



Besondere Risiken medikamentöser Therapie bei alten Menschen

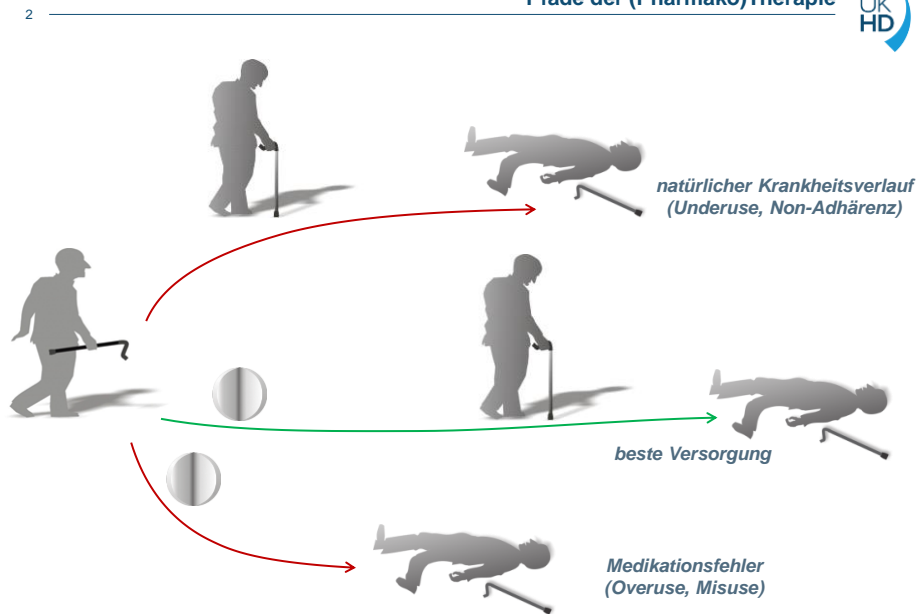
Walter E. Haefeli

Universitätsklinikum Heidelberg | Abteilung Klinische Pharmakologie und Pharmakoepidemiologie | Prof. Walter E. Haefeli, MD, FBPhS
walter.emil.haefeli@med.uni-heidelberg.de



LÄK HH 2019
Haefeli - Heidelberg

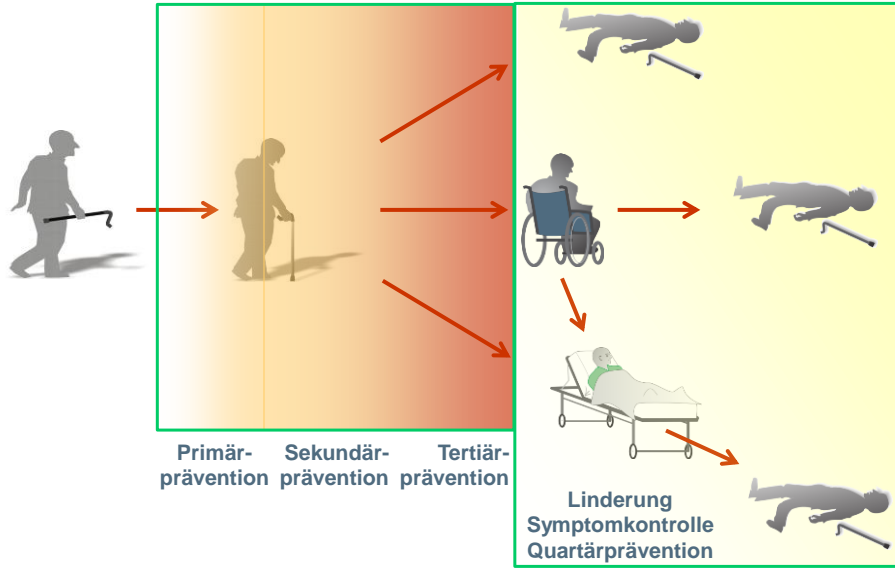
Pfade der (Pharmako)Therapie



Therapiebedürfnisse ändern sich mit zunehmendem Alter

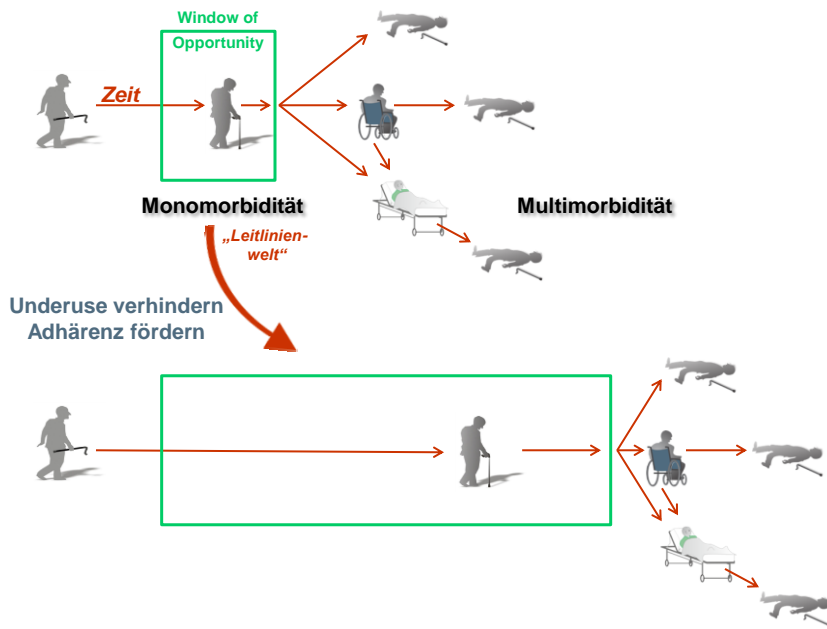


Betagte sind ein Moving Target, daran müssen sich die ärztlichen Maßnahmen ausrichten



