

Wirkung und Bedeutung von Vitamin K-Antagonisten

Kollegium für Hausarztmedizin: Antikoagulation in der Hausarztpraxis

Luzern, 19.06.2008

B. Lämmle, KPH-HZL,
Inselspital, Universität Bern



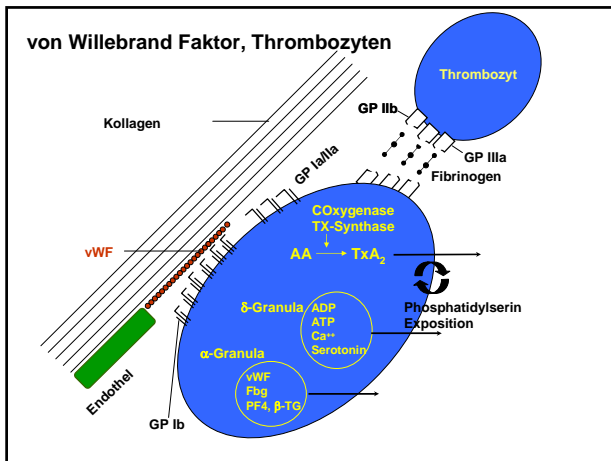
UNIVERSITÄT
BERN

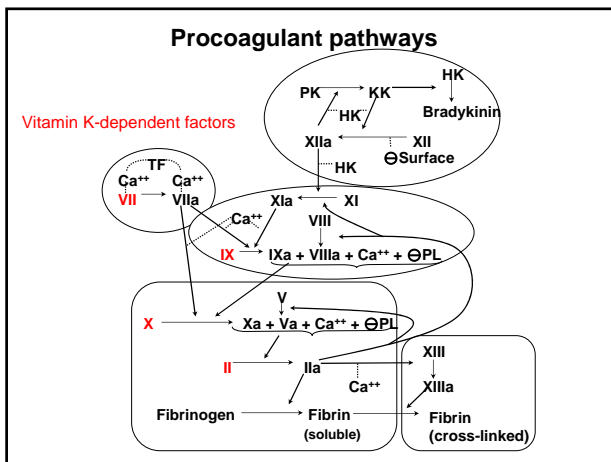
Phenprocoumon (Marcoumar®)

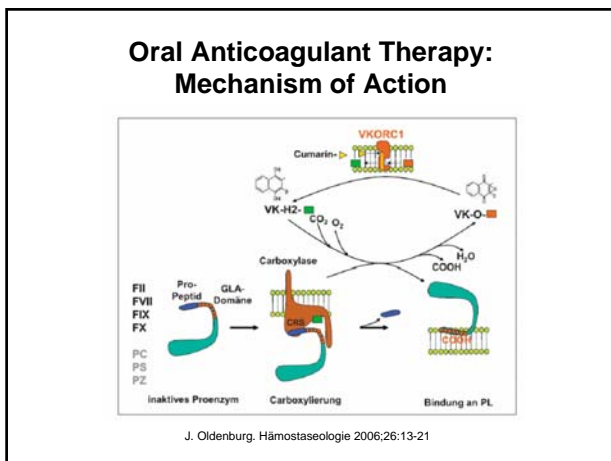
- Ein Medikament, das sich lange „gehalten hat“
- Hoch wirksam, breites Indikationsspektrum
- Extrem feine Steuerung der Dosierung, notwendige Laborkontrolle
- CAVE: Nebenwirkungen (Blutungen)

Hämostase

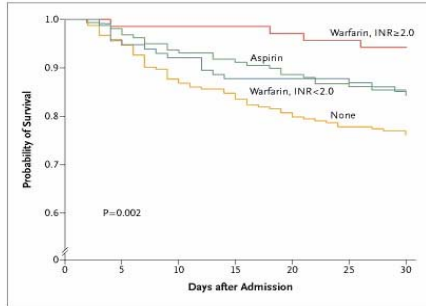
- Vaskuläre Hämostase
- Primäre Hämostase: von Willebrand Faktor, Thrombozyten
- Sekundäre Hämostase: Plasmatische Gerinnung → Fibrinbildung







Survival after ischemic stroke among patients with nonvalvular atrial fibrillation
(EM Hylek et al. NEJM 2003;349:1019-26)



EM Hylek et al. NEJM 2003;349:1019-26

Table 5. Incidence Rates of Ischemic Stroke and Intracranial Hemorrhage among Patients with Nonvalvular Atrial Fibrillation Who Were Taking Warfarin, According to the International Normalized Ratio (INR) at the Time of the Stroke.*

