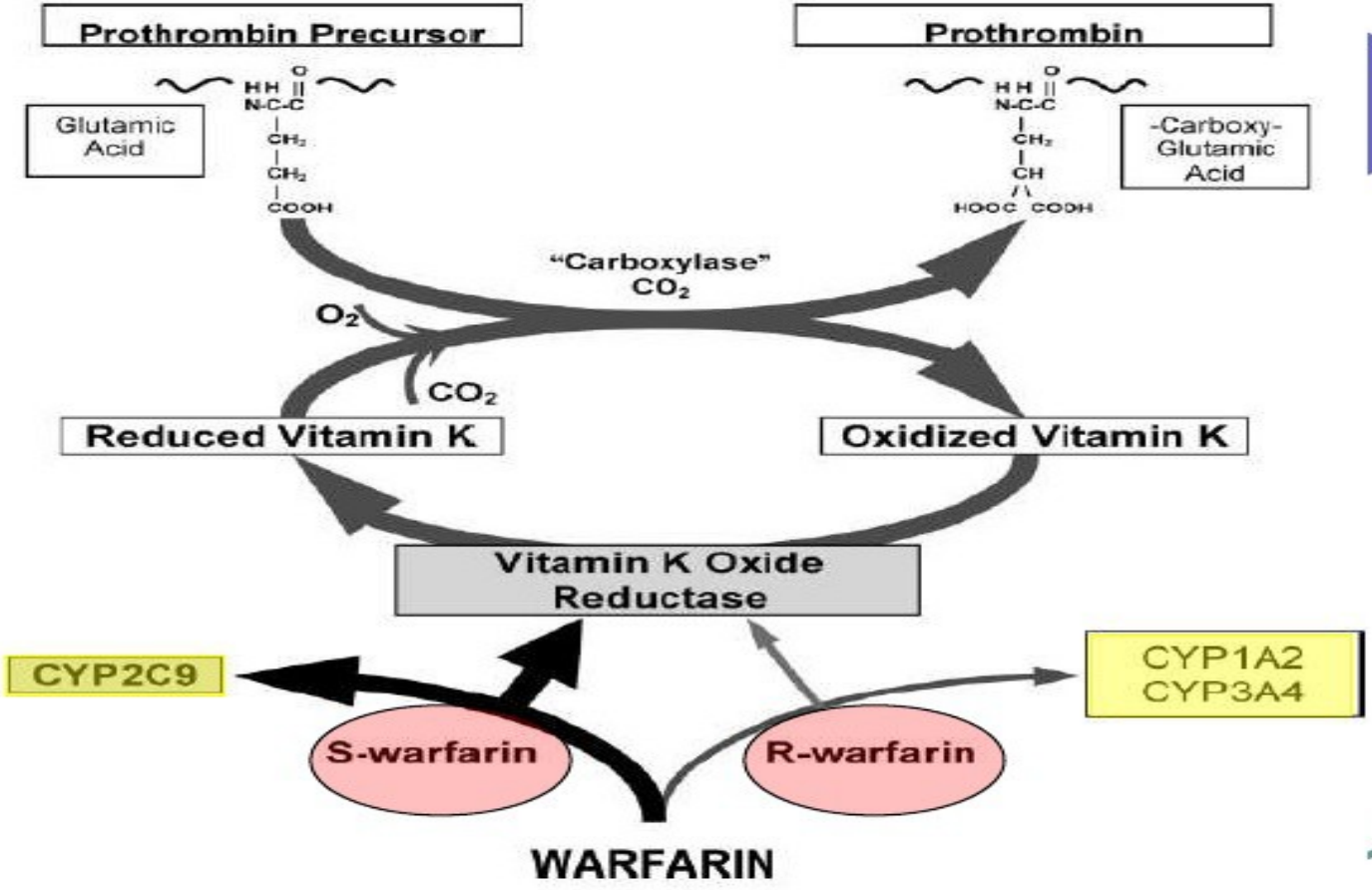
По-добри ли са витамин К-антагонистите?

Доц. Иван Груев д.м.
НМТБ ”Цар Борис III”

Определение

- **Витамин К антагонистите са група медикаменти, които противодействат на кръвосъсирването чрез инхибиране на връщането на витамин К-епоксид обратно към активната редуцирана форма на вит. К. Те действат само ин виво като потискат образуването на плазмените фактори II, VII, IX и X в черния дроб.**
- **Треминът “антагонисти на вит. К” е неточен, тъй като те не антагонизират директно действието на вит К, а противодействат на рециклирането му в активна форма**

Механизъм на действие

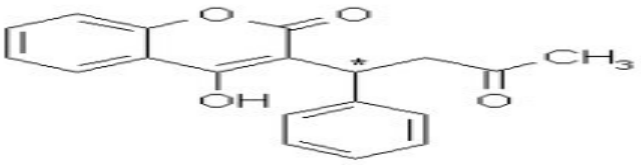


Pharmacology and Management of the Vitamin K Antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines 8ed. CHEST 2008;133;160s-198s.

История

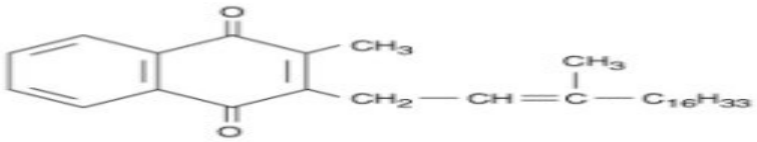
Oral Anticoagulants

1924 – Hemorrhagic disease in cattle due to feeding of spoiled sweet clover (contained bishydroxy coumarin)



warfarin
* chiral center

bishydroxycoumarin
(dicoumarol)



Phytonadione (vitamin K_1)

WARFARIN

Initially introduced as a rat pesticide in 1948

Approved for use in humans in 1954

WARNING: BLEEDING RISK

От историята към настоящето

Target Market

- Warfarin is the most commonly prescribed oral anticoagulant medicine on the market[3] and has been in use since 1954
- Roughly 2 million people take Warfarin each year in the United States alone. It is prescribed to patients who are at risk of developing blood clots. These conditions include:
  - Atrial fibrillation
  - Recurrent strokes
  - Deep venous thrombosis
  - Pulmonary embolism
  - Heart valve replacement[4]

Съвременни индикации за вит. К - антагонисти

Warfarin: Current Indications/Intensity

Indication	INR Range	Target
Prophylaxis of venous thrombosis (high-risk surgery) Treatment of venous thrombosis Treatment of PE Prevention of systemic embolism Tissue heart valves AMI (to prevent systemic embolism) Valvular heart disease Atrial fibrillation	2.0–3.0	2.5
Mechanical prosthetic valves (high risk) Certain patients with thrombosis and the antiphospholipid syndrome AMI (to prevent recurrent AMI)	2.5–3.5	3.0
Bileaflet mechanical valve in aortic position, NSR	2.0–3.0	2.5

