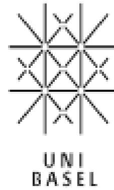
Confidence in practice with rivaroxaban in daily use

A Satellite Symposium sponsored by Bayer HealthCare Pharmaceuticals

Polypharmacy: Challenges in managing patients treated with NOACs and multiple comedications



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2015 EAHP Congress, Hamburg, Thursday, 26 March

Declaration of interests

- I am head of the Pharmaceutical Care Research Group of the University of Basel, Switzerland (part time 50%)
- I am owner and director of a community pharmacy in Basel, Switzerland (part time 50%)
- I received travel support and honoraria to attend this meeting from Bayer HealthCare Pharmaceuticals
- I have no further conflicts of interest and this talk reflects my personal views

- But,… I like Jazz music and one of my favorites is the Dave Brubeck Quartet and his masterpiece "Take Five"

Take Five

1. **What is polypharmacy?**
2. **Is polypharmacy always hazardous?**
   - Helmut – a case
3. **Polypharmacy - what is the risk for drug-drug interactions?**
4. **How do we manage novel OACs in patients on multiple medications - focus on adherence?**
5. **What are the lessons learned?**

Defining Polypharmacy: Take Five

- **No general cut-off (n= 4, 5, 6,….10)[1]**
- **Polypharmacy (N > 5) is an independent risk factor for morbidity and mortality[2]**
- **Increases continuously (year-by-year)[3]**
- **Drivers: Age + multimorbidity + new guidelines[1]**

1) Payne RA. Br J Gen Pract. 2011;61(583):83–84
2) Hajjar ER et al. Am J Geriatr Pharmacother. 2007;5:345–51
3) Hovstadius B. BMC Clin Pharmacol. 2010;10:16

Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care

Rupert A. Payne[1,*], Gary A. Abel[1], Anthony J. Avery[2], Stewart W. Mercer[3] and Martin O. Roland[1]

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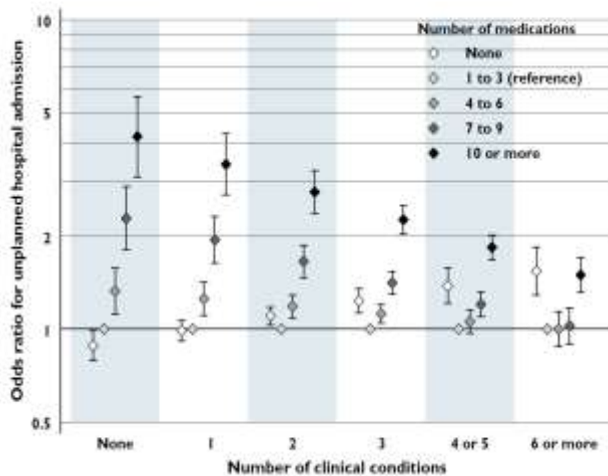

Unplanned hospitalisation is strongly associated with number of regular medications.

However, the effect is reduced in patients with multiple conditions, with only the most extreme levels of polypharmacy associated with increased admissions.

Assumptions that polypharmacy is always hazardous and represents poor care should be tempered by clinical assessment of the conditions for which those drugs are being prescribed.

Polypharmacy

- No general cut-off (n= 4, 5, 6,….10)[1]
- Polypharmacy (N > 5) is an independent risk factor for morbidity and mortality[2]
- Increases continuously (year-by-year)[3]
- Drivers: Age + multimorbidity + new guidelines[1]
- **The best intervention(s) for improving polypharmacy involves an interprofessional approach that often includes a clinical pharmacist[4]**
- **…it is clear that when pharmacists play a proactive role in performing medication reviews and in the active education of other healthcare professionals, pharmacotherapy for older patients is improved[5]**

1) Payne RA. Br J Gen Pract. 2011;61(583):83–84
2) Hajjar ER et al. Am J Geriatr Pharmacother. 2007;5:345–51
3) Hovstadius B. BMC Clin Pharmacol. 2010;10:16
4) Maher RL et al. Expert Opin Drug Saf. 2014;13(1):57–65
5) Spinwine A et al. Drugs Aging. 2012;29(6):495–510

Medication Review: Impact on health outcomes of hospitalised patients

We found no evidence of effect on all-cause mortality (risk ratio (RR) 0.98; 95% CI 0.78-1.23) and hospital readmissions (RR 1.01; 95% CI 0.88-1.16), but a **36% relative reduction in emergency department contacts (RR 0.64; 95% CI 0.46-0.89).**

This risk reduction is **equal to a number needed to treat of 9 for the high risk population** and 28 for the low risk population.

