Basic Science Summer School

European Heart House, Sophia Antipolis, France

18 June 2017 – 22 June 2017

Session III

Thrombosis and coagulation

June 19 2017

13:30-15:00

Novel oral anticoagulants: mechanisms of action and therapeutic indications

Raffaele De Caterina

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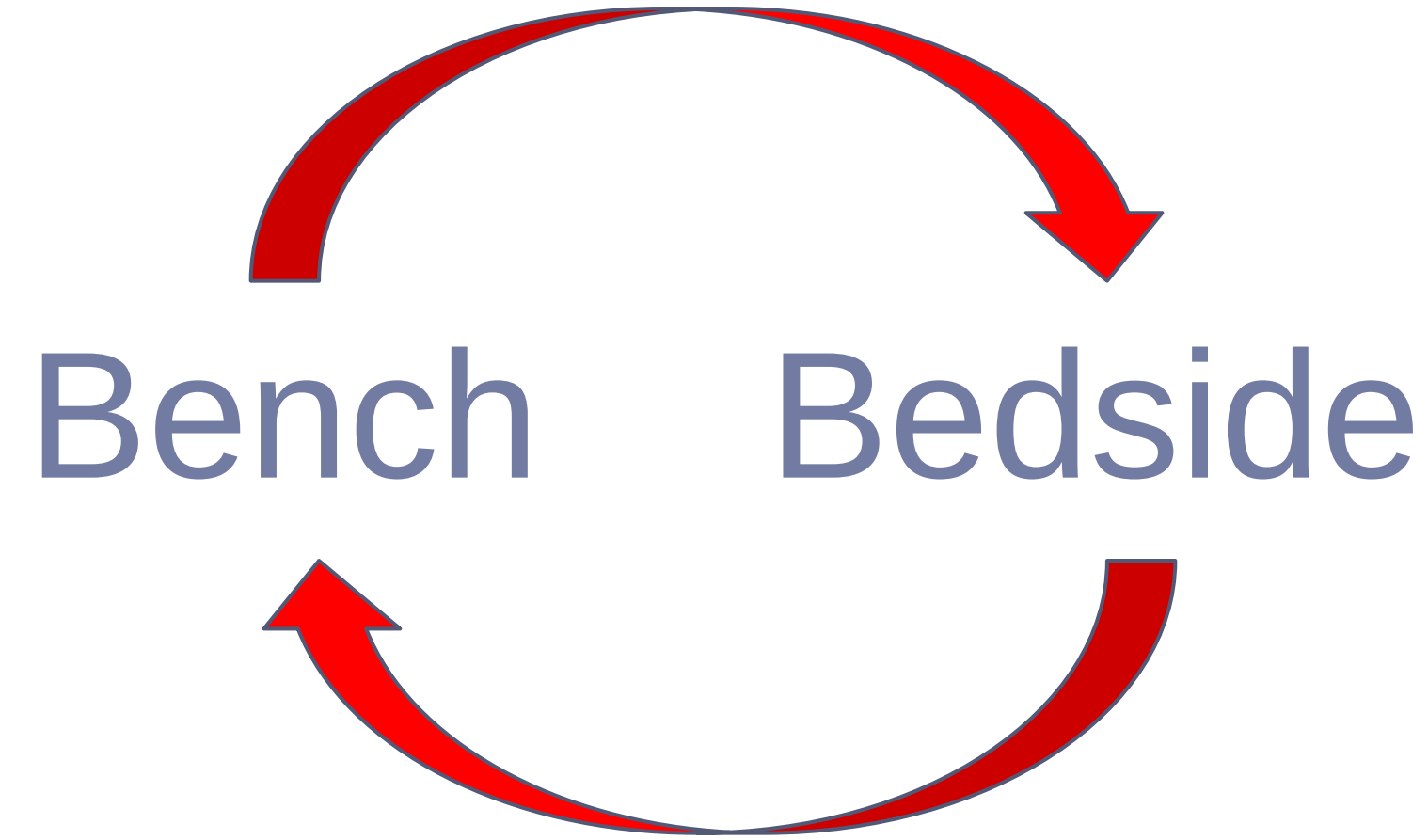
"G. Monasterio" Foundation – Pisa, Italy

June 19, 2017 – 14:15-15:00

Prof. Raffaele De Caterina
Conflicts of Interest

- Co-author ESC Guidelines on Atrial Fibrillation 2010-2012
- Steering Committee member, National Coordinator for Italy, and Co-author of APPRAISE-2, ARISTOTLE, AVERROES, ENGAGE-AF, Re-DUAL PCI
- Fees, honoraria and research funding from Sanofi-Aventis, Boehringer Ingelheim, Bayer, BMS/Pfizer, Daiichi-Sankyo, Novartis, Merck

Why talking about clinical trials to basic scientists



Agenda

- The history of oral anticoagulation
- The NOAC revolution
- Highlights from clinical trials: from bedside to bench
  - Once day vs twice day
  - Intracranial hemorrhage
  - New treatment indications

