** sulfonylurea
    - **A** ACE-I
    - **D** diuretics (including MRA)
    - **M** metformin
    - **A** ARB
    - **N** NSAID
    - **S** SGLT2-I

Specific drugs to delay progression of CKD

- ✓ACE-inhibitors and angiotensine receptor blockers (ARB, sartans)

- ✓Sodiumglucose cotransporter 2 inhibitors (SGLT2-I, gliflozins)
- ✓Finerenone (a novel mineralocorticoid receptor antagonist (MRA))

Poll: ACE-I and ARB in CKD

- ✓Remember Albert?
- ✓1 year later:
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 143/85mmHg
  - ✓eGFR: 56 ml/min/1,73m²
  - ✓UACR: 42 mg/g creatinine

- ✓Poll: Should this patient receive an ACE-I or ARB?
  A. Yes, this is clearly recommended.
  B. Yes, this could be considered.
  C. No, not yet.

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ACE-I and ARB in CKD

- ✓Large meta-analysis by Xie et al. (2016)
  - ✓Clear benefits on renal and cardiovascular end points
  - ✓No effect on cardiovascular or all cause mortality
  - ✓Results difficult to interpret
- ✓Smaller meta-analyses by Cochrane and KDIGO in “pure” renal trials
  - ✓Confirm benefits on renal end points
  - ✓No effect on cardiovascular morbidity or mortality or all cause mortality
- ✓Almost all data comes from 3 large trials in patients with diabetes and 2 small trials in patients without diabetes

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ACE-I and ARB in CKD

- ✓Conclusion:
  - ✓Mostly studied in patients with CKD and diabetes
  - ✓Mainly evidence for a renoprotective effect
  - ✓Effect on cardiovascular events less clear
  - ✓Greatest evidence for beneficial effects in patients with severe albuminuria
  - ✓Less (in patients with diabetes) or insufficient (in patients without diabetes) evidence for beneficial effects in patients with moderate albuminuria

ACE-I and ARB in CKD

- ✓KDIGO recommendation
  - ✓Patients with diabetes:
    - ✓Recommended for all patients with high blood pressure, CKD and moderately to severe albuminuria (G1-4, A2-3)
  - ✓Patients without diabetes:
    - ✓Recommended for all patients with high blood pressure, CKD and severe albuminuria (G1-4, A3)
    - ✓Suggested for all patients with high blood pressure, CKD and moderate albuminuria (G1-4, A2)

- ✓Titrate to maximum tolerated dose

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Feedback poll: ACE-I and ARB in CKD

- ✓Albert
  - ✓65 years, good health, no diabetes, dyslipidaemia
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- ✓Poll: Should this patient receive an ACE-I or ARB?
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  C. No, not yet.

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Poll: Recent developments in drug therapy for CKD

- ✓Remember Albert?
- ✓You started him on an ACE-inhibitor titrated to maximal tolerated dose but after 2 months his values remain more or less the same:
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of an SGLT2-I?
  - A. No, because he has no diabetes.
  - B. Yes, he qualifies for the use of an SGLT2-I, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.
  - C. Yes, he qualifies for the use of an SGLT2-I. I would certainly prescribe it.

BCFi CBiP

Poll: Recent developments in drug therapy for CKD

- ✓Remember Albert?
- ✓You started him on an ACE-inhibitor titrated to maximal tolerated dose but after 2 months his values remain more or less the same:
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  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of finerenone?
  - A. No, because he has no diabetes.
  - B. Yes, he qualifies for the use of finerenone, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.
  - C. Yes, he qualifies for the use of finerenone. I would certainly prescribe it.
  - D. FinereHOW? Never heard of it before.

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SGLT2-I in CKD

- ✓Sodium-glucose cotransporter 2-inhibitors (gliflozins)
  - ✓Initially developed to reduce blood glucose in people with diabetes
  - ✓In early development: evidence for lowering proteinuria and improving renal hemodynamics
  - ✓In cardiovascular outcomes trials: evidence for a significant benefit on renal outcomes, but < 25% of included patients had CKD
  - ✓Primary kidney trials with canagliflozin (CREDENCE), dapagliflozin (DAPA-CKD) and empagliflozin (EMPA-KIDNEY)

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SGLT2-I in CKD

- ✓CREDENCE 2019 (Folia oktober 2019)
  - ✓Canagliflozine (Invokana®) 100 mg vs placebo
  - ✓4401 patients with type 2-diabetes, eGFR 30-90 ml/min/1,73m² and severe albuminuria (G2-3, A3)
  - ✓All patients on stable, maximum tolerated dose ACE-I or ARB
  - ✓Primary endpoint: composite of ESRD, doubling of serumcreatinine or death from renal or cardiovascular causes: HR 0,70 (95%CI 0,59 to 0,82); NNT: 22 over 2,6 jaar
  - ✓Also statistically significant reductions for composite endpoints of CV death, AMI and stroke, with or without heart failure hospitalisations, but not for cardiovascular and all cause mortality

SGLT2-I in CKD

- ✓DAPA-CKD 2020 (Folia februari 2021)
  - ✓Dapagliflozine (Forxiga®) 10 mg vs placebo
  - ✓4504 patients, e-GFR 25-75 ml/min/1,73 m² and moderate to severe albuminuria (UACR > 200 mg/g) (G2-3(4), A(2-)3)
  - ✓2/3 with type 2-diabetes; 1/3 without
  - ✓All patients on stable, maximum tolerated dose ACE-I or ARB

  - ✓Primary endpoint: composite of ESRD, >50% decrease in GFR or death from renal or cardiovascular causes: HR 0,61 (95%CI 0,51 to 0,72); NNT 19 over 2,4 years
  - ✓Also significant reduction of all cause mortality (unexplained), but not of cardiovascular mortality, no data on cardiovascular morbidity
  - ✓Subgroupanalysis: results independent of diabetes status, GFR or UACR

SGLT2-I in CKD

- ✓EMPA-KIDNEY 2022 (Nieuwigheden Geneesmiddelen september 2023)
  - ✓Empagliflozin 10 mg (Jardiance®)
  - ✓ 6609 patients with
    - ✓ or GFR 20-45 ml/min/1,73m² (G3b-4, A1-3)
    - ✓ or GFR 45-90 ml/min/1,73m² and UACR > 200 mg/g (G2-G3a, A(2-)3)
  - ✓1/2 with diabetes, 1/2 without
  - ✓85% of patients on clinically appropriate dose ACE-I or ARB

  - ✓Primary endpoint: composite of ESRD, > 40% decrease in GFR or death from renal or cardiovascular causes: HR 0,72 (95%CI 0,64 tot 0,82); NNT: 26 over 2 years
  - ✓No significant reduction of cardiovascular or all cause mortality, no data on cardiovascular morbidity
  - ✓Subgroupanalysis: results independent of diabetes status or GFR, only significant benefit in patients with severe albuminuria (A3), not in patients with mild tot moderate albuminuria (A1-2)

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SGLT2-I in CKD

- ✓Comments
  - ✓All trials were terminated early, which tends to overestimate effects in the intervention group
  - ✓Almost all patients received a stable, maximum tolerated dose ACE-I or ARB
  - ✓Investigated population enlarged from CREDENCE over DAPA-CKD to EMPA-KIDNEY:
    - ✓Inclusion of patients without diabetes, with roughly same efficacy
    - ✓GFR-range from 20-90 ml/min/1,73m², without clear differences in efficacy, no patients with GFR < 20/ml/min/1,73m² included
    - ✓Inclusion of patients with less severe albuminuria, but only evidence for beneficial effect in patients with severe albuminuria

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SGLT2-I in CKD

- ✓Contra-indications
  - ✓Type 1-diabetes
  - ✓Antecedents of ketoacidosis under treatment with SGLT2-I

- ✓Adverse events
  - ✓Hypoglycaemia (in patients with diabetes, in association with other hypoglycaemic agents)
  - ✓Genital and urinary tract infections
  - ✓Rare but severe: ketoacidose, gangrene of Fournier, lower limb amputations

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SGLT2-I in CKD

- ✓Renal indications in SPC:
  - ✓Canagliflozine: no specific renal indication, only type 2-diabetes in general
  - ✓Dapagliflozine and empagliflozine: treatment of chronic kidney disease (without further specifications)
- ✓Recommendations
  - ✓KDIGO recommends SGLT2-I as first line treatment in patients with CKD and diabetes and GFR > 20 ml/min/1,73m², alongside metformin
  - ✓Not incoporated yet in guidelines for patients with CKD without diabetes
- ✓Reimbursement in B
  - ✓All gliflozines: reimbursed (A, a prioiri) on certain conditions in type 2-diabetes
  - ✓Dapagliflozine: additionally reimbursed (B, a priori) in patients with chronic kidney disease with or without diabetes and GFR < 60 ml/min/1,73m² and UACR > 200 mg/g
  - ✓Empagliflozine: not yet reimbursed for CKD without diabetes

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Feedback poll:
Recent developments in drug therapy for CKD

- ✓Albert
  - ✓started on an ACE-inhibitor titrated to maximal tolerated dose 2 months ago
  - ✓65 years, good health, no diabetes, dyslipidaemia
  - ✓Blood pressure 130/81mmHg
  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

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  - **B. Yes, he qualifies for the use of an SGLT2-I, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.**
  - C. Yes, he qualifies for the use of an SGLT2-I. I would certainly prescribe it.