Christensen M and Lundh A. Cochrane Database Syst Rev. 2013. doi: 10.1002/14651858.CD008986.pub2.

Helmut (1942)

- **Helmut complains about hypotension in the afternoon (115/80)**
- **CVI in July 2013**
- **Hearth rhythm problems**
- **April 2014: 24h BP-Measurement:**
  - Daytime 133/80
  - Night interval: 120/77
  - Early Morning: 117/70

St nut (m), 26.5.1942 — 16.2.15 — 16.2.16

Rp — Dauerrezept

SERETIDE 250 Diskus Inh Plv 60 Dos — 1 OP
DS: Bei Bedarf
1-0-1-0

ATORVASTATIN Mepha Lactabs 20 mg 100 Stk — 1 OP
DS: Täglich
0-0-1-0

AVODART Kaps 0.5 mg 90 Stk — **Dutasterid** — 1 OP
DS: Täglich
1-0-0-0

BILOL Filmtabl 2.5 mg 100 Stk — **Bisoprolol** — 1 OP
DS: Täglich
1-0-0-0

DUODART Kaps 0.5mg/0.4mg 90 Stk — **Dutasterid/Tamsulosin** — 1 OP
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VASCORD Filmtabl 20/5 mg 98 Stk — **Olmesartan/Amlodipin** — 1 OP
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VITAMIN D3 Wild Öl 500 IE/Tropfen 10 ml — 1 OP
DS: Täglich
3-0-0-0

XARELTO Filmtabl 20 mg 98 Stk — 1 OP
DS: Täglich
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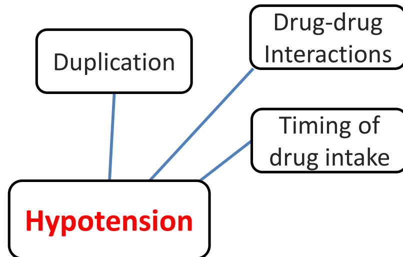
Medication Review
→ Mapping PhC-Issues



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3 - 0 - 0 - 0

XARELTO Filmtabl 20 mg 98 Stk
DS: Täglich
1 - 0 - 0 - 0

DDI Check with mediQ.ch (Only in German)

	amlodipin ...	atorvastatin...	bisoprolol ...	dutasterid ...	fluticason ...	olmesartan ...	rivaroxaba...
atorvastatin...	■						
bisoprolol ...	■	■					
dutasterid ...	?	?	?				
fluticason ...	■	?	?	?			
olmesartan ...	■	■	■	?	?		
rivaroxaba...	■	■	■	?	?	?	
salmeterol ...	?	?	■	?	■	?	?
tamsulosin...	■	■	■	■	■	?	?

Synergistic combination

Pharmacodynamic additive effects on BP

Atorvastatin may (?) inhibit CYP3A-related hepatic metabolism of Tamsulosin; but no clinical relevance expected

In patients with Asthma or COPD avoid pharmacodynamic antagonism; use cardioselective beta-blocker

Rivaroxaban may cause hypotension. At initiation, blood pressure should be monitored and Bisoprolol needs careful dosing. But, no relevant PK interaction

Drug-drug interactions

Lexi-Comp Online™ Interaction Lookup

Risk Rating C: Monitor therapy
Risk Rating D: Consider therapy modification
Risk Rating X: Avoid combination

Significant lower risk for potential DDIs (C;D;X)

- Rivaroxaban n=50
- Warfarin n=198

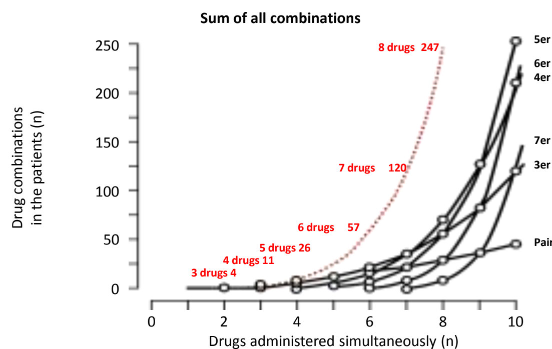
- Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms
- Based on in vitro investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein)

- **Not recommended, if possible substitute:**
  - Strong Inhibitors of CYP3A4 and P-gp (azole-antimycotics, protease-inhibitors)
- **Avoid unless patient is closely observed for signs/symptoms of thrombosis:**
  - Strong Inducers of CYP3A4 (Hypericum, rifampicin, barbiturates)
- **Close clinical surveillance in presence of multiple risk factors:**
  - Clarithromycin + Rivaroxaban → Bioavailability = 150% (clinically not relevant)
  - + renal insufficiency -> ??