Съвременни индикации при механични клапни протези

Mechanical Prosthetic Heart Valves

Patient Characteristics	Recommendation
Bileaflet mechanical valve in the aortic position, left atrium of normal size, NSR, normal ejection fraction	Goal INR 2.5; range, 2.0–3.0
Tilting disk valve or bileaflet mechanical valve in the mitral position	Goal INR 3.0; range, 2.5–3.5*
Bileaflet mechanical aortic valve and AF	Goal INR 3.0; range, 2.5–3.5*
Caged ball or caged disk valves	Goal INR 3.0; range, 2.5–3.5; and aspirin therapy (80–100 mg/d)
Additional risk factors	Goal INR 3.0; range, 2.5–3.5; and aspirin therapy (81 mg/d)
Systemic embolism, despite adequate therapy with oral anticoagulants	Goal INR 3.0; range, 2.5–3.5; and aspirin therapy (81 mg/d)

* Alternative: goal INR 2.5; range, 2.0–3.0; and aspirin therapy (80–100 mg/d)

ESC Guidelines 2011 for the management of cardiovascular diseases during pregnancy

Chairperson

Vera Regitz-Zagrosek
Charite Universitaetsmedizin Berlin,
Institute for Gender in Medicine,
Berlin, Germany

European Heart Journal 2011, doi: 10.1093/eurheatj/ehr218

Valvular Heart Disease (II)

- Oral anticoagulation (OAC) with vitamin K antagonists are the safest therapy to prevent valve thrombosis and are therapy of choice during the second and third trimester (IC).
- During the first trimester continuation of OAC should be considered when warfarin daily dose is < 5 mg (IIaC).
- With higher dose requirements, unfractionated or low-molecular weight heparin should be considered with strict dose adjustment according to APTT or anti-Xa levels (weekly control) (IIaC).
- At the 36th week, OAC should be discontinued and replaced by dose-adjusted heparin (IC).

European Heart Journal 2011, doi: 10.1093/eurheartj/ehr218

2014 version

ESC Guidelines on Hypertrophic Cardiomyopathy

Chairperson
Perry M. Elliott (UK)

www.escardio.org/guidelines European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Atrial fibrillation/atrial flutter

Recommendations	Class	Level
Unless contra-indicated, oral anticoagulation with VKA (target INR 2.0–3.0) is recommended in patients who develop persistent, permanent or paroxysmal AF, to prevent thromboembolism.	I	B
Antithrombotic therapy is recommended for patients with atrial flutter, as for those with AF.	I	C
Assessment of the risk of bleeding with the HAS-BLED score should be considered when prescribing antithrombotic therapy (whether with VKA or antiplatelet therapy).	IIa	B
Restoration of sinus rhythm, by DC or pharmacological cardioversion with intravenous amiodarone, should be considered in patients presenting with recent-onset AF.	IIa	C
Amiodarone should be considered for achieving rhythm control and to maintain sinus rhythm after DC cardioversion.	IIa	B
ß-Blockers, verapamil and diltiazem are recommended to rate control in patients with permanent or persistent AF.	I	C

www.escardio.org/guidelines European Heart Journal (2014);35:2733–2779 - doi:10.1093/eurheartj/ehu284

Indications for antithrombotic therapy after valvular surgery

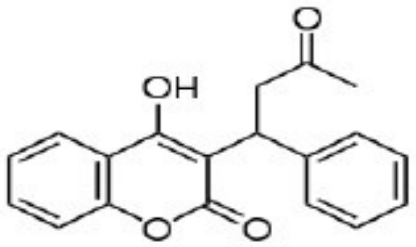
	Class	Level
Oral anticoagulation is recommended lifelong for all patients with a mechanical prosthesis.	I	B
Oral anticoagulation is recommended lifelong for patients with bioprostheses who have other indications for anticoagulation.	I	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis and concomitant atherosclerotic disease.	IIa	C
The addition of low-dose aspirin should be considered in patients with a mechanical prosthesis after thromboembolism despite adequate INR.	IIa	C
Oral anticoagulation should be considered for the first 3 months after implantation of a mitral or tricuspid bioprosthesis.	IIa	C
Oral anticoagulation should be considered for the first 3 months after mitral valve repair.	IIa	C
Low-dose aspirin should be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIa	C
Oral anticoagulation may be considered for the first 3 months after implantation of an aortic bioprosthesis.	IIb	C

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs109 & European Journal of Cardio-Thoracic Surgery 2012 - doi:10.1093/ejcts/ezs455).

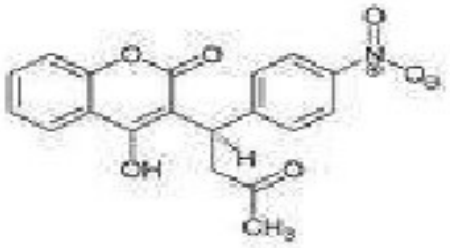
Най- популярни представители

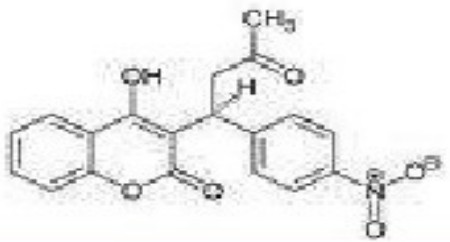
ANTAGONISTAS VIT. K

- WARFARINA



- ACENOCUMAROL





Pharmacology and Management of the Vitamin K Antagonists: American College of Chest Phrysicians Evidence-Based Clinical Practice Guidelines 8ed. CHEST 2008;133;160s-198s.