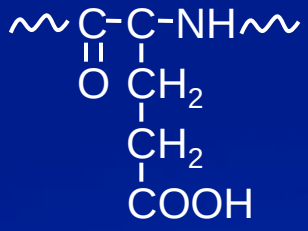
Agenda

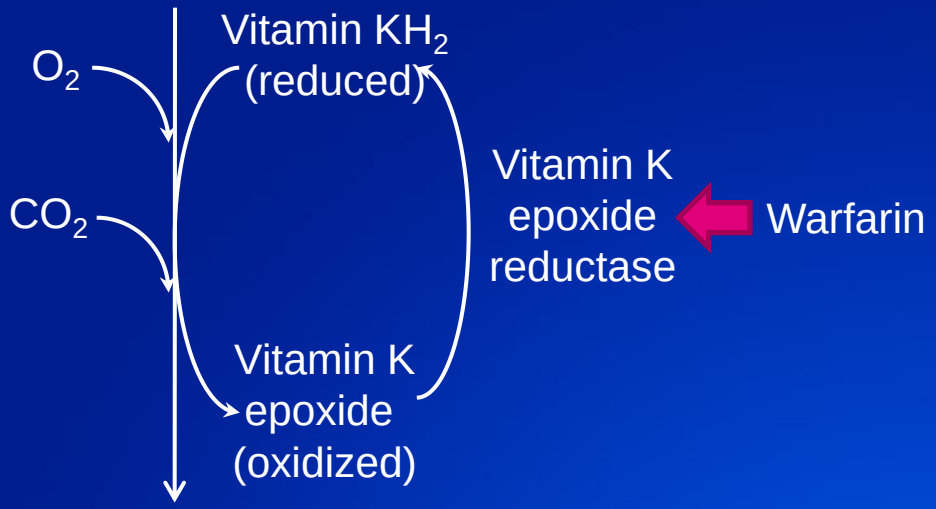
- The history of oral anticoagulation

Oral anticoagulants: warfarin

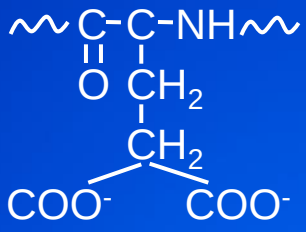
- Dosing
  - Oral; varies, depending on coagulation monitoring tests
- Monitoring
  - Usually monthly, testing INR
  - INR target of 2.5, range 2.0–3.0
- Adverse events
  - Bleeding, bruising
  - Many significant and potential food and drug interactions
- Unique advantage
  - Only anticoagulant available for long-term use