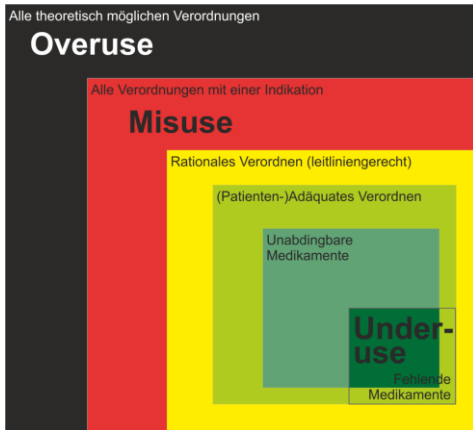
Haefeli (unpublished)

Monomorbidität vs. Multimorbidität



Haefeli (unpublished)

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- ... das Machbare (**Übersorgung**)
- ... Richtiges falsch eingesetzt (**Fehlversorgung**)
- ... alles Wirksame
- ... das individuell Sinnvolle (gezieltes Unterlassen)
- ... das Unabdingbare
- ... das Vergessene (**Unterversorgung**)

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Besondere Risiken:

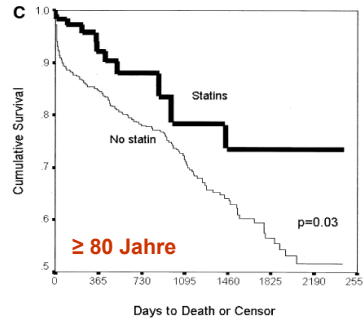
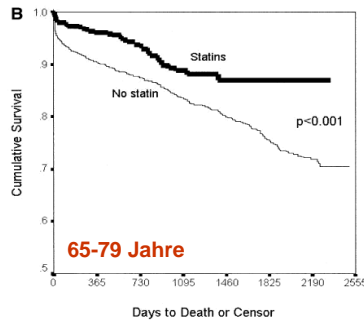
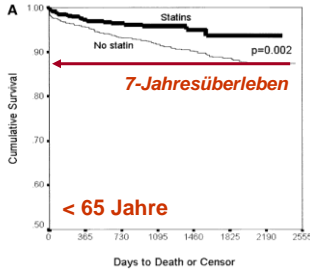
1. **Underuse - Overuse / PIM**
2. **Wechselwirkungen**
3. **Darreichungsformen**
4. **Hitzewellen**



7 Altersabhängiger Einfluss von Uneruse: Sekundärprävention mit Statinen



7220 Patienten mit KHK (> 70 % Stenose) mit und ohne Statin-Verordnung bei Entlassung

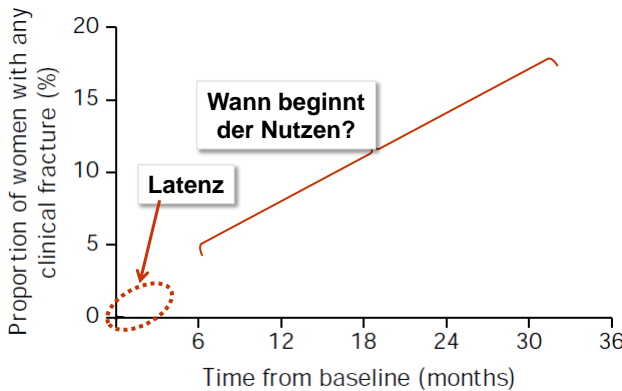


J Am Coll Cardiol 2002;40:1777

8 Time to Benefit



FIT trial, Alendronat vs. Placebo postmenopausale Frauen mit Osteoporose und Wirbelfraktur



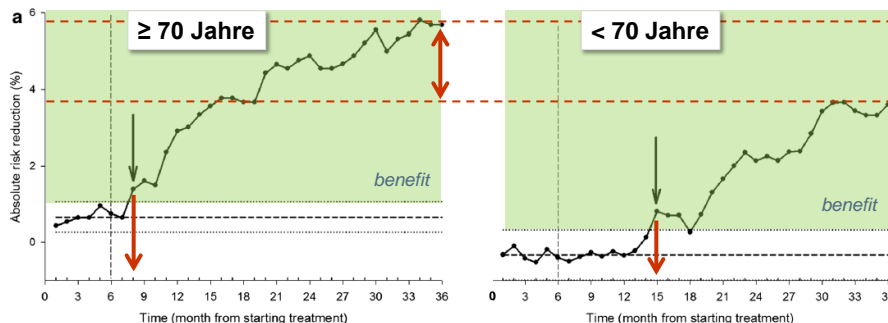
	Placebo (n=1005)	Alendronate (n=1022)
Age distribution		
<65 years	15.8%	16.7%
65-74 years	56.8%	57.4%
75-81 years	27.4%	25.8%
Mean (SD) age in years	71.0 (5.6)	70.7 (5.6)