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Finerenone in CKD

- ✓Finerenone (Kerendia®) is a novel mineralocorticoid receptor antagonist (MRA, other molecules in this class: spironolactone, eplerenone)
- ✓Finerenone is a nonsteroidal MRA, highly selective for the mineralocorticoid receptor
- ✓Other (side-)effects profile than spironolacton and eplerenone
- ✓In small studies of short duration: decrease of albuminuria with spironolactone and eplerenone; not investigated on a large scale (AE)

Finerenone in CKD

FIDELIO-DKD 2020 (Folia maart 2023)	FIGARO-DKD 2021 (Folia maart 2023)
5674 patients with type 2 diabetes and CKD with - or GFR 25-60 ml/min/1,73m² and UACR 30-300 mg/g (G3(-4) A2) - or GFR 25-75 ml/min/1,73m² and UACR > 300 mg/g (G(2-)3(-4) A3)	7352 patients with type 2 diabetes and CKD with - or GFR 25-90 ml/min/1,73m² and UACR 30-300 mg/g (G2(-4) A2 - or GFR > 60 ml/min/1,73m² and UACR > 300 mg/g (G1-2 A3)
Finerenone 20 mg vs placebo Reduced initial dose (10 mg) if GFR < 60 ml/min/1,73m², augmented after 1 month if stable GFR and K < 4,8 mmol/l	
All patients on a stable, maximum tolerated dose ACE-I or ARB	
All patients had a serum K concentration below 4,8 mmol/l	
Patients with heart failure excluded	

Finerenone in CKD

FIDELIO-DKD (2020)	FIGARO-DKD (2021)
Renal end point (composite of ESRD, > 40% decrease in GFR, renal mortality)	
HR 0,82 (95%CI 0,73 to 0,93); NNT 29 over 3 years	HR 0,87 (95%CI 0,76 to 1,01)
Cardiovascular end point (composite of cardiovascular mortality, nonfatal AMI, nonfatal CVA, heart failure hospitalisations)	
HR 0,86 (95%CI 0,75 to 0,99); NNT 42 over 3 years	HR 0,87 (95%CI 0,76 to 0,98); NNT 47 over 3,5 years
No significant effect on cardiovascular or all cause mortality	
Effect consistent across GFR- and UACR- subgroups	

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Finerenone in CKD

- ✓Comments
  - ✓Almost all patients received a stable, maximum tolerated dose ACE-I or ARB
  - ✓No data in heart failure patients yet
  - ✓Clear evidence for patients with GFR 25-60 ml/min/1,73m² and UACR > 30 mg/g from FIDELIO-DKD
  - ✓Results from FIGARO-DKD more difficult to interpret: more heterogenous population and negative result on renal end point
  - ✓Patients with GFR < 25 ml/min/1,73m² not included
  - ✓Could the other, older (and cheaper) MRA have the same effects in this population?

Finerenone in CKD

- ✓Contra-indications
  - ✓Hyperkaliaemia
  - ✓Note that severe renal insufficiency still is a contra-indication for the use of spironolactone and eplerenone
- ✓Adverse events
  - ✓Hyperkaliaemia remains a concern
  - ✓No endocrine adverse events with finerenone (gynaecomastia, amenorrhoe, impotence)
- ✓Interactions
  - ✓Increased risk of hyperkaliaemia in association with other kalium-sparing drugs (NSAID, trimethoprim, heparins, ACE-I and ARB) or kalium supplements
  - ✓Finerenone is a substrate of CYP3A4

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Finerenone in CKD

- ✓Indication in SPC
  - ✓Only in patients with CKD and diabetes
  - ✓All stages of CKD, in the presence of albuminuria
- ✓Recommendations
  - ✓KDIGO suggests use of finerenone in patients with CKD and diabetes and GFR > 25 ml/min/1,73m², normal serum kalium concentration and albuminuria (UACR > 30 mg/g)
  - ✓Finerenone can be added to ACE-I/ARB and SGLT2-I.
- ✓Reimbursement in B
  - Reimbursed (B, a priori), largely within the limits of FIDELIO-DKD inclusion and exclusion criteria

BCFi CBiP

Poll: Recent developments in drug therapy for CKD

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  - ✓eGFR: 50 ml/min/1,73m²
  - ✓UACR: 45 mg/g creatinine

- ✓Poll: Does he qualify for the use of finerenone?
  - **A. No, because he has no diabetes.**
  - B. Yes, he qualifies for the use of finerenone, but evidence in people like Albert (G3A2) is less clear. I'm in doubt whether to prescribe it or not.
  - C. Yes, he qualifies for the use of finerenone. I would certainly prescribe it.
  - D. FinereHOW? Never heard of it before.

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Which drug to chose?

- ✓ACE-I or ARB remains first choice
  - ✓SGLT2-I and finerenone not investigated as first line-therapy
  - ✓Years of experience, well known safety profile
  - ✓Cheap (5-7,5 €/month)
  - ✓Also used to treat frequent comorbidities (hypertension, heart failure)
  - ✓Best evidence in patients with CKD with severe albuminuria

- ✓SGLT2-I and/or finerenone can be added
  - ✓No direct comparisons
  - ✓Very few data on triple association
  - ✓New drugs, no long term experience, no long term data on efficacy and safety
  - ✓More expensive (50-70€/month)
  - ✓Principally evaluated in diabetes, not yet incorporated in guidelines for people without diabetes
  - ✓Only reimbursed under certain conditions

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Which drug to chose?

	SGLT2-I	Finerenone
Indication	Canagliflozin: only in diabetes Dapagliflozin and empagliflozin: also without diabetes All CKD classes (without further specification)	Only in type 2-diabetes Only in CKD with albuminuria
Trial evidence	Less clear evidence in mild to moderate albuminuria	Best evidence in CKD G3 A2-3, no evidence in GFR < 25/ml/min/1,73m² Exclusion of patients with heart failure
KDIGO recommendation	Recommended as first-line hypoglycaemic agent alongside metformin No receommendation yet outside diabetes	Suggested in patients with CKD and diabetes with albuminuria
Adverse events	Rare but severe: keto-acidosis, gangrene of Fournier, amputations	Hyperkaliaemia greatest concern
Reimbursement in B	Canagliflozin only in type 2-diabetes on certain conditions Dapagliflozin also outisde diabetes (G3-4 A(2-)3) on certain onditions Empagliflozin not yet outside diabetes	Only in type 2-diabetes (G3(-4) A2-3) on certain conditions

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Take home

- ✓CKD classification (C-)G-A
- ✓Whole patient approach
- ✓Not everything at once, focus on the long term
- ✓Don’t forget
  - ✓Non-pharmalogical interventions
  - ✓Underlying and comorbid conditions
  - ✓Adapt posologies and avoid nephrotoxic drugs
  - ✓Sick day rules
- ✓Specific drugs to delay CKD progression
  - ✓ACE-I or ARB remains first choice
  - ✓SGLT2-I and/or finerenone can be added, in some patients, in accordance with evidence base, approved indication and reimbursement conditions