Фармакология

PHARMACOLOGY

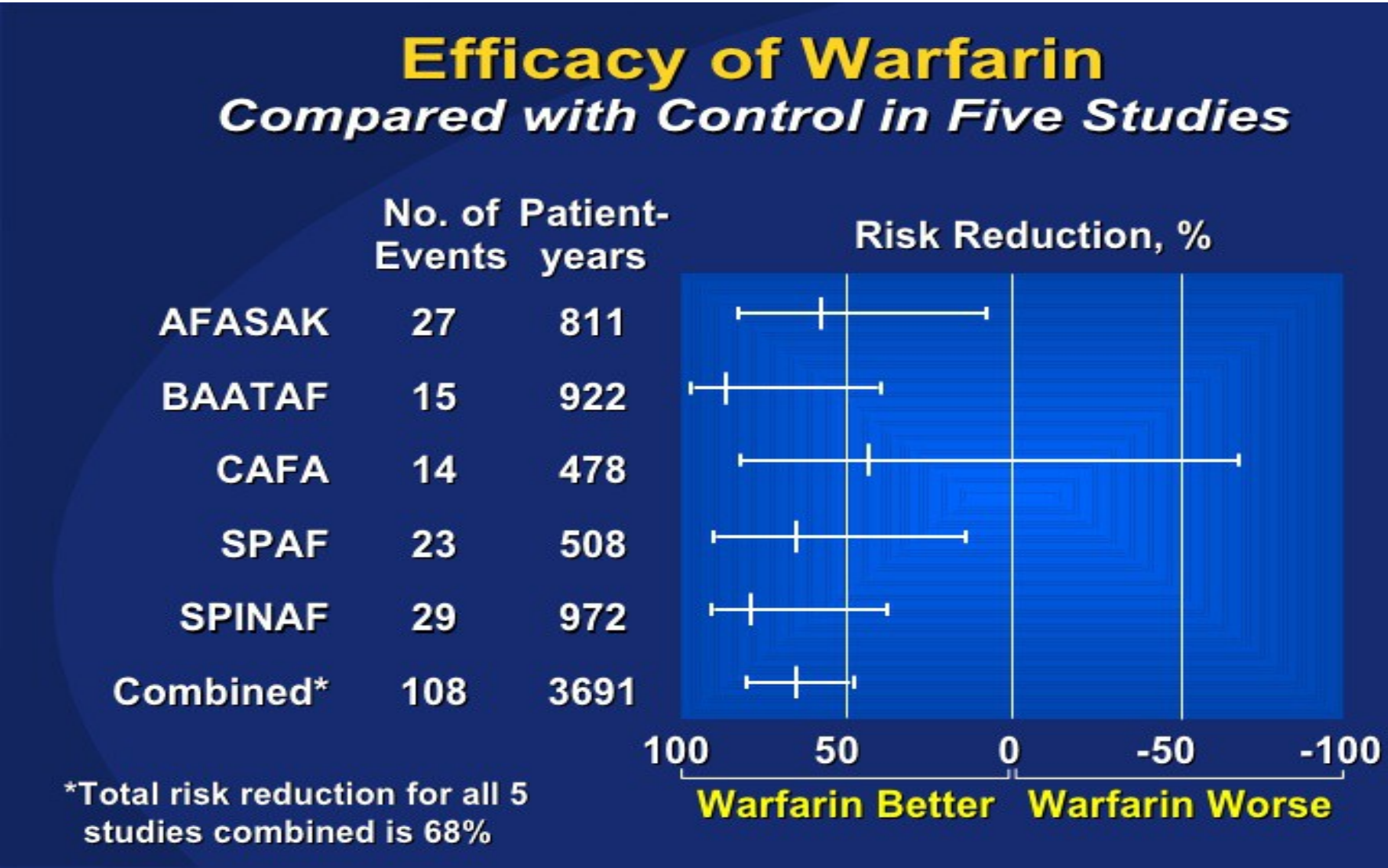
- Mechanism of action : It inhibit vita-K dependant synthesis of biologically active forms of calcium dependant clotting factor f2,f7,f9,f10 as well as regulatory factors protein c,s,z.
- Pharmacokinetics : RS warfarin, S warfarin 5 times potent than R warfarin, rapidly and completely absorbed from intestine, 99% plasma protein bound,half-life 2.5days
- Metabolism : R warfarin- CYP1A2 to 6-hydroxywarfarin, 8-hydroxywarfarin, S warfarin CYP2C9 to 7-hydroxywarfarin
- Excretion: Renal (92%)
- Routes of administration:oral or intravenous
- Bioavailability:100%

Фармакокинетика и дозировки

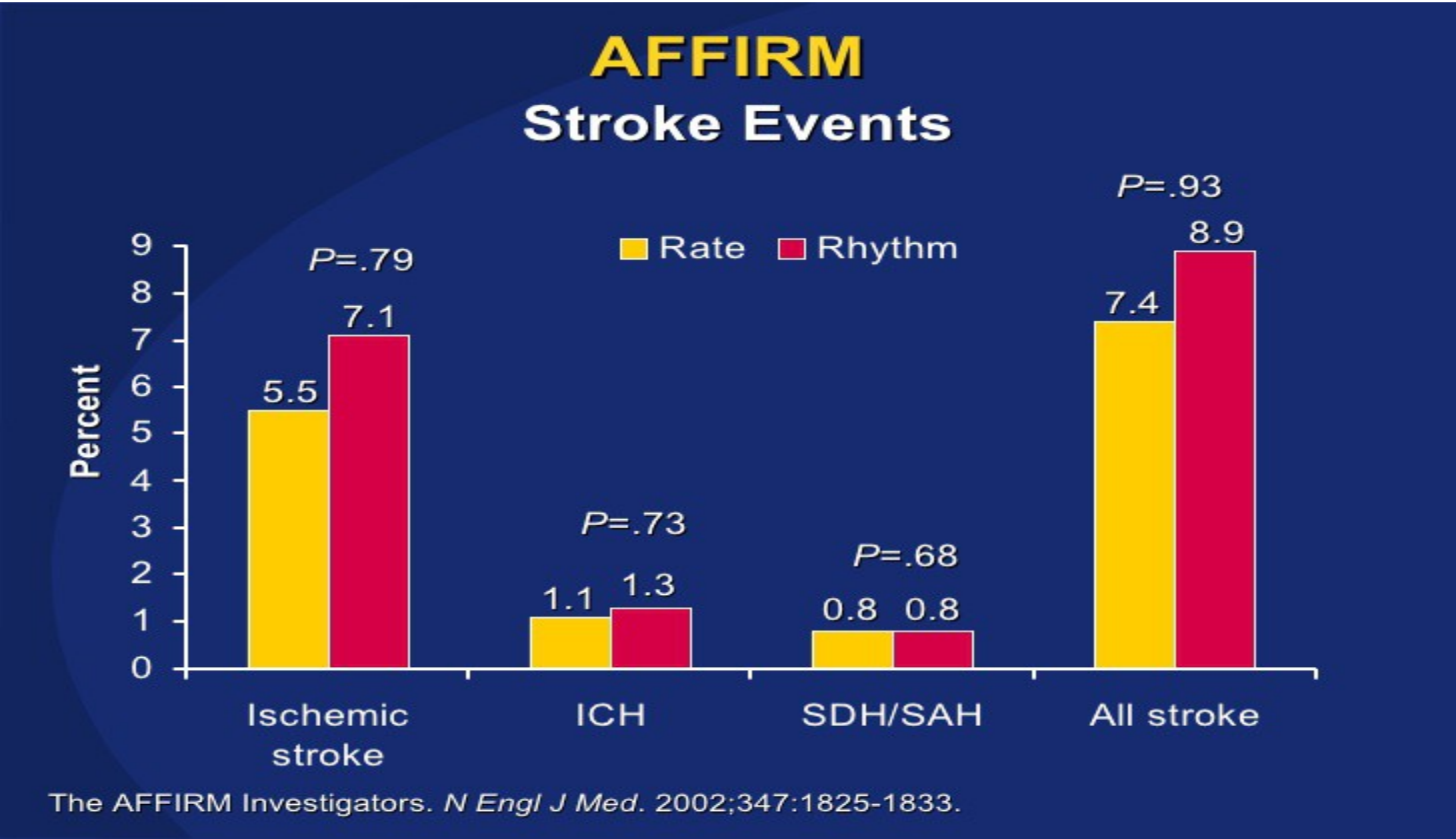
Pharmacokinetics & dosage of oral Anticoagulants :

DRUG	t½ (hr)	DURATION OF ACTION (days)	DOSAGE LOADING (mg)	DOSAGE MAINTENANCE(mg)
Bishydroxy coumarin	25-100	4-7	200 for 2 days	50-100
Warfarin sodium	36-48	3-6	10-15	2-10
Ethylbiscoum acetate	24	1-3	900	300-600
Aceno coumarol	18-24	2-3	8-12	2-4
Phenindione	5	1-3	200	50-100

Висока ефективност-”Златен Стандарт” !