Lancet 1996;348:1535

Statistical process control: Time-to-Benefit



FIT-Trial, Alendronat vs. Placebo
postmenopausale Frauen mit Osteoporose



Drugs Aging 2016;33:347

Screening-Werkzeuge



- Substanz-orientiert + Indikation + v.a. negative Vorschläge
- Substanz-orientiert + v.a. negative Vorschläge
- Patienten-orientiert + positive und negative Vorschläge

	PILA	DOLA	DOLA+
Total number	9	26	38
In Europe	6	12	11
In North America	2	12	17
In Asia	-	-	7
In Australia	1	2	1
In South America	-	-	-
In other regions	-	-	2
Developed for hospitalized patients	-	5	6
Developed for nursing home residents	-	2	7
Developed for community-dwelling patients	1	10	5
Developed for undetermined or more than one setting	8	9	20
Delphi method used to develop the tool	5	10	17
Scoring system included	1	5	4
RCT with relevant clinical outcomes (e.g., ADRs, falls, hospitalization, mortality or pain) excluding those for multiple tool testing	4+/1-	0	0+/5-*
All RCT with relevant clinical outcomes (e.g., ADRs, falls, hospitalization, mortality, or pain)	4+/1-	0	1+/7-*

PILA: patient-in-focus listing approaches; DOLA: drug-oriented, mostly negative listing approaches

Eur J Clin Pharmacol 2019;75:619

oft ausgelöst durch Wechselwirkungen oder Drug-Disease-Interaktionen

Overuse

STOPP-2 Kriterien (N = 85 Kriterien)

- z.B. B2. Verapamil or diltiazem with NYHA Class III or IV heart failure (may worsen heart failure).
- B3. Beta-blocker in combination with verapamil or diltiazem (risk of heart block).

Weitere Skalen und Listen
 → FORTA (fit for the aged) (Underuse und Overuse)
 → STOPPfrail (Overuse in Gebrechlichen)
 → Beers list, Priscus list (negativ Listen mit PIMs / overuse)

Underuse

START-2 Kriterien (N = 34 Kriterien)

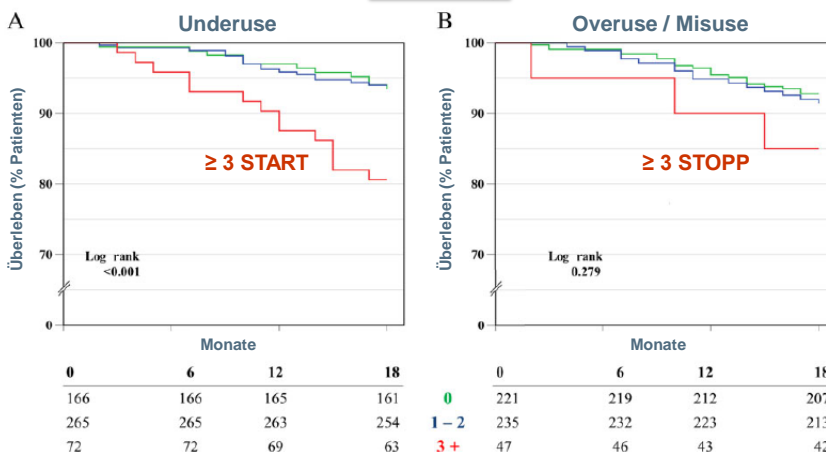
- z.B. 5. Statin therapy with a documented history of coronary, cerebral or peripheral vascular disease, unless the patient's status is end-of-life or age is > 85 years.

Weitere Skalen und Listen
 → FORTA (fit for the aged) (Underuse und Overuse)

Age Ageing 2017;46:600 / 2015;44:213, Dtsch Arztebl Int 2010;107:543, Drugs Aging 2014;31:131

503 ambulante Patienten > 80 Jahre, zu Hause lebend
prospektive Kohortenstudie

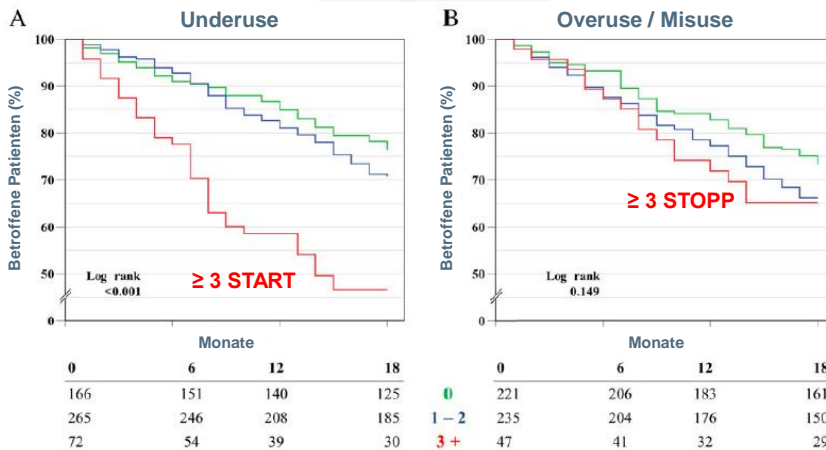
Mortalität



Br J Clin Pharmacol 2016;82:1382

503 ambulante Patienten > 80 Jahre, zu Hause lebend
prospektive Kohortenstudie

Hospitalisierung



Br J Clin Pharmacol 2016;82:1382

ESTHER-Kohorte, 989 ambulante Patienten mit mind. 1 AM
und 7 ausgewählten START-Kriterien und