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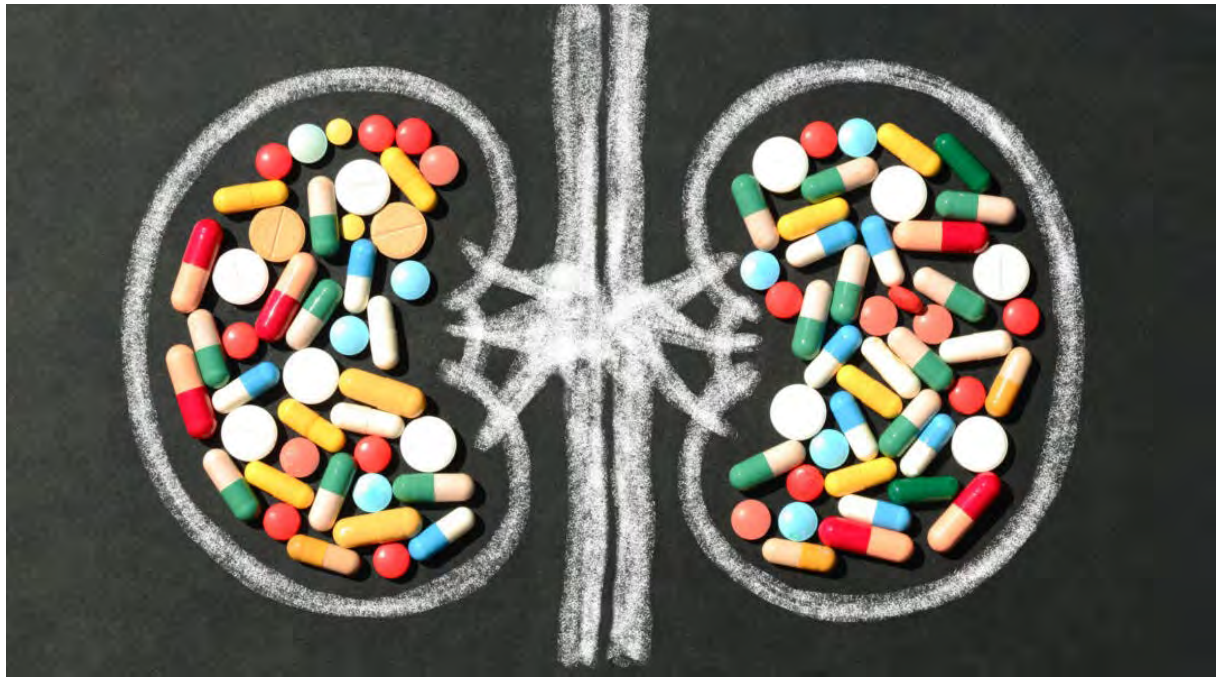
Recent developments in drug therapy for chronic kidney disease (CKD)

Thank you for your attention.



Questions?

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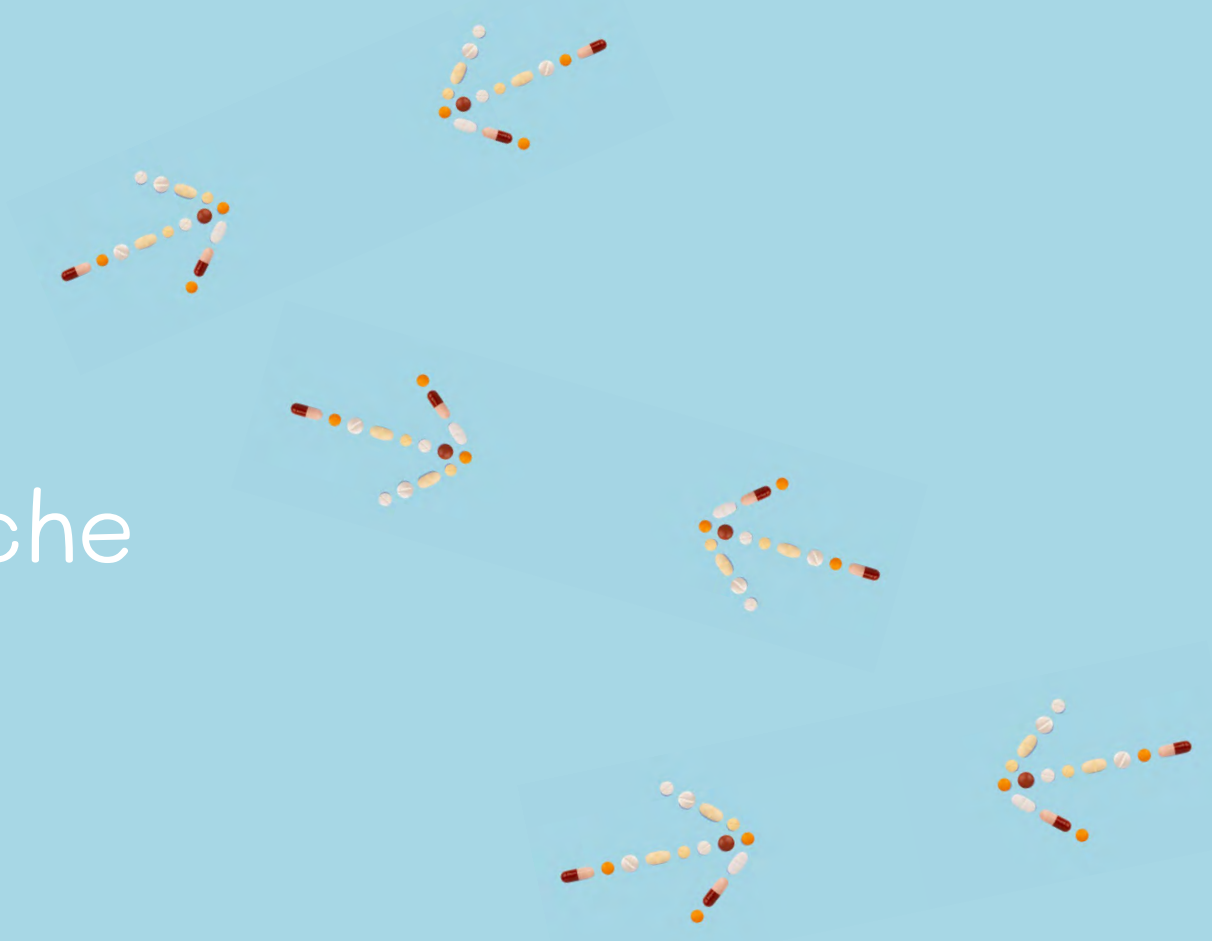
Farmacotherapeutische actualiteit 2023



De rol van P-glycoproteïne (P-gp) bij geneesmiddeleninteracties

Ann Van Ermen MPharmSc, PhD

✓I do not have conflicts of interest

Why this topic?

A patient on chronic treatment with the **DOAC dabigatran** reports that she suffers from nose bleeding and bruises. She started a few days before **clarithromycin**.

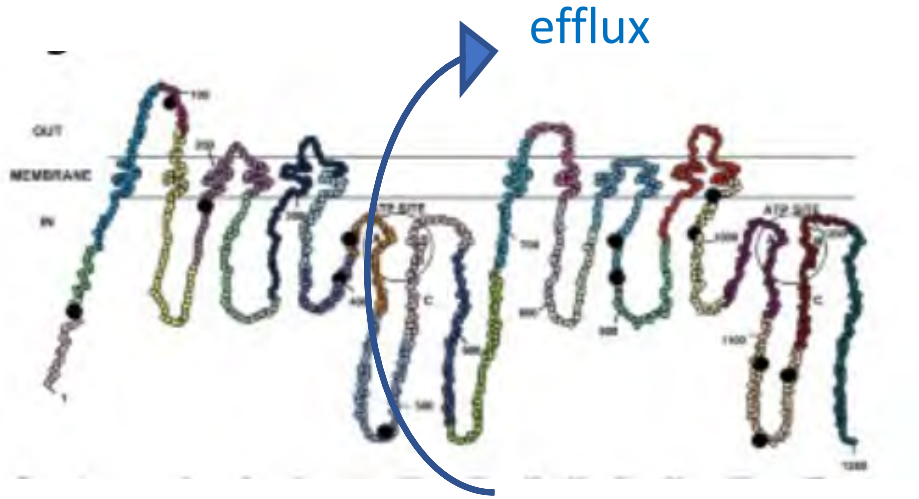
An interaction is suspected : clarithromycin can have increased the plasmalevels of dabigatran, leading to bleeding.