Precursors of clotting Factors: prothrombin, VII, IX, X, protein C, protein S





Active clotting Factors: prothrombin, VII, IX, X, protein C, protein S



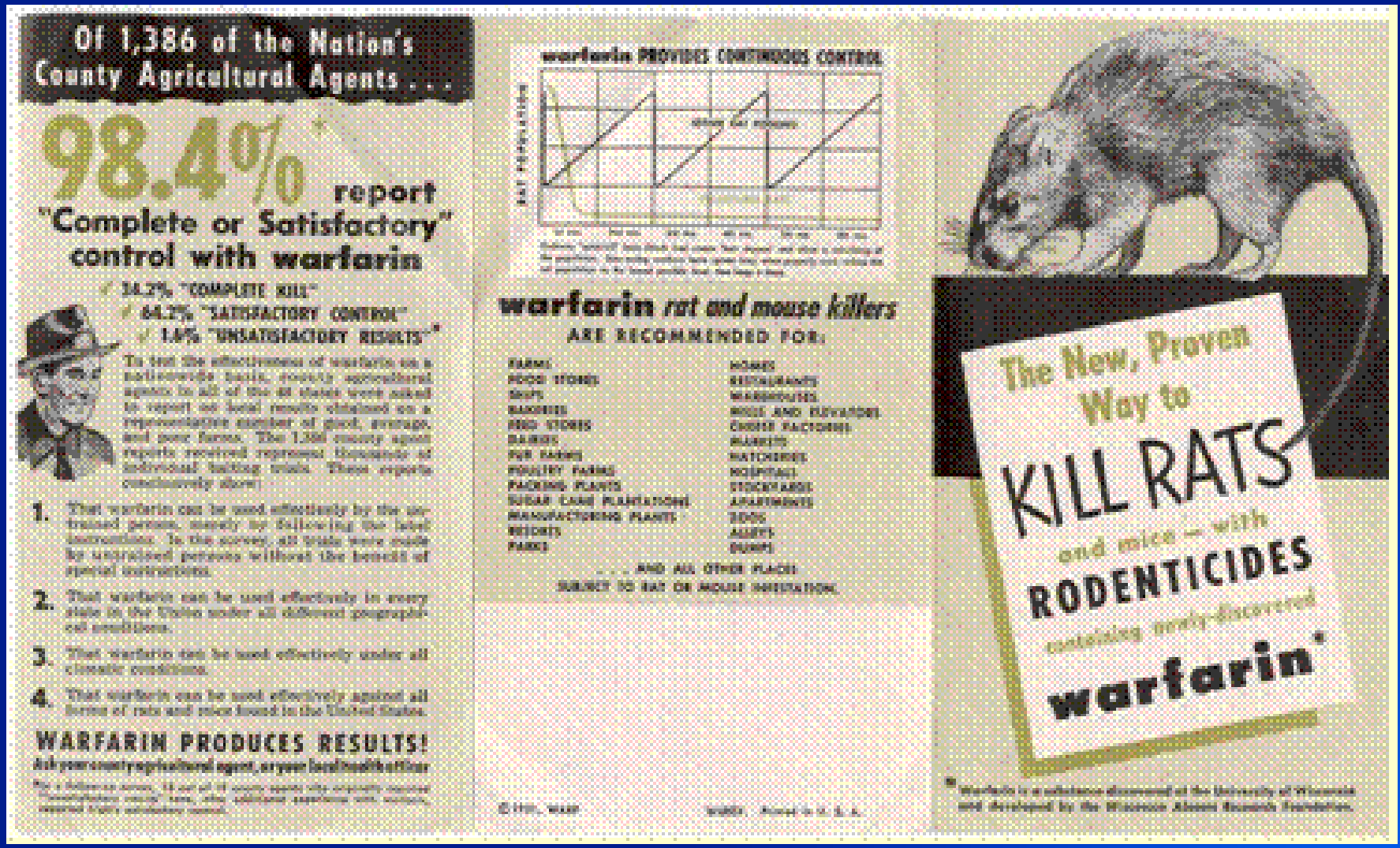
Harvey & Champe. *Pharmacology* 1997

The discovery of warfarin

- The sweet clover problem
- Link's isolation of the oral anticoagulant