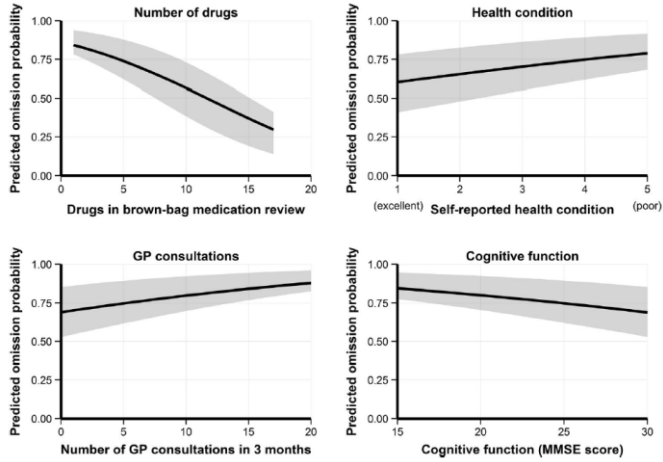
Table 1 Number of underlying conditions of selected START-2 criteria relevant for inclusion in two follow-ups of the ESTHER cohort study. The prevalence of each criterion is presented as frequency of the number of participants with the underlying condition and percentage of all 989 included participants

Criterion	Description	Condition present (underuse present)			
		1st follow-up		2nd follow-up (3 Jahre später)	
		n (n with underuse)	% of total (% of n patients with condition)	n (n with underuse)	% of total (% of n patients with condition)
ausgewählte START-Kriterien					
A3	Antiplatelet therapy with a documented history of atherosclerotic coronary, cerebral, or peripheral vascular disease ^a	563 (263)	56.9 (46.7)	589 (306)	59.6 (52.0)
A4	Antihypertensive therapy where systolic blood pressure consistently exceeded 160 mmHg ^b	161 (29)	16.3 (18.0)	102 (0)	10.3 (0.0)
A5	Statin therapy with a documented history of coronary, cerebral, or peripheral vascular disease, unless the participant's age is above 85 years ^a	563 (268)	56.9 (47.6)	589 (311)	59.6 (52.8)
A6	ACE inhibitor or AT1 blocker with chronic heart failure (ACE: angiotensin-converting enzyme; AT1: angiotensin-II-receptor-subtype-1)	248 (70)	25.1 (28.2)	276 (89)	27.9 (32.2)
A7	β-blocker therapy in patients with chronic stable angina	284 (84)	28.7 (29.6)	308 (78)	31.1 (25.3)
B1	Regular inhaled β2-agonist or anticholinergic agent for mild-to-moderate asthma or COPD ^c	410 (312)	41.5 (76.1)	468 (350)	47.3 (74.8)
B2	Regular inhaled corticosteroid for moderate/severe asthma or COPD ^c	59 (38)	6.0 (64.4)	38 (21)	3.8 (55.3)

Ø 70,3 %
Ø 73,2 %

Eur J Clin Pharmacol 2016;72:877

ESTHER, 989 ambulante Patienten mit mind. 1 AM und 7 ausgewählten START-Kriterien (multivariate Analyse)

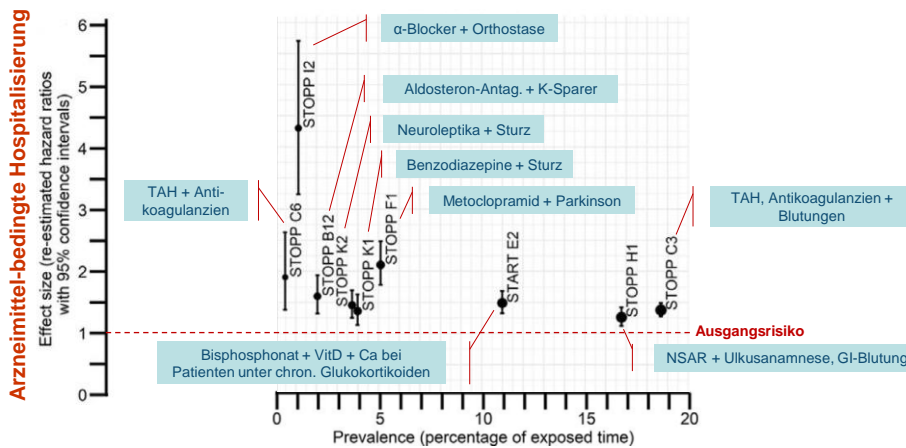


Verschlechterung der QoL in 3 Jahren

ohne Underuse: 1,29 %
mit 1 Underuse: 1,74 % (p = 0,002)