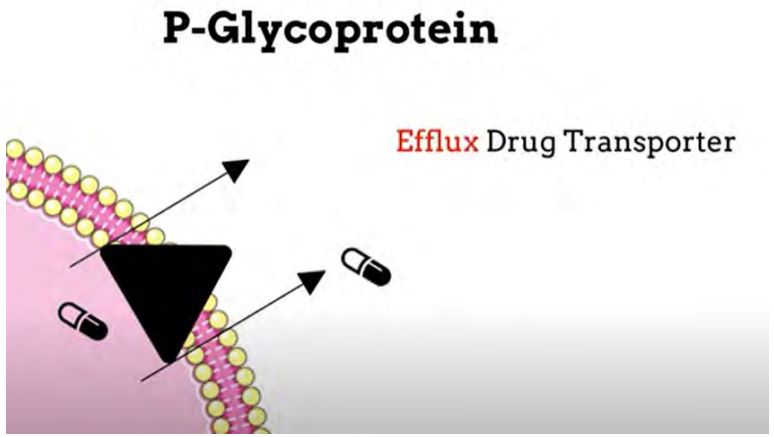
Curious to know more about this interaction?

Scope of the presentation

- What is P-gp?
- How can P-gp impact drug response and cause drug-drug interactions?
- P-gp-substrates, -inhibitors and –inducers in our BCFI/CBIP publications
- Some clinically relevant drug interactions via P-gp
- P-gp in the blood-brain barrier
- Future prospects

What is P-gp? (P-Glycoprotein)





✓ P-glycoprotein (P-gp) is an efflux transporter, present in the membranes of certain cells.
✓ It actively pushes endogenous substances and drugs out of the cells (>< passive diffusion).
✓ “Protective” cellular/tissular function.

PS : First identified in cancer cells resistant to chimiotherapy : P-gp = MDR (Multi-Drug-Resistance)-protein.

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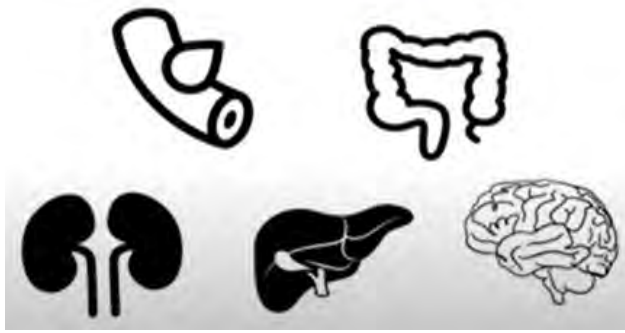
How can P-gp impact drug response?

P-Glycoprotein

Found in ...



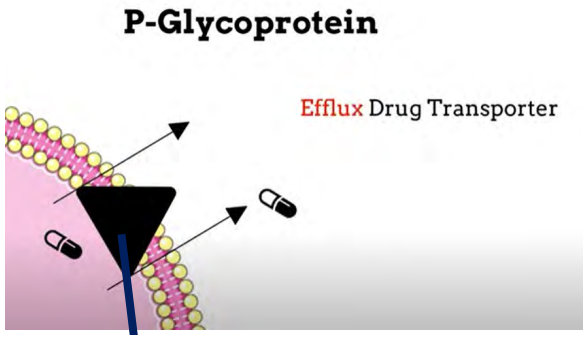
Affects ...

- absorption (in the intestine),
- distribution (to the brain, lymphocytes, testes, or placenta)
- elimination (in the urine and bile).

How can P-gp cause drug-drug interactions?

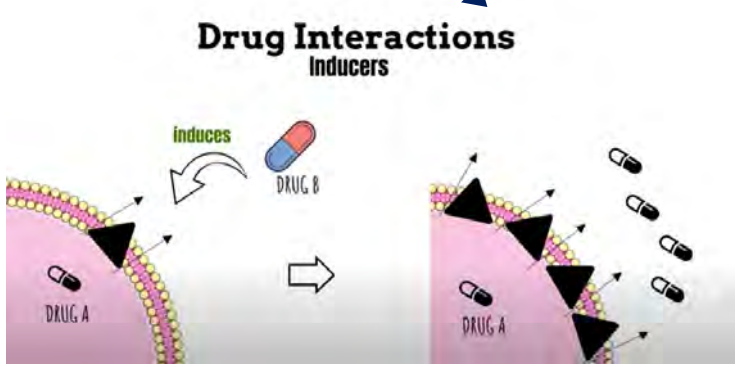
✓ Drug interactions occur because some drugs can

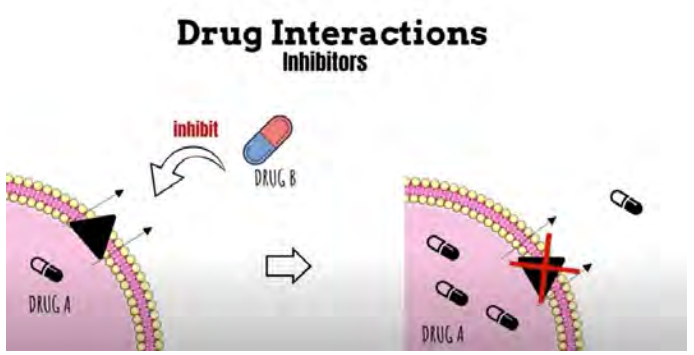
- induce the expression of P-gp (Inducers, ↑amount of P-gp) (slow effect)
- inhibit its activity (Inhibitors) leading to a risk of cellular toxicity (fast effect).



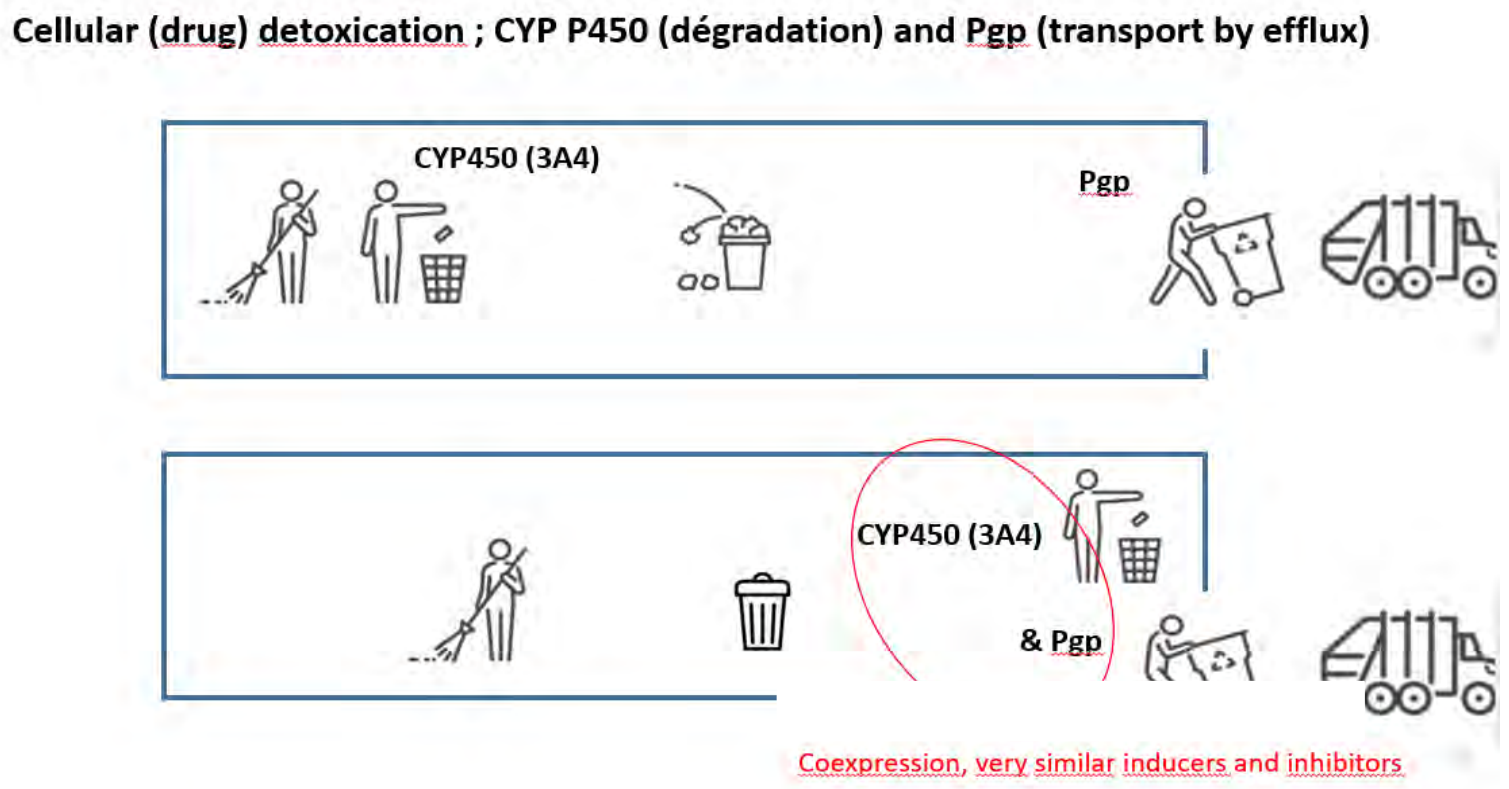
Increase drug (A) elimination

Increase drug (A) cellular tocicity





The interplay between P-gp and CYP3A4



✓ The tissue distribution of CYP3A4 (metabolism) and P-gp (transport) is similar

✓ There is considerable overlap between CYP3A4 and P-gp inhibitors, inducers, and substrates.