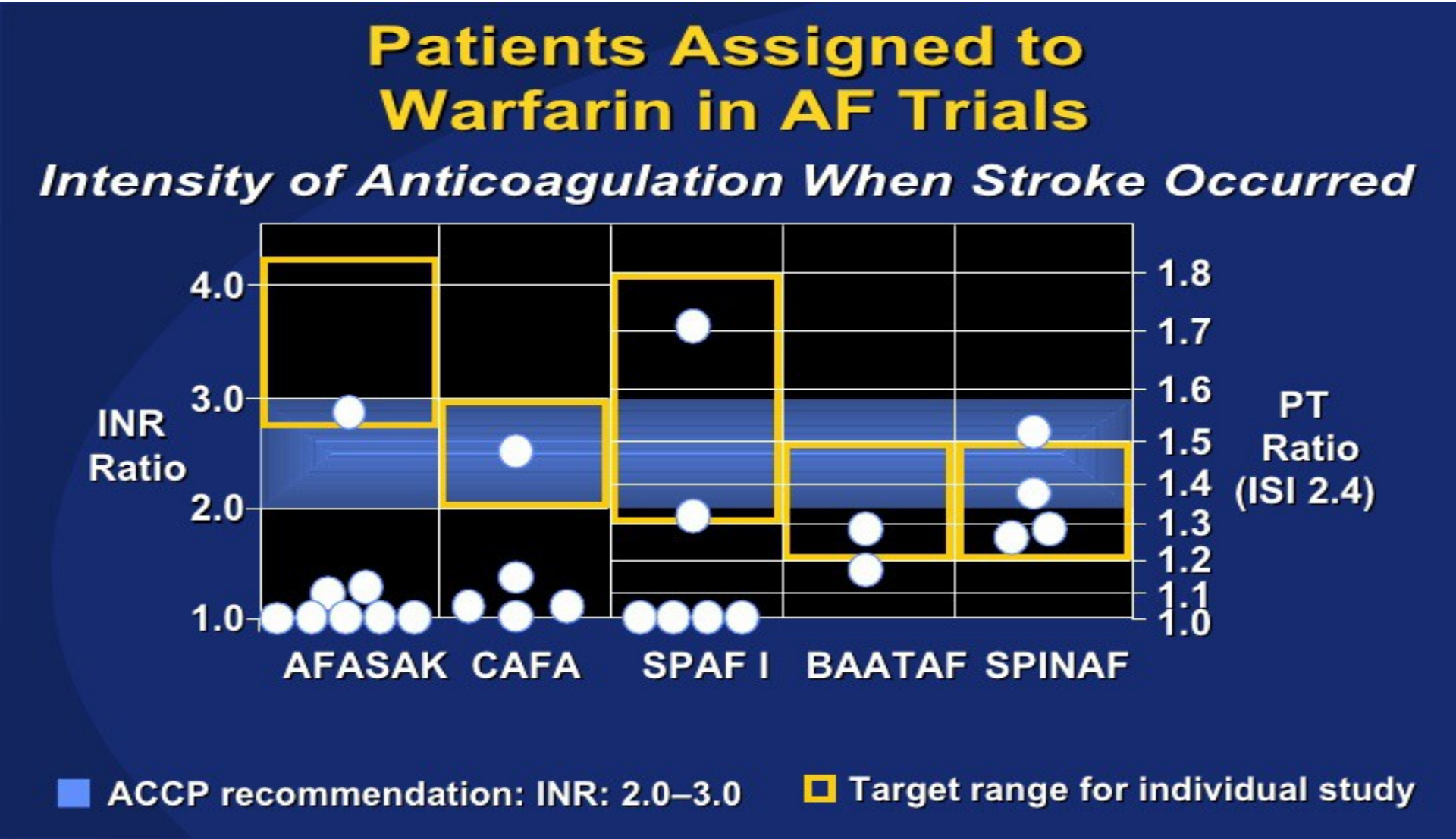


Висока ефективност !



The AFFIRM Investigators. *N Engl J Med*. 2002;347:1825-1833.

Но! Тесен терапевтичен прозорец!



Странични ефекти

- **ADVERSE EFFECTS :**

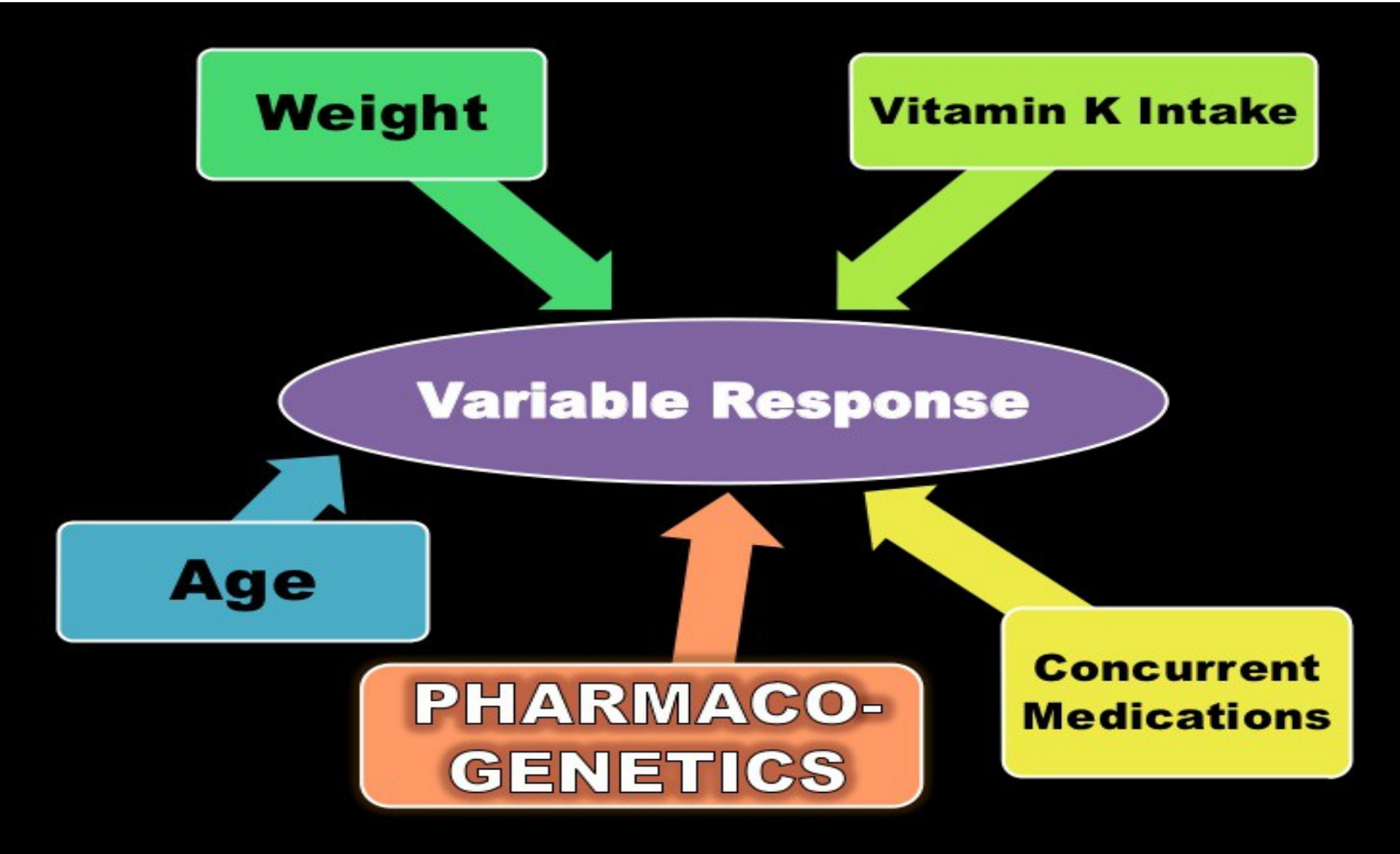
1. Bleeding- antidote: Vit.K
2. Teratogenic
3. Agranulocytosis
4. nephropathy
5. Hepatitis
6. orange urine