Eur J Clin Pharmacol 2016;72:877

AOK-BW, 30'000 ambulante Patienten mit mind. 1 AM und 14 ausgewählten START- und 50 STOPP-Kriterien

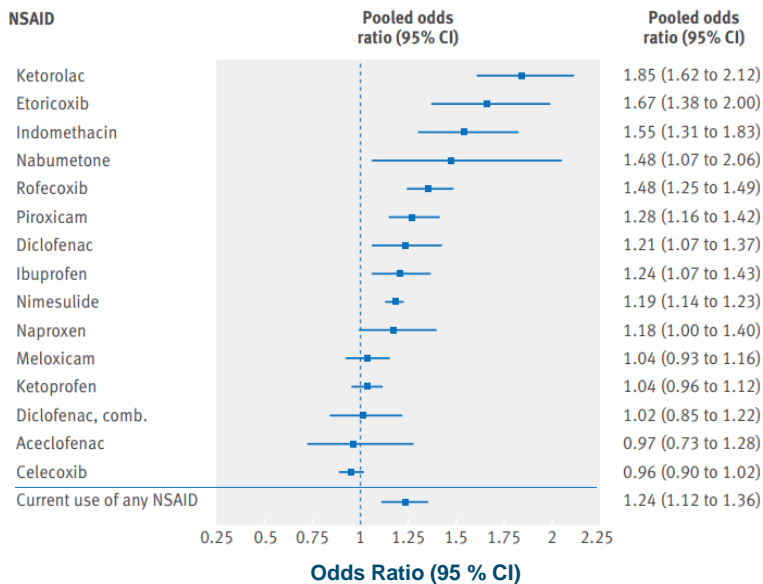


Value Health 2018;21:1390

Hospitalisierungsrisiko wegen Herzinsuffizienz



unter NSAR



NSAID = NSAR = nicht-steroidale Antirheumatika

BMJ 2016;354:14857

Varianten von Drug-Disease-Interaktionen



Krh + AM → Krh ↑
(Verschlechterung der Grundkrankheit, Rezidiv)

- NSAR + Herzinsuffizienz (→ Hospitalisierung)
- Infliximab + NYHA III-IV (→ Tod)
- NSAR + Ulkuseiden (→ Ulkuszidiv)
- Psoriasis + Betablocker (→ Exazerbation)
- Risperidon + Parkinson (→ Exazerbation)
- Levofloxacin + Myasthenia gravis (→ Intubation)
- Adalimumab + aktive Infektionen (Tbc) (→ Tod)
- FRIDs + Sturzneigung (→ Frakturen)

Krh/Zustand + AM → neue Krh
(Auslösen einer anderen, neuen Krh/Symptomatik)

- Gd-KM + Niereninsuffizienz (→ nephrogene systemische Fibrose)
- Niereninsuffizienz + Metformin (→ Lactazidose)
- Niereninsuffizienz + Pethidin (→ epileptiforme Syndrome)
- Niereninsuffizienz + Aminoglykoside (→ Taubheit)
- HLA-A*3101 + Oxcarbazepin (→ SJS, TEN)
- Adipositas + Norelgestromin (→ tiefe Vv-Thrombose)
- Anticholinergika + Inkontinenz (→ kognitive Einschränkung)

Krh + AM → exzessive AM-Toxizität
(ungewöhnlich schlechte Verträglichkeit)

- Aminoglykoside + Niereninsuffizienz (→ Nierenversagen)
- Glibenclamid + Niereninsuffizienz (→ Hypoglykämie)
- Rivaroxaban + Polypharmazie (→ Blutung)

AM: Arzneimittel, FRIDs: Fall Risk-Increasing Drugs, KM: Kontrastmittel, Krh: Krankheit, NSAR: nicht-steroidale Antirheumatika, SJS: Stevens-Johnson-Syndrom, TEN: Toxisch-epidermale Nekrolyse

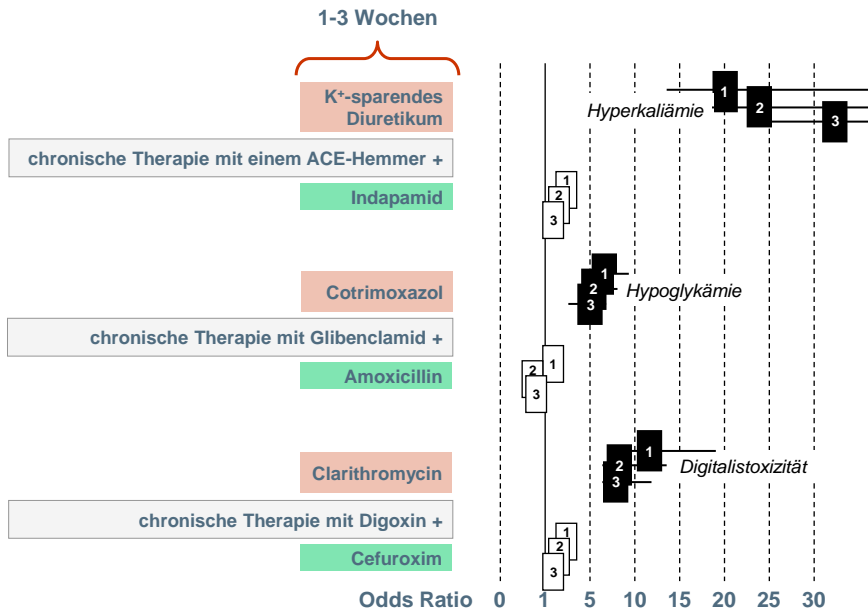
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2. Wechselwirkungen
3. Darreichungsformen
4. Hitzewellen