- From test tube to rat poison – Karl Link
- From rat poison to clinical application

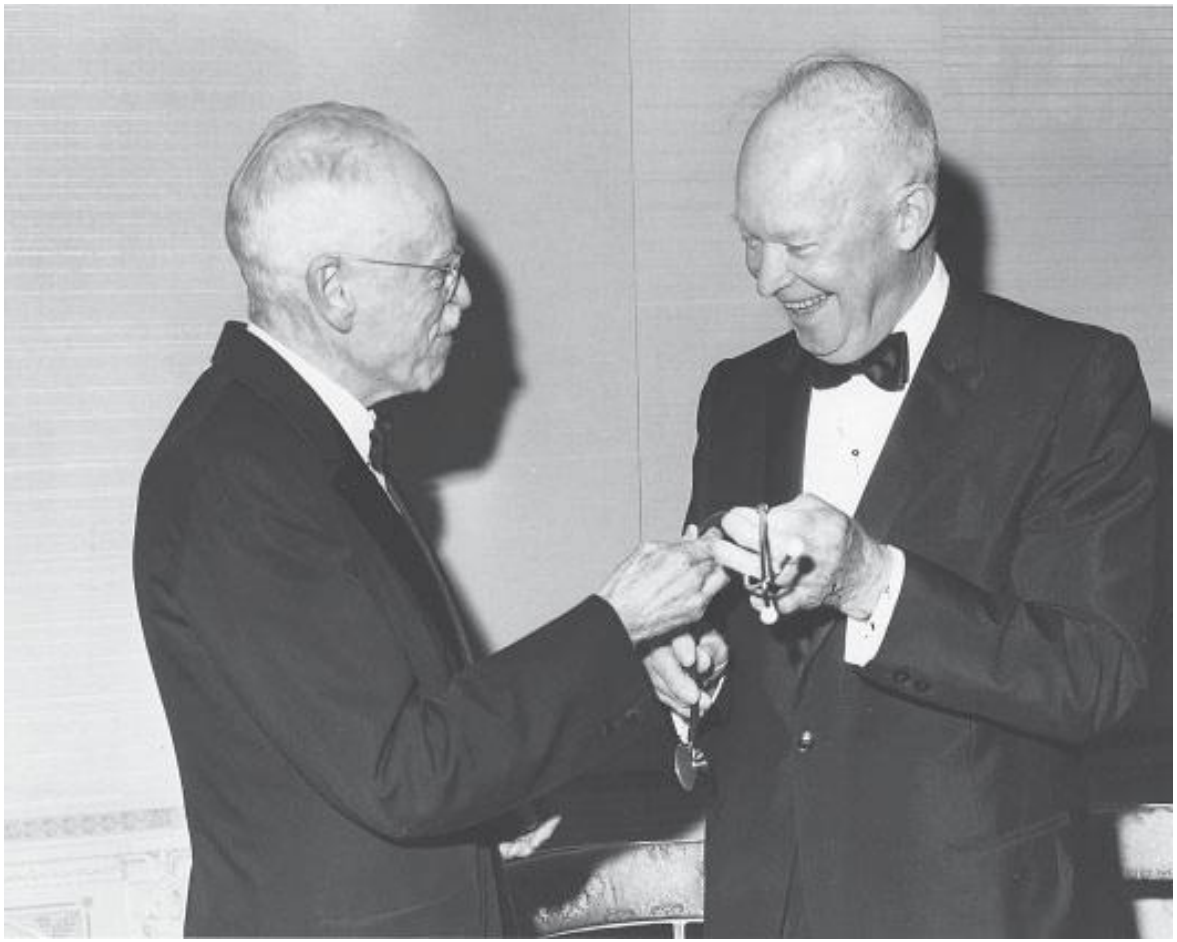
WARF

1951 advertisement for warfarin



Eisenhower's Billion-Dollar Heart Attack — 50 Years Later

Franz H. Messerli, M.D., Adrian W. Messerli, M.D., and Thomas F. Lüscher, M.D.