} by phenindione

Кървене!


DO NOT
ENTER
AMBULANCE
ONLY
TOBACCO-FREE
AMBULANCE
EMERGENCY
MEDICAL SERVICES
Each year, more than 40,000
patients are treated in the emergency
department for adverse events related
to warfarin use.
JAMA. 2006;296(15):1858-18

Вариабилен терапевтичен отговор!



Лекарствени взаимодействия

Table 34–2. Pharmacokinetic and Pharmacodynamic Drug and Body Interactions with Oral Anticoagulants.

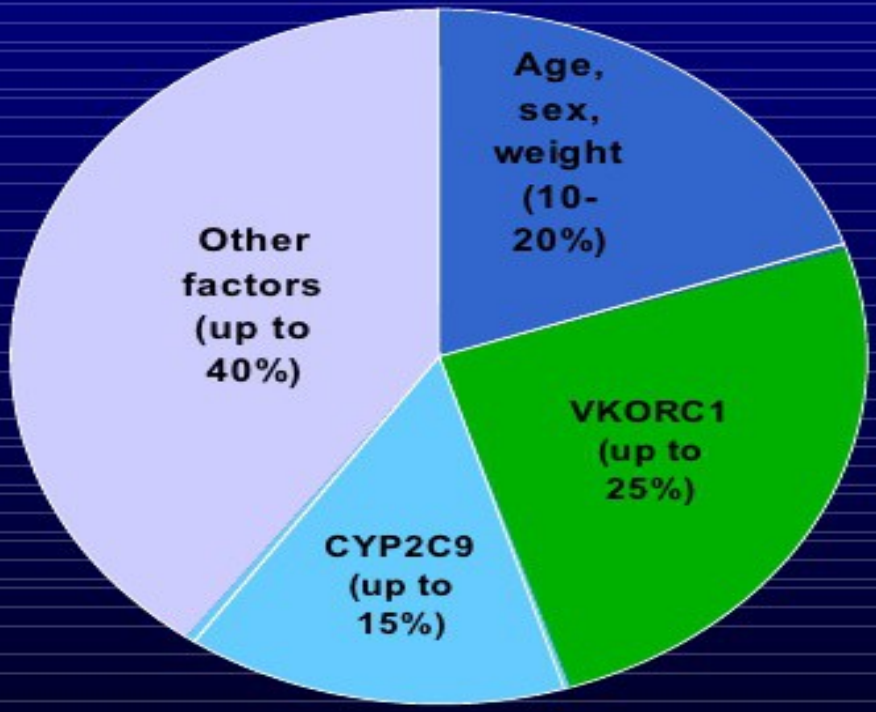
Increased Prothrombin Time		**Decreased Prothrombin Time**	
Pharmacokinetic	**Pharmacodynamic**	**Pharmacokinetic**	**Pharmacodynamic**
Amiodarone	**Drugs**	Barbiturates	**Drugs**
Cimetidine	Aspirin (high doses)	Cholestyramine	Diuretics
Disulfiram	Cephalosporins, third-generation	Rifampin	Vitamin K
Metronidazole[1]	Heparin		**Body factors**
Fluconazole[1]			Hereditary resistance
Phenylbutazone[1]	**Body factors**		Hypothyroidism
Trimethoprim-sulfamethoxazole	Hyperthyroidism		

[1] Stereoselectively inhibits the oxidative metabolism of the (*S*)-warfarin enantiomorph of racemic warfarin.

Фактори, определящи дозировките на витамин К -антагонистите

Factors that Correlate w/ Warfarin Dose

- Age
- Body surface area (BSA) or weight
- Amiodarone dose
- Other drugs (e.g. HMG CoA Reductase inhibitors)
- Target INR
- Race
- Sex
- Plasma vitamin K level
- Decompensated CHF or post-operative state
- The patient's genetic status with regard to polymorphisms



Кой риск е по-голям?

Thrombo-embolic risk stratification

Balancing the risks and benefits of warfarin:

No warfarin if:

HAS-BLED > $CHADS_2$ or

HAS-BLED >2 in $CHADS_2$ 0/1

HAS-BLED >3 in $CHADS_2$ 2

Using this algorithm would reduce >10% of major bleeds

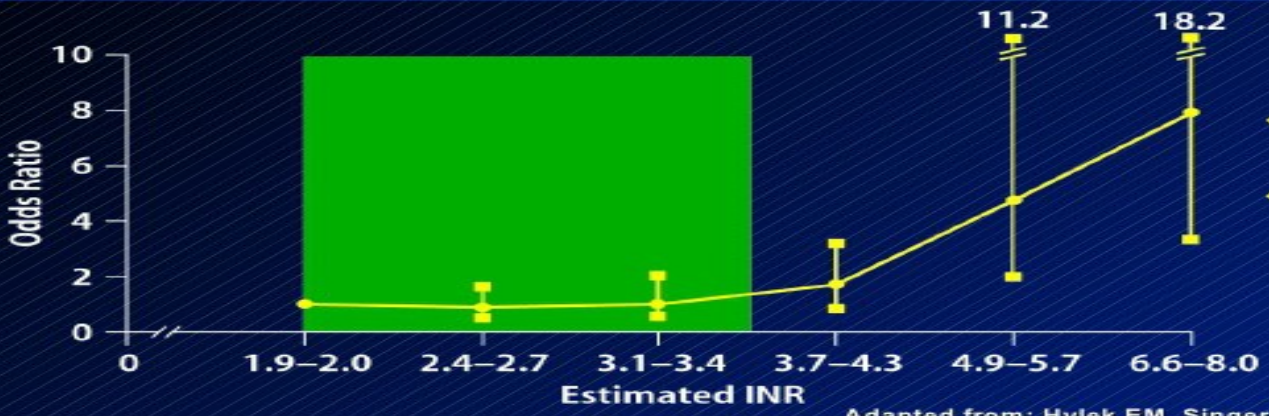
Риск от кървене и тромбоза при определени клинични ситуации