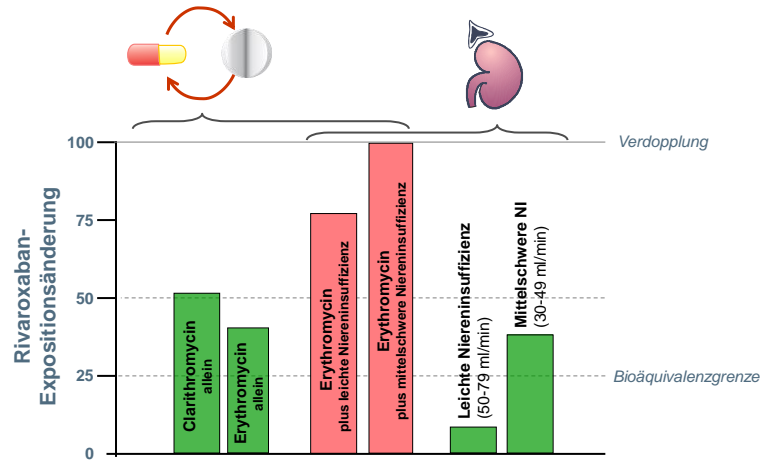
Zeitliche Risikoentwicklung wegen Interaktionen

Hospitalisierung von 909 Patienten > 65 Jahre



Konsequenzen mehrerer gleichzeitiger Eliminationsstörungen

Interaktion plus Niereninsuffizienz bei Rivaroxaban
= Drug-drug- und Drug-Disease-Interaktion



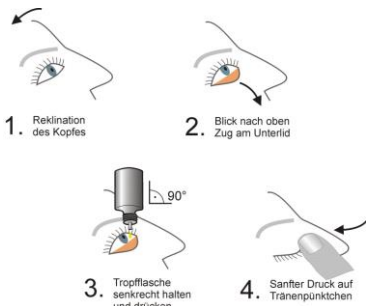
J Clin Pharmacol 2014;54:1-407

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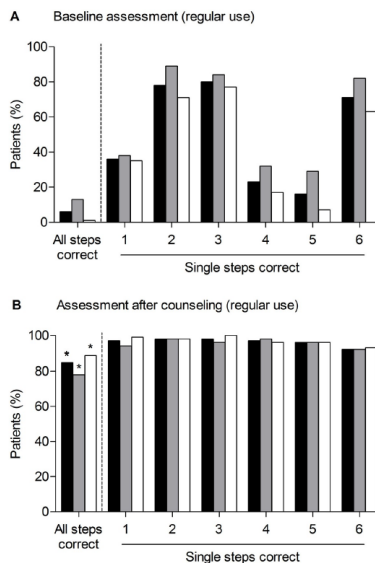
Administration steps

- Hand washing*
- Instillation of a single drop
- Instillation into the conjunctival sac
- Eyelid closure for approximately one minute
- Concomitant nasolacrimal occlusion
- Avoid touching the dropper tip

Applikationsprobleme: Augentropfen



91 erwachsene Patienten
(46 in Interventionsgruppe)