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P-gp-substrates, -inhibitors and –inducers in our BCFI/CBIP drug formulary

9.3.1. Colchicine

Colchicine vermindert de inflammatie veroorzaakt door de vorming van urinezuurkristallen in de gewrichten; het heeft op zich geen analgetisch effect.

Interacties

- Verhoogd risico van myopathie bij associëren met statines of fibraten.
- Colchicine is een substraat van CYP3A4 en van P-gp (zie Tabel Ic. in Inl.6.3. *en* Tabel Id. in Inl.6.3.), met risico van colchicine-intoxicatie (met o.a. rhabdomyolyse, neuropathie, beenmergdepressie, nier- en leveraantasting) bij associëren met CYP3A4-inhibitoren of P-gp-inhibitoren [zie Folia november 2009].

Repertorium > Inleiding > Inl.6.3. Interacties

Tabel Id. De substraten, inhibitoren en inductoren van P-glycoproteïne (P-gp)

De substraten, inhibitoren en inductoren waarvan men verwacht dat ze de klinisch meest relevante interacties zullen geven, zijn in vetjes aangeduid. Uiteraar wil dit niet zeggen dat interacties met niet-vetjes aangeduide geneesmiddelen geen risico inhouden. Voor meer informatie, zie Inl.6.3. Interacties van geneesmiddelen

Ctrl F

Substraten	Inhibitoren (↑ substraatplasmaconcentratie)	Inductoren (↓ substraatplasmaconcentratie)
Acalabrutinib, **afatinib**, **alfentanil**, ambrisentan, amisulpride, amitriptyline, **apixaban**, **atazanavir**, atorvastatine, **azithromycine**, **binimetinib**, **brentuximab vedotin**, budesonide, canagliflozine, carvedilol, **ceritinib**, cetirizine, **ciclosporine**, **citalopram**, clopidogrel, **cobimetinib**, **colchicine**, **dabigatran**, **dabrafenib**, darolutamide, **dasatinib**, **daunorubicine**, desloratidine, dexamethason, **digoxine**, diltiazem, **docetaxel**, **domperidon**, **doxorubicine**, **droperidol**, **edoxaban**, elbasvir, eletriptan, eliglustat, emtricitabine, **erlotinib**, **erythromycine**, ethinylestradiol, **etoposide**	Abemaciclib, **amiodaron**, azithromycine, brigatinib, **ciclosporine**, **clarithromycine**, diltiazem, erythromycine, glecaprevir, idebenon, isavuconazol, **itraconazol**, ivacaftor, **ketoconazol**, **lapatinib**, ledipasvir, pibrentasvir, propafenon, ranolazine, **ritonavir**, **saquinavir**, **tepotinib**, ticagrelor, vandetanib	Apalutamide, carbamazepine, lorlatinib, **rifampicine**, **sint-janskruid**

Methodology described in Inl.2.1.6.

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Some important substrates (Table Id)

- ✓ Anti-HIV-drugs: e.g. **atazanavir***, **fostemsavir**, maraviroc*, ritonavir*, **saquinavir***…
- ✓ DOAC's: **apixaban*, dabigatran, edoxaban, rivaroxaban***
- ✓ Opioids: **alfentanil*, fentanyl***, **morphine**
- ✓ **Ciclosporin***
- ✓ **Colchicine***
- ✓ **Digoxin**
- ✓ **Domperidone***
- ✓ Loperamide*
- ✓ …

In our interactions e-learnings : the "usual suspects" !

* also substrate of CYP3A4

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Some important inhibitors (Table Id)

- ✓ Anti-HIV-drugs: **ritonavir***, **saquinavir***
- ✓ Macrolide-antibiotics: azithromycin, **clarithromycin***, erythromycin*
- ✓ Antimycotics (azole-derivates): isavuconazol, **itraconazol***, **ketoconazol***
- ✓ Immunosuppressive drug: **ciclosporin**
- ✓ Anti-aritmicum: **amiodaron**
- ✓ Calcium-channel blockers: diltiazem, **verapamil***

- ✓ Grapefruit*

* also (potent) CYP3A4-inhibitor

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Some important inducers (Table Id)

- ✓ Carbamazepine*
- ✓ **Rifampicin***
- ✓ **St John's Wort***

* also (potent) CYP3A4-inducer

Some clinically relevant drug interactions via P-gp

- ✓colchicine + P-gp-inhibitors
- ✓DOAC’s + P-gp-inhibitors / P-gp-inducers
- ✓ciclosporin + P-gp-inhibitors / P-gp-inducers

colchicine + P-gp-inhibitors

Folia
Pharmacotherapeutica

Ik wil me abonneren

Folia Pharmacotherapeutica november 2009

PDF-versie

Geneesmiddelenbewaking: colchicine-intoxicatie ten gevolge van interactie met CYP3A4- inhibitoren of inhibitoren van P-glycoproteïne

Colchicine (Colchicine Opocalcium®) wordt gebruikt bij jichtaanvallen. Terwijl dit geneesmiddel bij ons reeds lang beschikbaar is, werd colchicine in de Verenigde Staten pas recent als "geneesmiddel" geregistreerd en gecommercialiseerd. Bij de evaluatie van het registratiedossier heeft de

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colchicine + P-gp-inhibitors

- ✓ **Inhibitors**: e.g. clarithromycin, itraconazol, verapamil, some anti-HIV-drugs
- ✓ Consequence:
  - ↑ risk of (severe) intoxication (e.g. severe diarrhoea, myopathy, neuropathy, bonemarrow depression, renal- and hepatic complications)
  - Cases of life-threatening and fatal intoxications

- ✓ Do not use colchicine + (potent) inhibitor of CYP3A4 or P-gp (certainly in patients with hepatic or renal impairment)
- ✓ If not possible to avoid combination with P-gp-inhibitor: use lowest dose of colchicine and be alert for symptoms of intoxication (e.g. diarrhea)

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DOAC’s + P-gp-inhibitors / P-gp-inducers

DOAC’s: apixaban, edoxaban, dabigatran, rivaroxaban

- ✓ **Inhibitors**: e.g. clarithromycin, itraconazol, verapamil, some anti-HIV-drugs
- ✓ Consequence: ↑ risk of bleeding
- ✓ If possible, avoid combination. Monitor for signs and symptoms of bleeding. (+ instructions in SPC)

- ✓ **Inducers**: carbamazepine, rifampicin, St John’s wort
- ✓ Consequence: ↑ risk of thromboembolic effects (↓ therapeutic effect)
- ✓ If possible, avoid combination (replace inducer or DOAC) + instructions in SPC (depending on indication)

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ciclosporin + P-gp-inhibitors / P-gp-inducers

- ✓ **Inhibitors**: e.g. clarithromycin, itraconazol, verapamil, some anti-HIV-drugs
- ✓ Consequence: ↑ risk of nephrotoxicity
- ✓ Avoid (potent) inhibitors of P-gp. If not possible, monitor ciclosporin plasma concentrations and renal function