Xarelto (rivaroxaban) EMA SPC 2014

Polypharmacy - what is the risk for drug-drug interactions ?

- **In theory, exponential increase of "potential" DDIs**



- **In practice, "manifest" DDIs are rare**
- **However, most problems from DDIs are preventable**

Haefeli W: Schweiz Med Forum 2011;11(47):847–852

Helmut:
«According to the patient leaflet, Xarelto might be the cause»

- **Helmut retrieved this information from the patient leaflet:**

What is the risk associated with Xarelto?

The most common side effects with Xarelto (seen in between 1 and 10 patients in 100) are anaemia, dizziness, headache, bleeding in various parts of the body, hypotension (low blood pressure), haematoma (collection of blood under the skin), pain in the stomach and belly, dyspepsia (heartburn), nausea, constipation, diarrhoea, vomiting, pruritus (itching), rash, ecchymosis (bruising), pain in the extremities, decreased kidney function, fever, peripheral oedema (swelling, especially of the ankles and feet), decreased general strength and energy, increased levels of some liver enzymes in the blood and oozing of blood or fluid from the surgical wound in patients undergoing surgery.

- **Tip: always assume that the patient reads the leaflets**

Xarelto (rivaroxaban) EMA SPC 2014

Concerns about side effects

…"The package information leaflets, may exacerbate concerns as they list all possible side effects, leaving patients with outstanding questions and making it difficult to understand the likely risk…"[1]

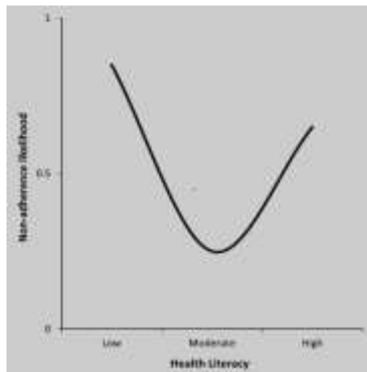
Beliefs about medicines[2]

- The necessity and concerns scales assess positive and negative attitudes toward medication
- Not valid as adherence measure!
- But helpful for counselling

The "Satisfaction with Information about Medicines Scale (SIMS)", a 17-item tool assesses the extent to which patients feel they have received enough information about prescribed medicines[3]

1) Horne R et al. PLoS ONE. 2013;8(12):e80633
2) Horne R and Weinman J. J Psychosom Med. 1999;47:555–67
3) Horne R. Quality in Health Care. 2001;10:135–40

Theoretical relationship between health literacy and non-adherence



Relevant research generally fails to find a significant relationship between non-adherence and health literacy.

A U-shaped relationship between these two conditions would explain why people with low health literacy will require different approaches to improving adherence.

High health literacy patients have a greater likelihood of intentional non adherence.

Ostini R. Int J Clin Pharm (2014) 36:36–44

DDI Check with mediQ.ch (Only in German)

L atorvastatin...
N L bisoprolol...
L dutasterid ...
fluticason ...
L olmesartan ...
N L rivaroxaba...
L salmeterol ...
N L tamsulosin...

Hepatic impairment
- Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C
- Rivaroxaban may be used with caution in cirrhotic patients with mild/moderate hepatic impairment if it is not associated with coagulopathy

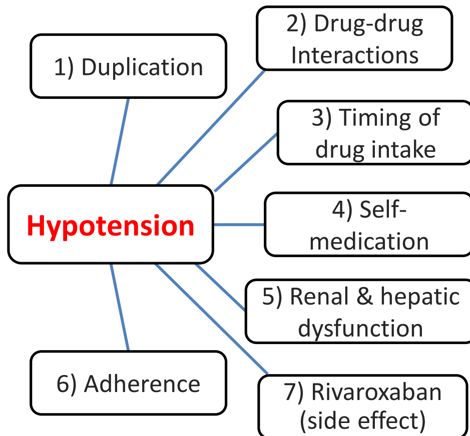
Renal impairment
- Rivaroxaban contraindicated in patients with CrCl <15 mL/min
- Rivaroxaban to be used with caution in patients with severe renal impairment (CrCl 15 - 29 mL/min.)
- Rivaroxaban should be used with caution in patients with renal impairment concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations