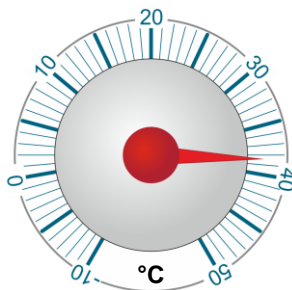


PLoS One 2019;14:e0212007

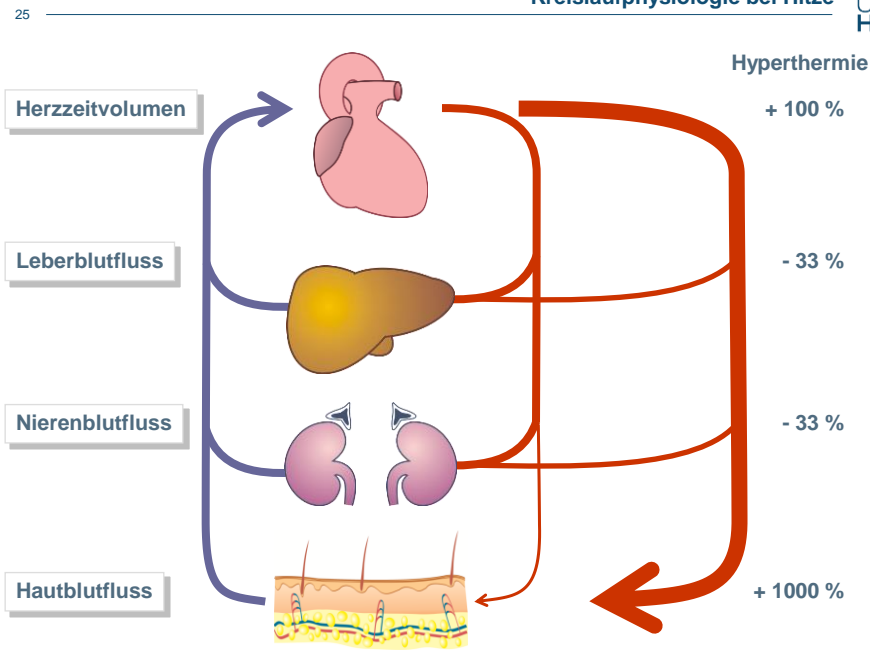
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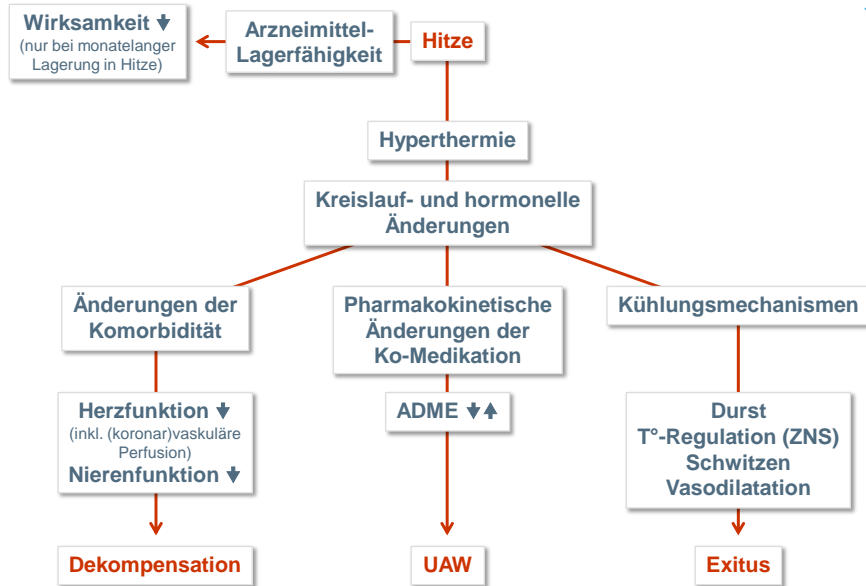
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Becker et al. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 2019 (im Druck)