Examples of Low & High Risk Invasive Procedures & Clinical Conditions

Risk of Thrombosis	Risk of Bleeding: Low	Risk of Bleeding: High
Low	Dental; cutaneous biopsies; open procedures; cataracts	Major thoracic, abdominal, or pelvic surgery; CNS surgery; polypectomy via colonoscopy
Low	AF; valvular heart disease ± aortic prosthesis; old DVT/PE	AF; valvular heart disease ± aortic prosthesis; old DVT/PE
High	Dental; cutaneous biopsies; open procedures; cataracts	Major thoracic, abdominal, or pelvic surgery; CNS surgery; polypectomy via colonoscopy
High	Prosthetic valves, esp. in mitral position; AF + history of CVA; very recent DVT/PE	Prosthetic valves, esp. in mitral position; AF + history of CVA; very recent DVT/PE

Тесен терапевтичен прозорец- стриктен контрол на INR

Risk of Intracranial Hemorrhage in Outpatients

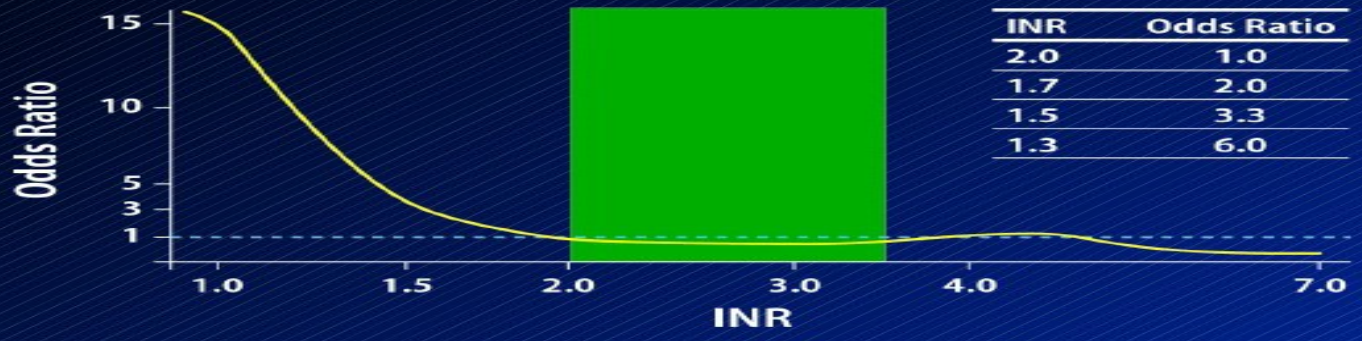


- PTR above 2.0 (INR of 3.7 to 4.3) increases the risk of bleeding
- The estimated odds ratio of subdural hemorrhage increased 7.6 fold as the PTR increased from 2.0 to 2.5 (INR 3.7–4.3 to 5.7–6.8)

Adapted from: Hylek EM, Singer DE, Ann Int Med 1994;120:897-902

Hylek, et al, studied the risk of intracranial hemorrhage in outpatients treated with warfarin. They determined that an intensity of anticoagulation expressed as a prothrombin time ratio (PTR) above 2.0 (roughly corresponding to an INR of 3.7 to 4.3) resulted in an increase in the risk of bleeding.

Lowest Effective Intensity for Warfarin Therapy for Stroke Prevention in Atrial Fibrillation



INR	Odds Ratio
2.0	1.0
1.7	2.0
1.5	3.3
1.3	6.0

INR below 2.0 results in a higher risk of stroke

Hylek EM, et al. NEJM 1996;335:540-546.

Симптоми на предозиране

Signs of Warfarin Overdosage

- Any unusual bleeding:
  - Blood in stools or urine
  - Excessive menstrual bleeding
  - Bruising
  - Excessive nose bleeds/bleeding gums
  - Persistent oozing from superficial injuries
  - Bleeding from tumor, ulcer, or other lesion

Поведение при висок INR с или без малко кървене

Managing Patients with High INR Values/ Minor or No Bleeding

Clinical Situation	Guidelines
INR >therapeutic range but <5.0, no clinically significant bleeding, rapid reversal not indicated for reasons of surgical intervention	Lower the dose or omit the next dose; resume warfarin therapy at a lower dose when the INR approaches desired range If the INR is only minimally above therapeutic range, dose reduction may not be necessary
INR >5.0 but <9.0, no clinically significant bleeding	Patients with no additional risk factors for bleeding; omit the next dose or two of warfarin, monitor INR more frequently, and resume warfarin therapy at a lower dose when the INR is in therapeutic range Patients at increased risk of bleeding: omit the next dose of warfarin, and give vitamin K_1 (1.0 to 2.5 mg orally) Patients requiring more rapid reversal before urgent surgery or dental extraction: vitamin K_1 (2–4 mg orally); if the INR remains high at 24 h, an additional dose of 1–2 mg

Поведение при висок INR и голямо кървене

Managing Patients with High INR Values/ Serious Bleeding

Clinical Situation	Guidelines
INR >9.0, no clinically significant bleeding	Vitamin K_1 (3–5 mg orally); closely monitor the INR; if the INR is not substantially reduced by 24–24 h, the vitamin K_1 dose can be repeated
	Serious bleeding, or major warfarin overdose (e.g., INR >20.0) requiring very rapid reversal of anticoagulant effect: Vitamin K_1 (10 mg by slow IV infusion), with fresh plasma transfusion or prothrombin complex concentrate, depending upon urgency; vitamin K_1 injections may be needed q12h
Life-threatening bleeding or serious warfarin overdose	Prothrombin complex concentrate, with vitamin K_1 (10 mg by slow IV infusion); repeat if necessary, depending upon the INR
Continuing warfarin therapy indicated after high doses of vitamin K_1	Heparin, until the effects of vitamin K_1 have been reversed, and patient is responsive to warfarin

За и против вит. К - антагонистите

Warfarin

Why We Hate It!	Maybe not so bad!
Narrow Therapeutic Window	Tremendously large experience
Sensitive to changes in diet	We know everything about it (Vitamin K-Dependent Factors: II, VII, IX, X, C, S)
Slow to act, very long half-life	Simple, standardized test for functional level (INR).
Numerous drug interactions	Reversal agents highly effective and readily available.
Wide range in therapeutic doses, difficult to predict.	Virtually no side effects except for bleeding.
Treacherous to use in cancer patients!	Cheap!

WARFARINDOSING

www.WarfarinDosing.org

- Home
- Dosing
  - Therapeutic Estimate
  - 3 Days: Refinement
  - 30 Days: Outcome
- Clinical Prediction Rule
- Patient Education Links
- Contact/ Feedback
- Online Resources

Doc:
Pat :
Version 1.0

Welcome to **WarfarinDosing.org**, a Web site to help doctors and other clinicians begin warfarin therapy by estimating the therapeutic dose in patients new to warfarin. Estimates are based on clinical factors and genotypes of two genes: cytochrome P450 2C9 and vitamin K epoxide reductase.