- ✓ **Inducers**: rifampicin, carbamazepine, St John's wort
- ✓ Consequence: ↑ risk of transplant rejection (kidney/liver/heart)! (↓ therapeutic effect)
- ✓ Avoid (potent) inducers of P-gp (combination with St John's wort is a contra-indication). If not possible to avoid combination: monitor ciclosporin plasma concentrations

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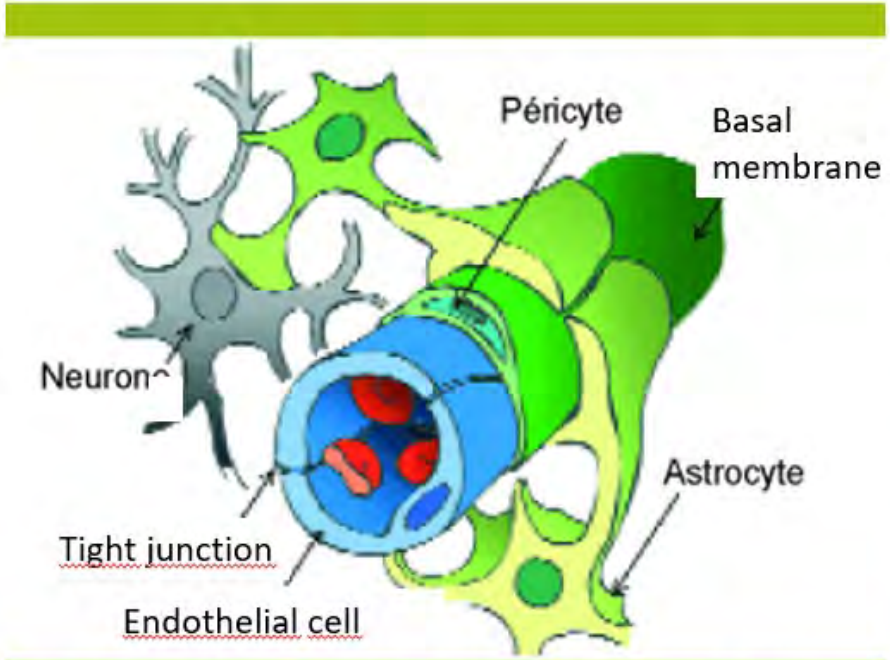
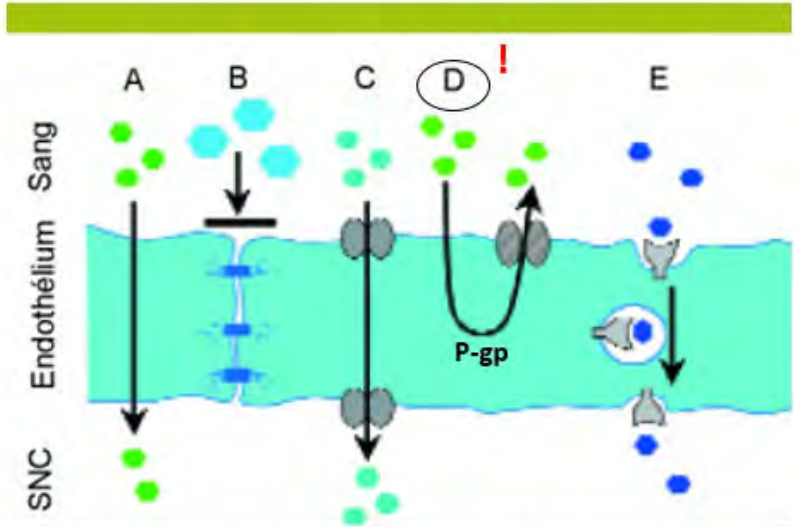
P-gp in the blood-brain barrier

✓ P-gp reduces the entry of drugs into the central nervous system.

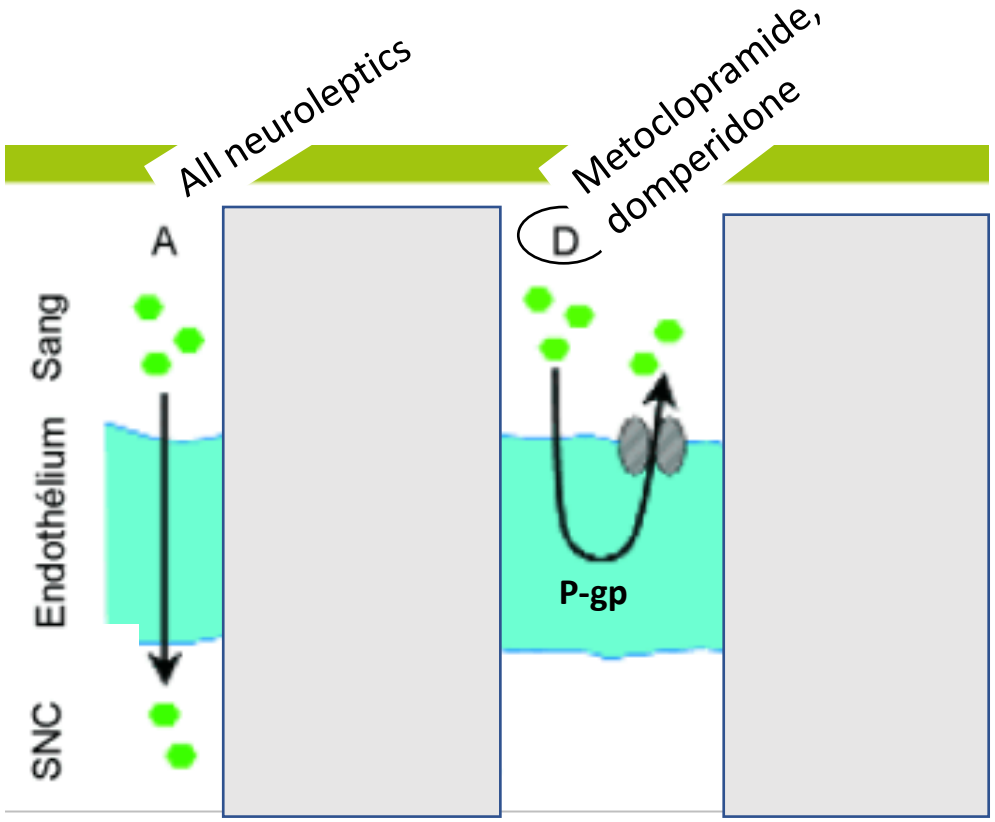


Histological components of the Blood-Brain Barrier

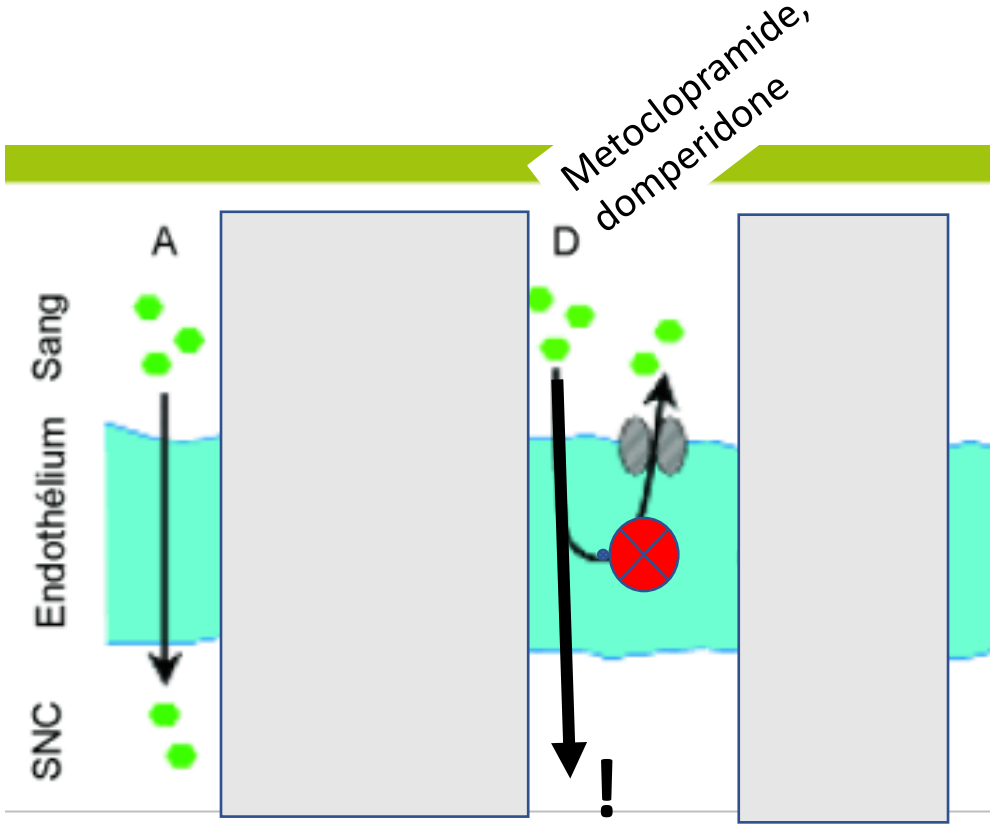


Different exchanges through the BBB.
A. Small lipophilic molecules, B no passage of large or hydrophilic molecules, C active transport, D active efflux (P-gp), E receptor or uptake sites mediated endocytosis