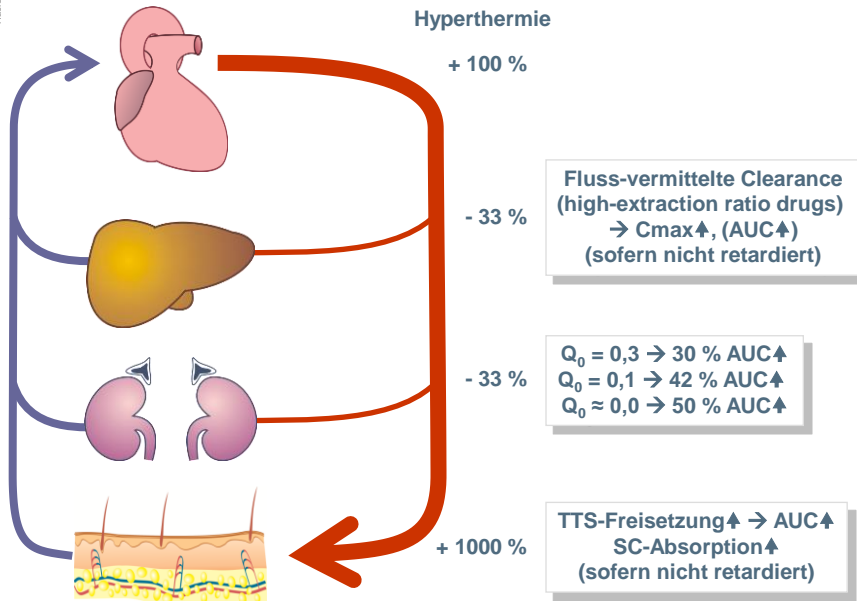


Clin Pharmacokinet 1998;34:311



Drug Saf 2008;31:109, Clin Pharmacokinet 1998;34:311

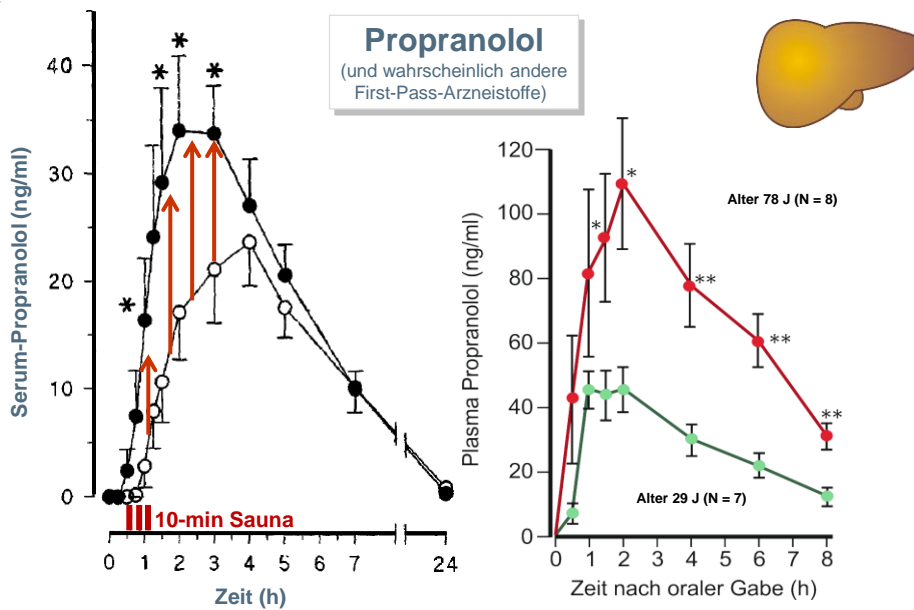
ADME: Absorption – Distribution – Metabolismus – Exkretion; AM: Arzneimittel; PK: Pharmakokinetik; UAW: unerwünschte Arzneimittelwirkung



SC: subkutan; TTS: transdermales therapeutisches System

Clin Pharmacokinet 1998;34:311

= Arzneimittel mit hohem oralem First-Pass-Effekt



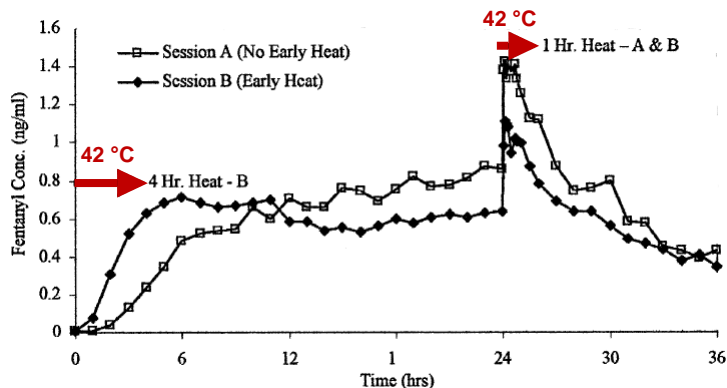
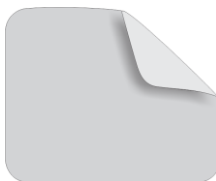
PK: Pharmakokinetik

Eur J Clin Pharmacol 1995;48:133, Br J Clin Pharmacol 1979;7:49

Opioid-Freisetzung aus TTS unter Hitzeapplikation



Fentanyl-Patch, gesunde Freiwillige



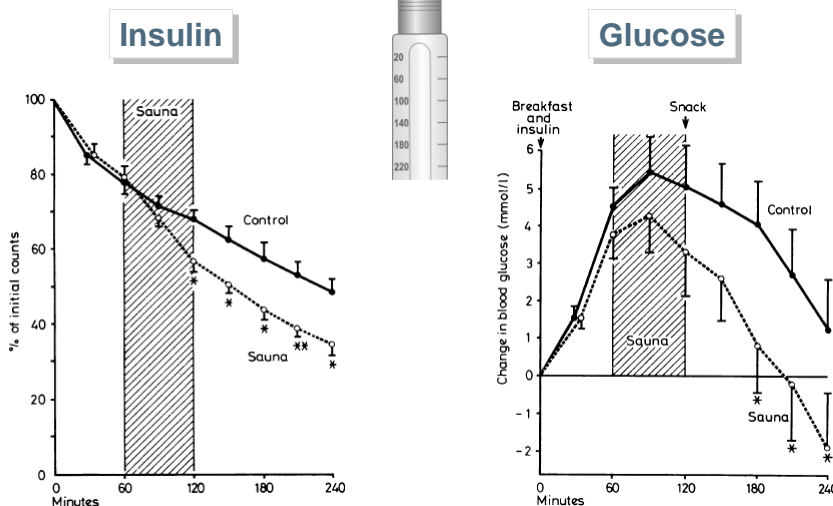
TTS: transdermales therapeutisches System

J Pain 2003;4:291

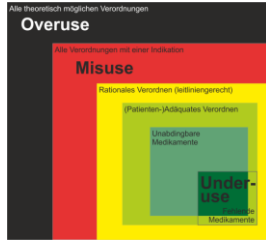
Subkutane Insulin-Freisetzung unter Hitzeapplikation



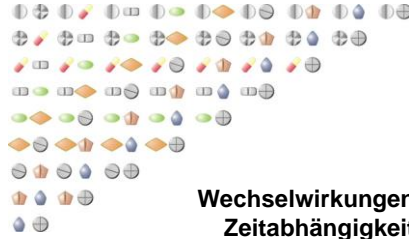
rasch freisetzendes Insulin, Diabetiker



Br Med J 1980;280:1411



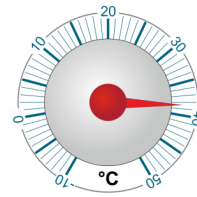
**Overuse
Underuse**



**Wechselwirkungen
Zeitabhängigkeit**



**transdermale Gabe
Augentropfen**



**sc Gabe
transdermale Gabe
First-Pass-AM**