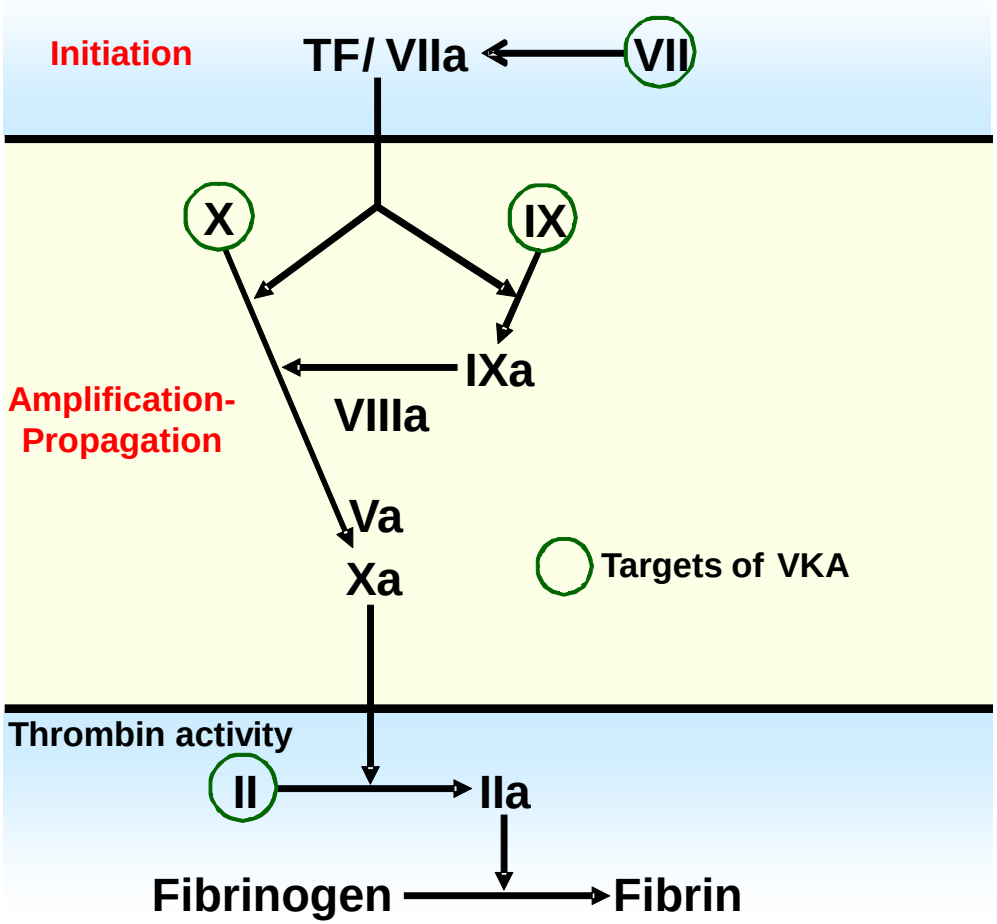


n engl j med 353;12
www.nejm.org
september 22, 2005

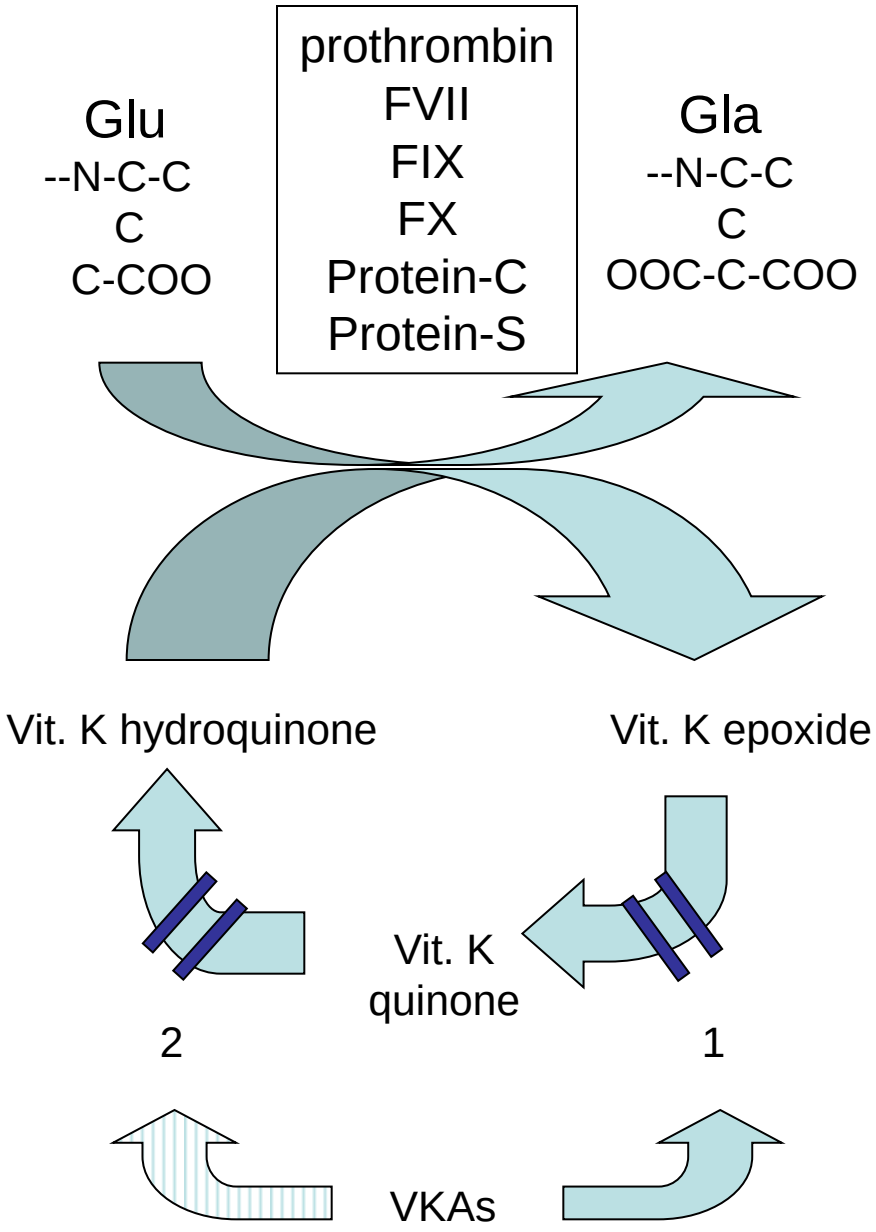
Dr. Paul Dudley White and Former President Dwight D. Eisenhower, 1963.

General mechanisms of coagulation and targets of anticoagulants (Section I)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease

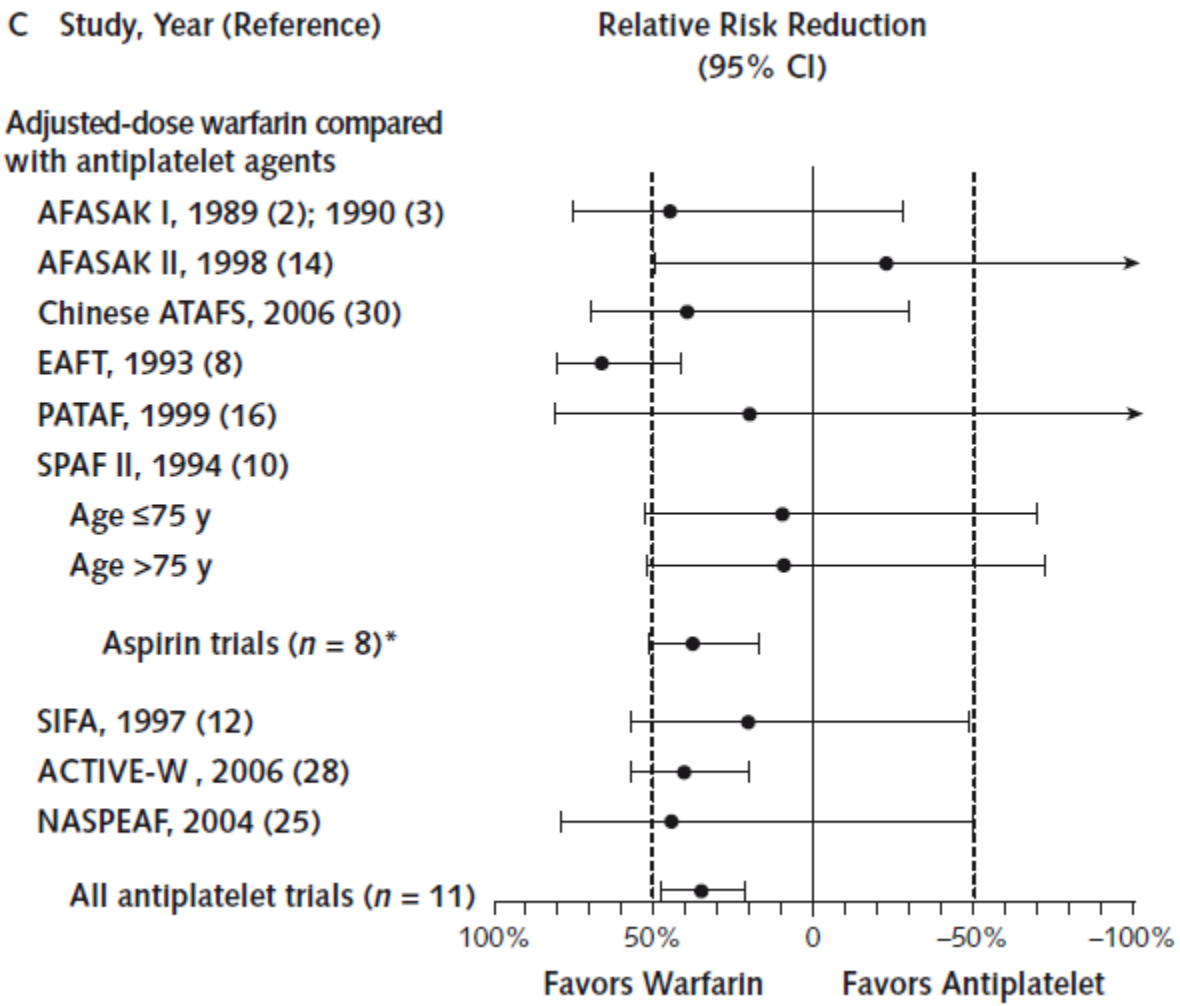


De Caterina R, Husted S, Wallentin L et al. Thromb Haemost, 2013, 109: 569–579



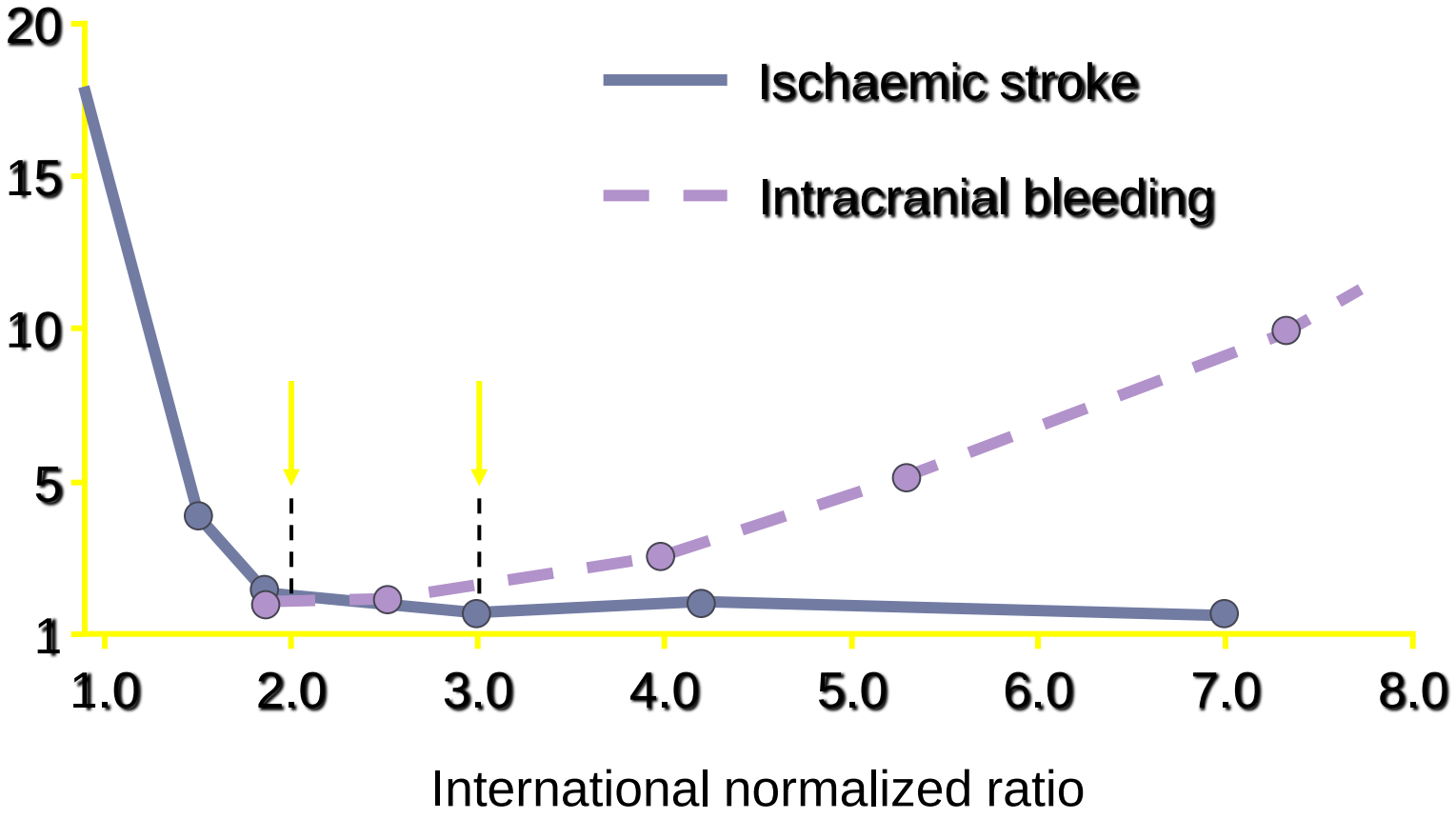
De Caterina R. et al, Thromb Haemost 2013; 110: 1087–1107