If you're new to WarfarinDosing.org we recommend that you enter "0" in the *patient number* field and then enter mock clinical and genetic information to see how estimates of the warfarin dose vary. Recommendations on this website are based on data from over 1000 patients. If all information is entered correctly, the initial estimate of therapeutic dose explains 53% of the variability in warfarin dose.

Intial Information

Please provide your information :

(•) New Patient ( ) Existing Patient

Patient Identifier* :

Days on warfarin of therapy so far : 0

(•) New to this site ( ) Returning to the site

Clinician Email* :

> CONTINUE

INR тест у дома!

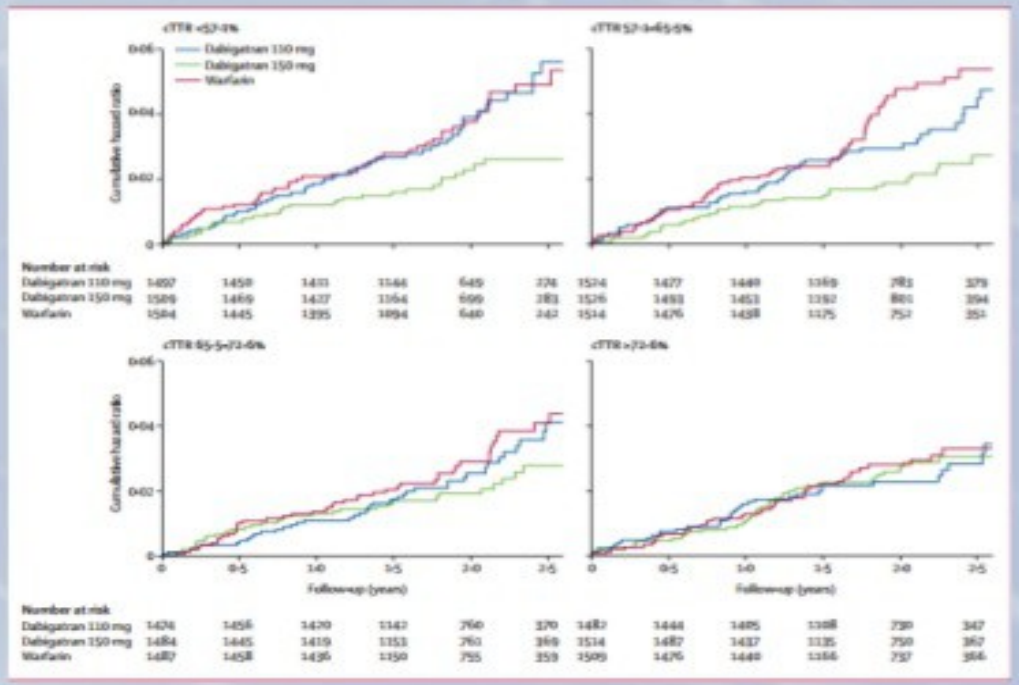
Възможни алтернативи

NOACs

Drug	Brand name	Target	Peak (h)	Half-life (h)	Bio	Renal excr. (%)	Drug interactions
Dabigatran	Pradaxa®	Factor IIa	1.5	14 - 17	8%	> 80%	P-glycoprotein
Rivaroxaban	Xarelto®	Factor Xa	2 - 3	7 - 11	80%	33%	CYP3A4 P-glycoprotein
Apixaban	Eliquis ®	Factor Xa	3	8 – 14	66%	25%	CYP3A4 P-glycoprotein
Edoxaban	Lixiana ®	Factor Xa	4	8 - 11	45%	35%	CYP3A4 P-glycoprotein

Наистина ли НОАК са по-ефективни?

Are NOACs really more effective?

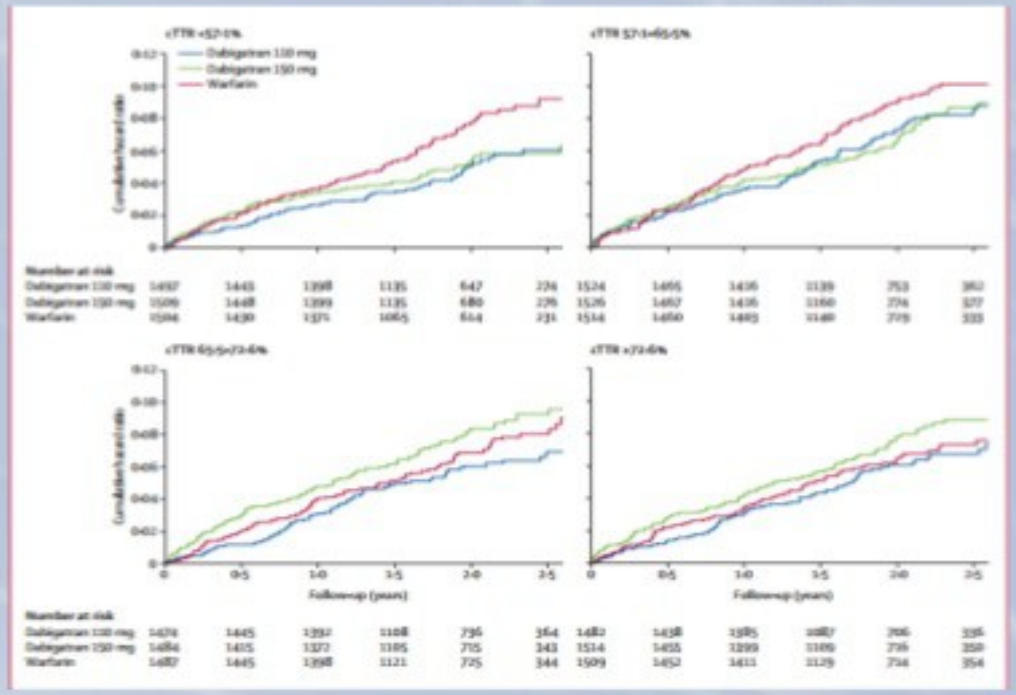


Wallentin L. Lancet. 2010 Sep 18;376(9745):975-83.

OHRI IRSO

Наистина ли НОАК са по-безопасни?

Are NOACs really safer?



Wallentin L. Lancet. 2010 Sep 18;376(9745):975-83.

OHRI IRSO

Има ли повишен риск от ОКС при НОАК?

New or unknown side effects?