Drugs and the blood-brain barrier (BBB)
Metoclopramide, domperidone,… (dopamine antagonists)

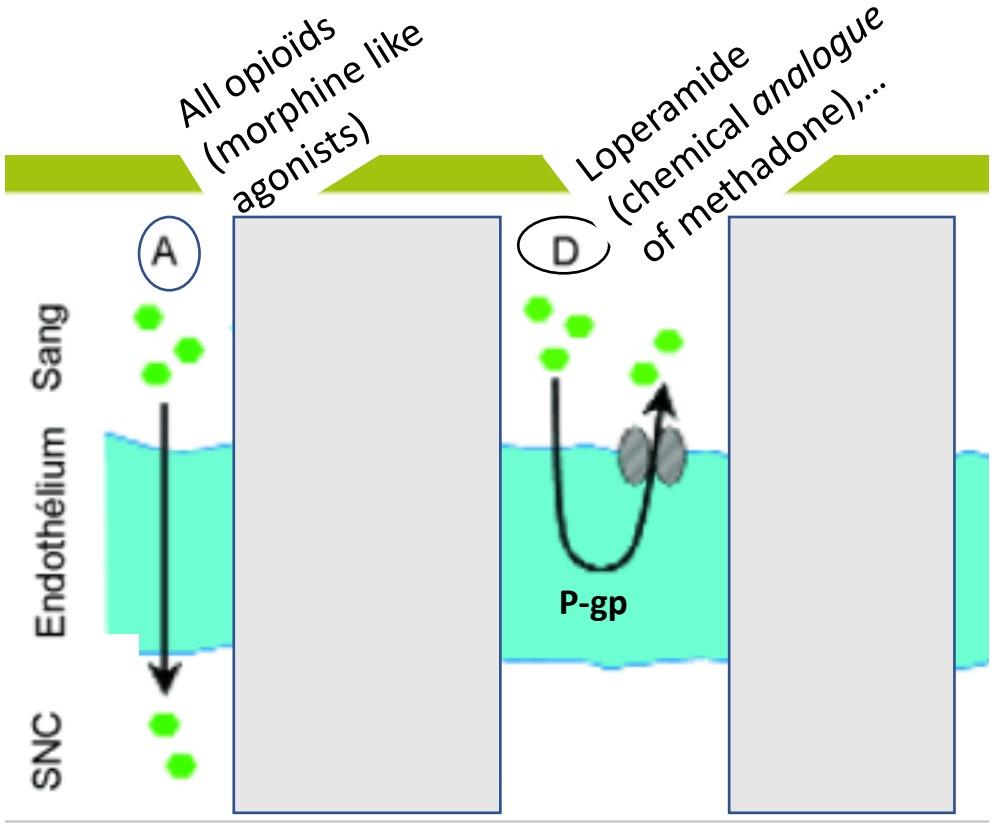


No central effects of these dopaminergic antagonists metoclopramide and domperidone.
Fast efflux by P-gp.

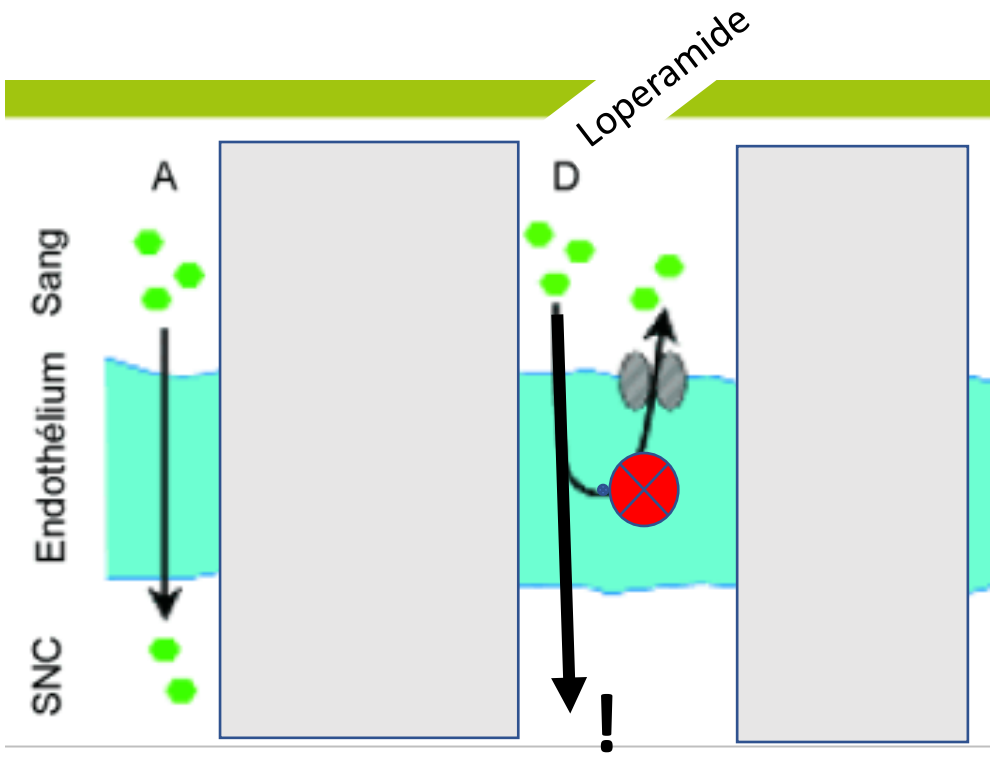


Interaction **with Pgp inhibitor**:
CNS effects, Dyskinesia, Dystonia, Parkinson like syndrome, Sedation.
Neuroleptic-like effects.

Drugs and the blood-brain barrier (BBB)
Loperamide (peripheral opiate agonist, antidiarrheic)

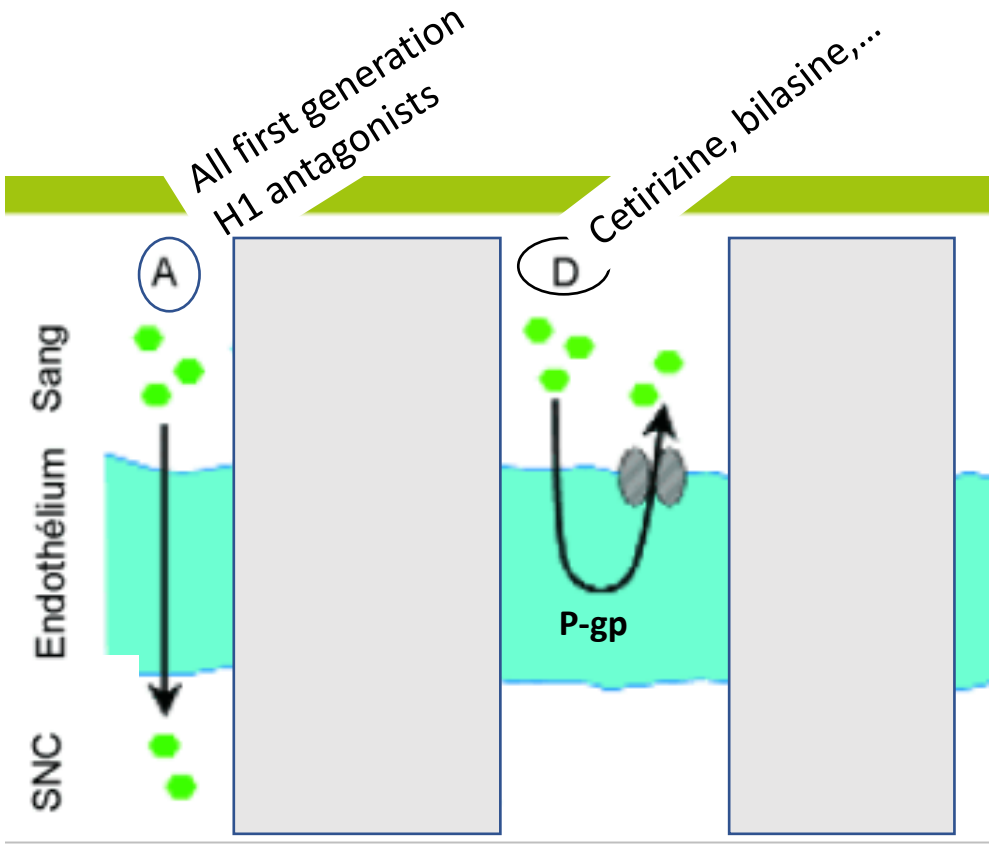


No central effects (morphine like analgesic) of loperamide. Fast efflux by P-gp.
Peripheral effects on digestive symptoms.