INR	Person-yr†	Stroke (95% CI) (N=152)		Intracranial Hemorrhage (95% CI) (N=58)	
		rate/100 person-yr	Person-yr‡	rate/100 person-yr	Person-yr‡
<1.5	556	7.7 (5.7–10.4)	561	0.5 (0.2–1.7)	
1.5–1.9	2847	1.9 (1.4–2.4)	2867	0.3 (0.1–0.6)	
2.0–2.5	3357	0.4 (0.3–0.7)	5400	0.3 (0.2–0.4)	
2.6–3.0	2388	0.9 (0.6–1.4)	2409	0.5 (0.3–0.9)	
3.1–3.5	834	0.7 (0.3–1.6)	843	0.6 (0.3–1.4)	
3.6–3.9	243	0.4 (0.1–2.9)	247	0.4 (0.1–2.9)	
4.0–4.5	144	1.4 (0.4–5.5)	147	2.7 (1.0–7.3)	
>4.5	115	2.6 (0.8–8.1)	118	9.4 (5.2–16.9)	

* CI denotes confidence interval.
† Differences in the numbers of person-years between stroke and intracranial hemorrhage reflect differences in the time at which data were censored.

OAT for secondary prevention after acute myocardial infarction
J.A. Cairns. Lancet 1994;343:497-8

Trial (yr)	Age	Reduction/100 patient years				Increase/100 patient years Major extra-cranial haemorrhage
		Recurrent MI	Cerebro-vascular events	Vascular events	All-cause mortality	
Sixty Plus (1980)	58	4.15*	1.05		2.05	2.8
WARIS (1990)	62	2.2*	1.33*		1.6*	0.4
ASPECT (1994)	61	2.8*	0.5*	3.1*	0.4	0.8
APT (1994)				1.6*	0.53*	

Vascular events among post-acute MI patients in recent trials of oral anticoagulation and antiplatelet therapy.
*p<0.05

Some recent developments/findings

- Self-management of OAT feasible
- Large interindividual variation of OA dose:
 - Cytochrome P450 CYP 2C9 polymorphisms: CYP 2C9*2 and 2C9*3 → lower metabolism of coumarins → lower dose needed (warfarin, acenocoumarol)
 - Vitamin K epoxide reductase (VKORC1) polymorphisms → coumarin sensitivity/resistance
- Low dose Vitamin K + OAT → more stable INR

Oral Anticoagulation: Side effects

- Bleeding complications
- Coumarin necrosis
- Coumarin hepatitis
- Alopecia
- Teratogenicity

OAT: Side effects, Bleeding

Bleeding complications:

- Review of observational studies: fatal bleeding 0.8/100 patient-years; major bleeding 4.9/100 pat-yrs; major/minor bleeding 15/100 pat-yrs (1)
- Inception cohort, prospective study on 2745 patients monitored by anticoagulation clinics: 0.25 fatal/100 pat-yrs; 1.1 major/100 pat-yrs; 6.2% minor/100 pat-yrs (2)
- Swiss practitioners, prospective study on 538 patients: 0 fatal; 4.3 leading to OAT withdrawal; 2.1 leading to hospitalization; 11.6 total bleeding/100 pat-yrs (3)

1) Landefeld et al. Am J Med 1993;95:315-28 2) Palareti et al. Lancet 1996;348:423-28
3) Marko et al. Schweiz Med Wschr 1992;122:732-41

Side effects: Coumarin Necrosis



Prevention:

- Avoid large loading dose of coumarins
- Simultaneous (LMW-) heparin until therapeutic INR for 2 consecutive days

Apparent Coumarin Resistance (I)

- 70-year-old patient, phenprocoumon for mitral valve prosthesis, INR values between 2.7-3.8 (target 3.0) during preceding year.
- Hospitalization at peripheral hospital for wasting, fever → Diagnosis of tuberculosis → Treatment with Rifater® (isoniazid, pyrazinamid, rifampicin) and ethambutol.
- INR after 1 week: 1.5, next day: 1.4
- Laboratory problem ? Phenprocoumon intake ?

Apparent Coumarin Resistance (II)

Conclusion:

- Pharmacokinetic **drug interference** (in this case induction of cytochrome P450 enzymes by **rifampicin**, accelerated inactivation of coumarin)
- **Practical guideline:** consider potential interference with each **added** or **withdrawn** drug (consult Compendium)

Note:

- Phenprocoumon metabolized by CYP450 2C9 and 3A4

Intramuscular phenylbutazone injection in patient under OAC treatment



- Avoid i.m. injections in patients under OAC therapy
- Consider drug interference, enhanced coumarin action by phenylbutazone

Many other potential pitfalls and problems with OAC therapy

- Compliance
- Laboratory problems with INR determination
- Bleeding with therapeutic INR values:
 - Think of „diagnostic bleeding“, e.g. underlying neoplasia
 - Concomitant hemostasis defect (thrombocytopenia, etc.)
 - Very rare FIX propeptide mutation (FIX < 3% while on OAC)
- Thromboembolic recurrence under adequate OAC:
 - Think of Trousseau syndrome

Conclusion

- Coumarins (including Phenprocoumon) are highly effective for treatment and prophylaxis of thromboembolic disease
- Bleeding is the major side effect