Antiplatelet drugs vs warfarin in stroke prevention in atrial fibrillation



Hart, R et al., *Ann Intern Med. 2007;146:857-867*

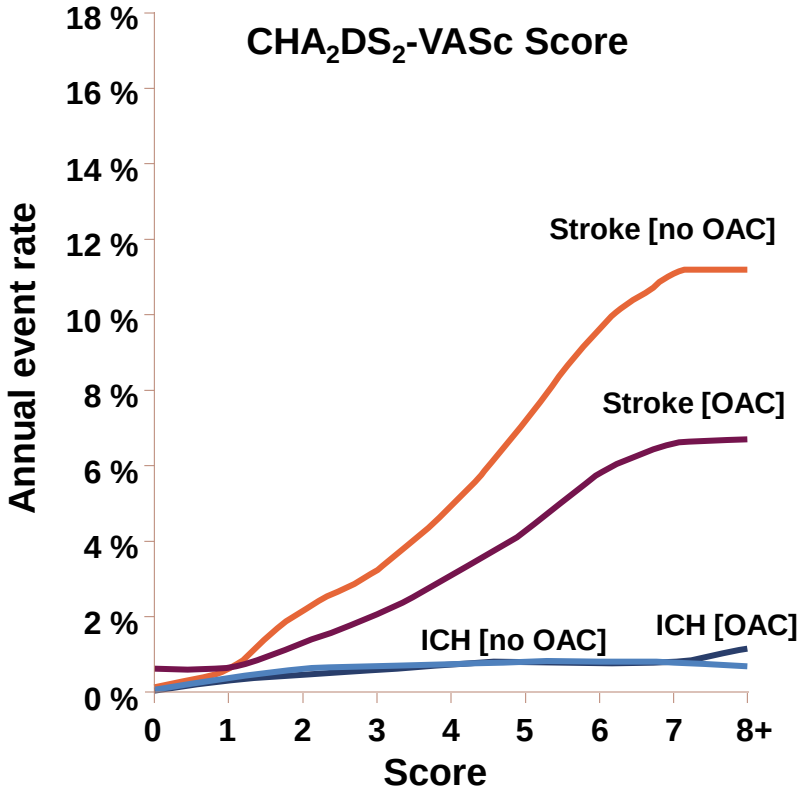
Adjusted odds ratios for ischaemic stroke and intracranial bleeding in relation to INR

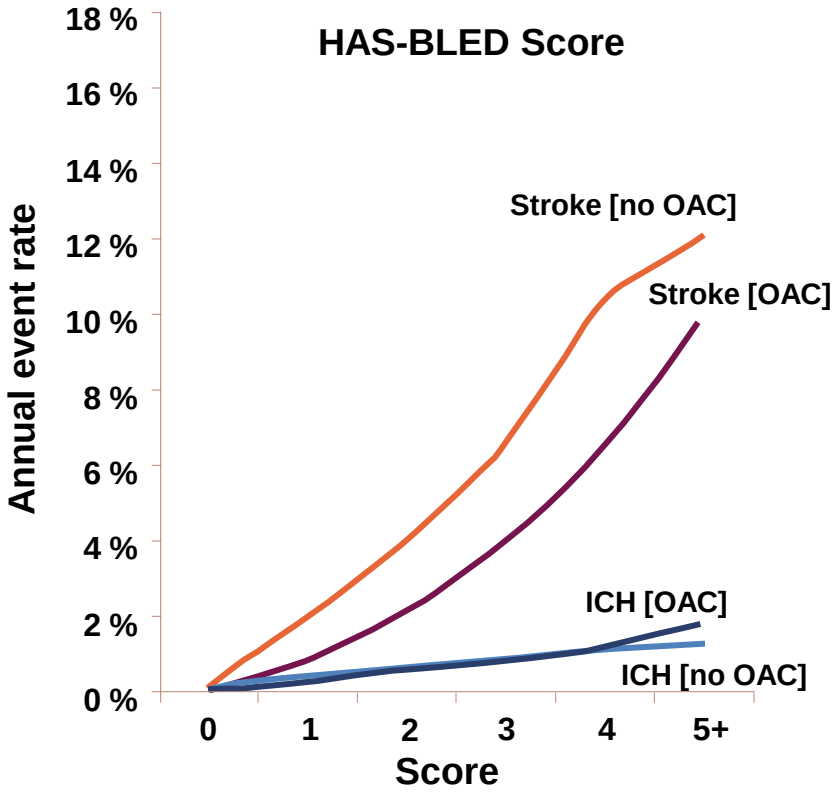


Adapted from Hylek EM. N Engl J Med 1996;335:540-6

The Risk of Ischemic Stroke "Without" OAC Exceeds the Risk of Intracranial Bleeding "With" OAC*