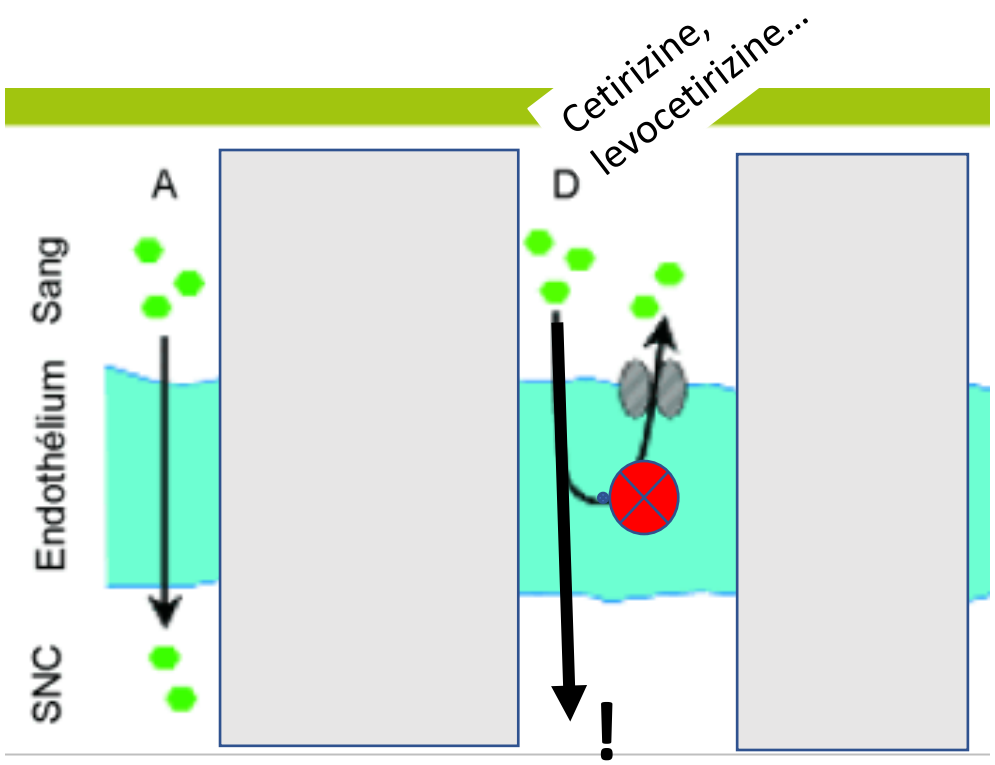


Interaction **with Pgp inhibitor**:
CNS effects, Sedation, respiratory depression, death.
Central opiate effects.

Drugs and the blood-brain barrier (BBB)
Cetirizine, Levocetirizine (non sedative H1 histamine antagonists)



No central effects of these more recent histamine antagonists. Fast efflux by P-gp.
Peripheral effects only on allergic symptoms.

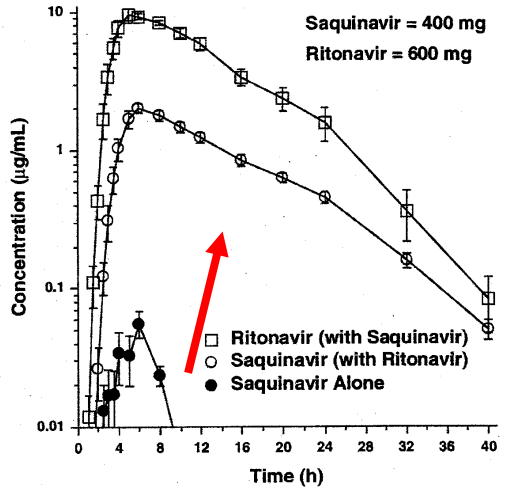


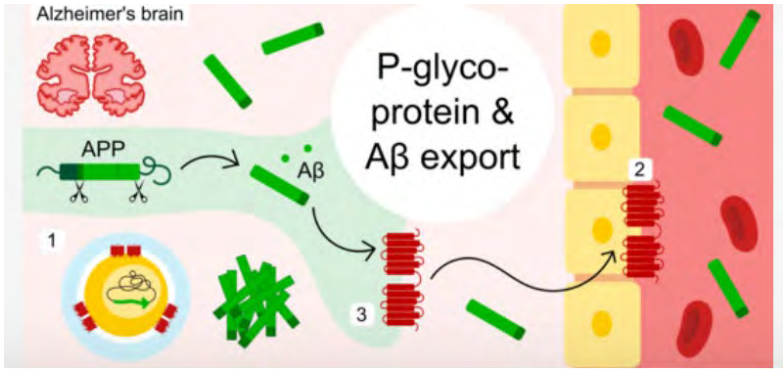
Interaction **with Pgp inhibitor**:
CNS effects, Sedation, vertigo, concentrations problems, sleep inducers.
Central antihistamiic effects.

Future prospects

✓Several effects of P-gp-inhibition or -induction are being investigated

- The example of co-medication of interest : saquinavir + ritonavir or lopinavir + ritonavir (anti-HIV) : ritonavir is a Pgp-inhibitor, increasing saquinavir or lopinavir concentrations and efficacy
- Mechanisms of tolerance to opioids ; anti-HIV and antibacterial resistance
- The role of P-gp in the export of ß-amyloid in Alzheimer's disease and the possible interest of a P-gp inducer …





Thank you for your attention!

Quiz 8

Question 1

✓Do all drugs of a same therapeutic class (e.g. all calcium channel blockers) behave similarly face to P-gp (are they all substrates or inhibitors, or inducers)?

1. Yes, I agree
2. No, I do not agree

Feedback quiz 8

Question 1

✓Do all drugs of a same therapeutic class (e.g. all calcium channel blockers) behave similarly face to P-gp (are they for example all inhibitors)?

1. Yes, I agree
2. No, I do not agree

Quiz 9

Question 2

✓The effect of a P-gp-inducer appears very fast (within a few hours).

1. Yes, I agree
2. No, I do not agree

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Feedback quiz 9

Question 2

✓The effect of a P-gp-inducer appears very fast (within a few hours).

1. Yes, I agree
2. No, I do not agree

Quiz 10

Question 3

✓A patient on chronic treatment with dabigatran asks if he can use a supplement with St John's wort. What do you answer?

1. I strongly advise against, but I discuss the necessity of another antidepressant.
2. No problem, I agree with the patients suggestion.

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Feedback quiz 10

Question 3

✓A patient on chronic treatment with dabigatran asks if he can use a supplement with St John's wort. What do you answer?

1. I strongly advise against, but I discuss the possibility of another antidepressant.
2. No problem, I agree with the patients suggestion.

EVALUATIE
Quiz 11 - 14

✓ Hoe tevreden ben je over dit symposium? Geef een score tot 10 voor volgende onderdelen:
- Inhoud
- Technische aspecten
- Algemene organisatie

✓ Welke datum of periode verkies je voor het symposium editie 2024?
- September – oktober
- November – december
- Andere

✓ Verkies je om een dergelijke opleiding in de voor- of namiddag te volgen?
- Voormiddag
- Namiddag
- Andere

✓ Heb je nog een opmerking of feedback?

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Bedankt voor uw aandacht!