MI or ACS

Study, y	Dabigatran, No. ACEv	Dabigatran, No. No Event	Control, No. ACEv	Control, No. No Event	Odds Ratio (95% CI)
RE-NOVATE,[16] 2007	13	2296	9	1133	0.71 (0.30-1.67)
RE-MODEL,[17] 2007	10	1372	4	690	1.26 (0.39-4.02)
PETRO,[18] 2007	2	443	0	70	0.79 (0.04-16.73)
RE-LY original,[2,3] 2009	175	11916	63	5959	1.39 (1.04-1.86)
RE-COVER,[19] 2009	4	1269	2	1264	1.99 (0.36-10.90)
RE-DEEM,[14] 2011	32	1458	4	313	1.72 (0.60-4.89)
RE-NOVATE II,[15] 2011	1	1009	1	1002	0.99 (0.06-15.90)
FE model					1.33 (1.03-1.71)

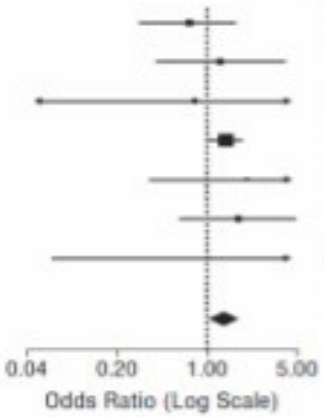


Figure 2. Risk of myocardial infarction and acute coronary syndrome across 7 studies, including original Randomized Evaluation of Long-term Anticoagulant Therapy (RE-LY) results. ACEv indicates acute coronary events; FE, fixed effects; PETRO, Prevention of Embolic and Thrombotic Events in Patients With Persistent AF Study; rectangles, odds ratios; limit lines, 95% CIs; diamond, overall odds ratio and 95% CI; and arrows, 95% CIs that exceed the limits of the graph (0.04-5.00).

OHRI IRSO

Uchino K et al. Arch Intern Med 2012;172(5):397-402.

НОАК може би имат предимства,но само при не-клапно ПМ!

- **FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves**
- Safety Announcement
  Additional Information for Patients
  Additional Information for Healthcare Professionals
  Data Summary

U.S. Food and Drug Administration
Protecting and Promoting Your Health

U.S. Food and Drug Administration
Protecting and Promoting Your Health

[12-19-2012] The U.S. Food and Drug Administration (FDA) is informing health care professionals and the public that the blood thinner (anticoagulant) Pradaxa (dabigatran etexilate mesylate) should not be used to prevent stroke or blood clots (major thromboembolic events) in patients with mechanical heart valves, also known as mechanical prosthetic heart valves. A clinical trial in Europe (the RE-ALIGN trial)1 was recently stopped because Pradaxa users were more likely to experience strokes, heart attacks, and blood clots forming on the mechanical heart valves than were users of the anticoagulant warfarin. There was also more bleeding after valve surgery in the Pradaxa users than in the warfarin users.

Достатъчно добри ли са НОАК при всички пациенти?

Are NOACs good anticoagulants?

Other high risk populations

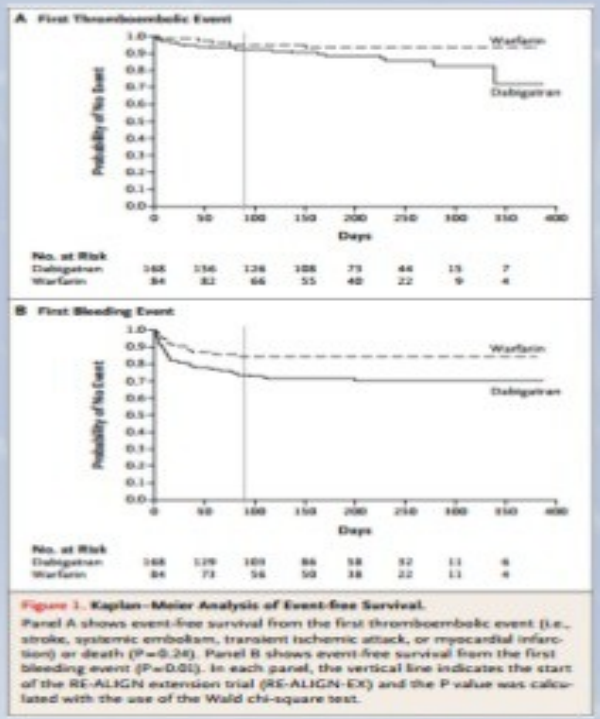


Figure 1. Kaplan–Meier Analysis of Event-free Survival.
Panel A shows event-free survival from the first thromboembolic event (i.e., stroke, systemic embolism, transient ischemic attack, or myocardial infarction) or death (P=0.24). Panel B shows event-free survival from the first bleeding event (P=0.01). In each panel, the vertical line indicates the start of the RE-ALIGN extension trial (RE-ALIGN-EX) and the P value was calculated with the use of the Wald chi-square test.

- Mechanical heart valves
- Trial terminated early after enrolling 252 patients
  - Dabigatran 150, 220 or 300 mg PO BID
  - Warfarin
- Increased rates of thromboembolic and bleeding complications with NOACs

OHRI IRSO

Eikelboom JW et al N Engl J Med. 2013 Sep 26;369(13):1206-14.

Какво да правим при пациенти на НОАК и нужда от спешна операция?

Ms MT

- Ms. MT is on dabigatran 150 mg po bid. Her CrCl is 35 cc/min. She is fell and presented to ER with left hip fracture
- Basic coagulation parameters
  1. Thrombin time > 60 s
  2. INR normal
  3. PTT 45 s
- When can the surgery be done? Keep in mind that morbidity/mortality is increased if delayed by > 48 hours
  - Does it manner if the anesthesiologist want to do a spinal?

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Какво да правим при пациенти на НОАК и нужда от тромболиза?

Ms MT

- Ms. MT is on rivaroxaban 20 mg po daily. Her CrCl is 45 cc/min. She presented to ER with new acute stroke symptoms. Investigations showed that she would be a candidate for thrombolytics.
- Last dose of rivaroxaban was 12 hours ago.
- Basic coagulation parameters
  1. Thrombin time normal
  2. INR normal
  3. PTT normal
  4. Anti-Xa is 0.4
- Can she receive thrombolytics?

Заключение

- **Антагонистите на вит. К си остават златен стандарт в превенцията на тромбоемболичните усложнения. Терапевтичният опит с тях е вече над 60 години при възможно най-широк кръг от индикации.**
- **Всички нови антикоагуланти са сравнявани с тях при хипотеза “нон инфериорити”. При поддържане на достатъчно дълго време в терапевтичния прозорец витамин. К антагонистите са еквипотентни на НОАК.**
- **Добрата съпричастност от страна на пациента и лекуващия лекар и стриктното следене на ИНР са гаранция за дългогодишна ефективна и безопасна употреба на вит.К антагонистите.**
- **Възможността за лесно мониториране на ефекта в много случаи е предимство , а не недостатък! Все още има много неизвестни при периоперативното маниториране и поведение при употреба на НОАК.**
- **Трудните и най- рискови клинични състояния като пациенти с клапни пороци и изкуствени клапи, пациентите с ХКМП и антифосфолипиден синдром, както и бремнните си остават “запазена територия” за вит. К антагонистите!**
- **Вит. К антагонистите имат евтин и достъпен антидот и ясни алгоритми за поведение при кървене и предозиране.**
- **Вит. К антагонистите са значително по-евтини!**

Благодаря за вниманието!

EDITORIAL PROGRAMS

Novel Oral Anticoagulants vs Warfarin: The Truth is Relative

Dr John Mandrola calculates the absolute risk reductions from recent meta-analyses comparing the novel anticoagulants with warfarin and finds that they are not as impressive as the widely reported relative risk reductions.

theheart.org on Medscape, December 18, 2013