N: Dose adjustment for renal dysfunction

L: Dose adjustment for liver dysfunction

Xarelto (rivaroxaban) EMA SPC 2014

Medication Review
→ Mapping PhC-Issues



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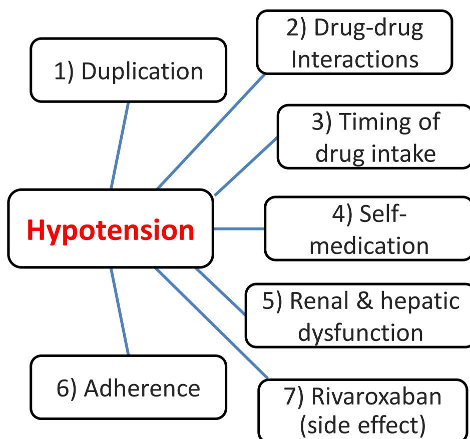
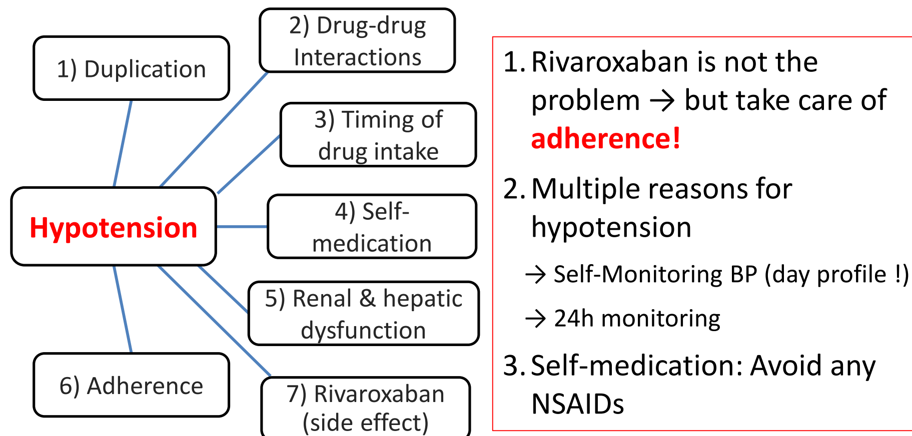
Audience survey question 1

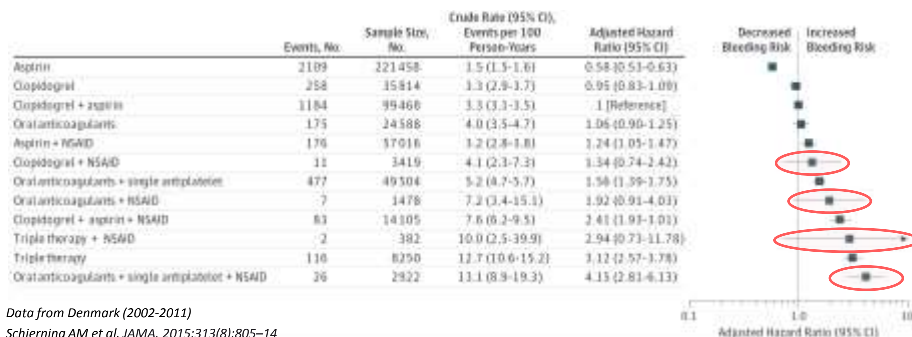


What is the major care issue in this case?

What is the major care issue in this case?



Association of NSAID Use With Risk of Bleeding and Cardiovascular Events in Patients Receiving Antithrombotic Therapy After Myocardial Infarction



	Events, No.	Sample Size, No.	Crude Rate (95% CI), Events per 100 Person-Years	Adjusted Hazard Ratio (95% CI)
Aspirin	2109	221458	1.5 (1.5-1.6)	0.58 (0.53-0.63)
Clopidogrel	258	35814	3.3 (2.9-3.7)	0.95 (0.83-1.08)
Clopidogrel + aspirin	1184	99468	3.3 (3.1-3.5)	1 [Reference]
Oral anticoagulants	175	24588	4.0 (3.5-4.7)	1.06 (0.90-1.25)
Aspirin + NSAID	176	37016	3.2 (2.8-3.8)	1.24 (1.05-1.47)
Clopidogrel + NSAID	11	3419	4.1 (2.3-7.3)	1.34 (0.74-2.42)
Oral anticoagulants + single antiplatelet	477	49504	5.2 (4.7-5.7)	1.58 (1.39-1.75)
Oral anticoagulants + NSAID	7	1478	7.2 (3.4-15.1)	1.92 (0.91-4.03)
Clopidogrel + aspirin + NSAID	83	14105	7.6 (6.2-9.5)	2.41 (1.93-3.01)
Triple therapy + NSAID	2	382	10.0 (2.5-39.9)	2.94 (0.73-11.78)
Triple therapy	110	8250	12.7 (10.6-15.2)	3.12 (2.57-3.78)
Oral anticoagulants + single antiplatelet + NSAID	26	2922	13.1 (8.9-19.3)	4.15 (2.81-6.13)

Data from Denmark (2002-2011)

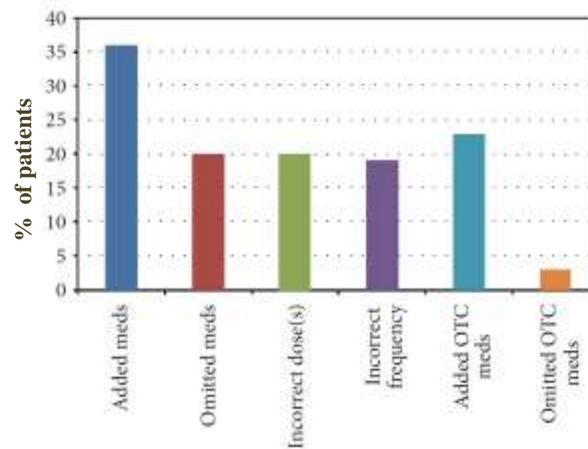
Schjerning AM et al. JAMA. 2015;313(8):805–14

Rivaroxaban: No clinically significant pharmacokinetic or pharmacodynamic interactions. But, care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk.
(Xarelto (rivaroxaban) EMA SPC 2014)

Adherence to polypharmacy – a major challenge

Adherence to Medications after Hospital Discharge (24-48h later) in the Elderly (> 65y)

Types of non-adherence in patients taking prescribed and OTC-medications

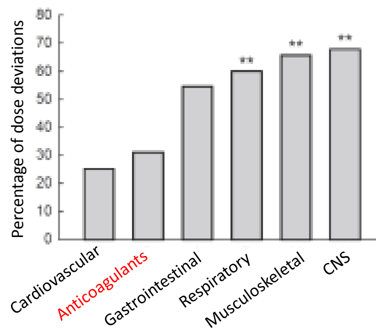


Mulhem E et al. Int J Family Med. 2013. doi: 10.1155/2013/901845

Drug therapy in the elderly: What doctors believe and patients actually do

348 persons, > 75 years Denmark, 1998

- Disagreement concerning drugs used in 22%, doses in 71%, regimens prescribed by the GP in 66%.
- Of all patients, only 21% knew the consequences of omission of the drugs



Guess what deviation do you expect with NOACs compared to Vit K antagonists (VKA)

1) **Same deviation as for VKA**
2) **Lower deviation**
3) **Higher deviation**
4) **No deviation**

Barat I et al. BJCP 2002; 51(6):615-622

Pharmacist-led fee-for-services medication review

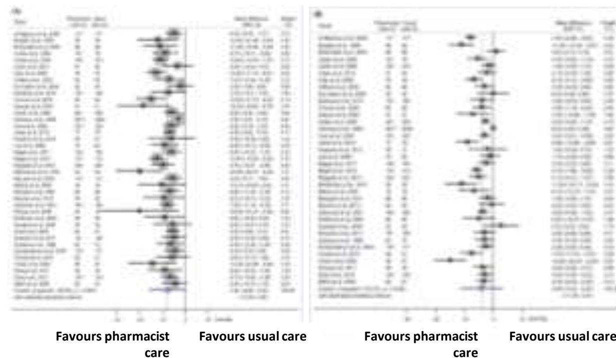
Hatah E et al. BJCP 2014;77(1):102–15

'The majority of the studies (57.9%) showed improvement in medication adherence. Fee-for-service pharmacist-led medication reviews showed positive benefits on patient outcomes.

Interventions that include a clinical review had a significant impact on patient outcomes by attainment of target clinical biomarkers and reduced hospitalization.'

Tailored interventions for specific disease, eg blood pressure

Forest plot of the mean difference in (A) systolic and (B) diastolic blood pressure with pharmacist care compared with usual care group. n=number of participants.



Pharmacist interventions – alone or in collaboration with other healthcare professionals – improved BP management.

Valérie Santschi et al. J Am Heart Assoc 2014;3:e000718

Lessons learned …….Take Five

1. Treatment guidelines rarely consider polypharmacy with respect to multimorbidity, except for DDIs
2. Most issues with polypharmacy are manageable, but deprescribing is a critical process
3. DDIs with NOACS are less critical in «healthy patients»; take care with risky patients!
4. Adherence is a general issue – treatment with NOACS probably show similar pattern of adherence, unless patient education and pharmaceutical care support medication management
5. Stay well informed on new developments in anticoagulation therapies – a lot of research is ongoing