Relation between risk scores and annual event rates of ischemic stroke and ICH in relation to use of oral anticoagulation in 159,013 Swedish AF patients followed up for 1.5±1.1 years (2005–2008)





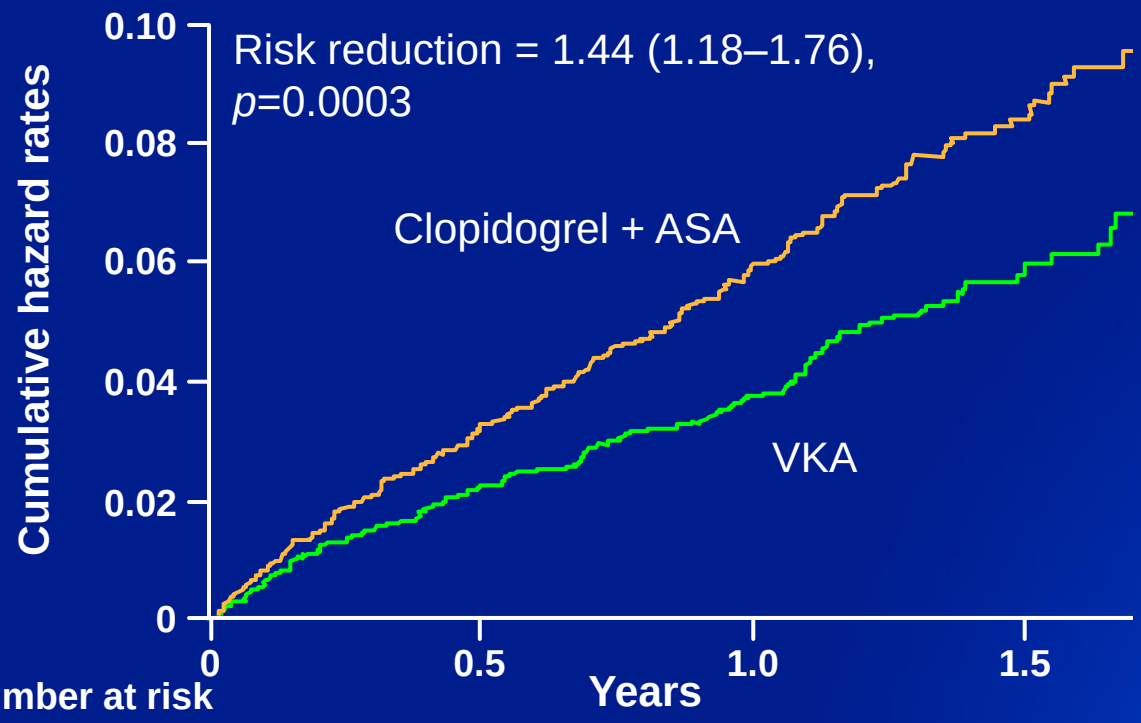
*Except those with a very low risk of stroke
OAC = oral anticoagulants; ICH = intracranial hemorrhage

1. Friberg L, et al. *Circulation.* 2012;125:2298-2307.

AF: ACTIVE-W trial

- No benefit from adding clopidogrel to ASA vs VKA

Cumulative risk of primary outcome



Number at risk				
Clopidogrel + ASA	3,335	3,152	2,389	927
Oral VKA	3,371	3,221	2,458	924

- Stopped early
- Efficacy
  - VKA: 165 (3.93%/year)
  - Clopidogrel/ASA: 234 (5.5%/year)
- Safety
  - No significant difference in major haemorrhage rates
  - VKA: 2.2%
  - Clopidogrel/ASA: 2.4%

ACTIVE Writing Group. *Lancet* 2006; Hohnloser. *US Cardiovascular Disease* 2007

Warfarin: contraindications

- Pregnancy
  - Associated with developmental abnormalities
- Threatened abortion, eclampsia and pre-eclampsia
- Recent surgery
  - CNS; eye; traumatic surgery, resulting in large open surfaces
- Bleeding tendencies associated with active ulceration or overt bleeding
  - GI, GU or RT
  - Cerebrovascular haemorrhage aneurysms– cerebral, dissecting aorta
  - Pericarditis and pericardial effusions
  - Bacterial endocarditis
- Unsupervised patients with
  - Senility
  - Alcoholism
  - Psychosis, or
  - Other lack of patient co-operation
- Spinal puncture
- Any diagnostic or therapeutic procedures with potential for uncontrollable bleeding
- Miscellaneous
  - Major regional
  - Lumbar block anaesthesia
  - Malignant hypertension
  - Known warfarin hypersensitivity

CNS, central nervous system; GI, gastrointestinal; GU, genitourinary; RT, reproductive tract

www.rxlist.com/cgi/generic/warfarin_ad.htm

Warfarin: drug interactions

- Many drugs have the potential to interact with warfarin

Specific drugs reported

acetaminophen
alcohol
allopurinol
aminosalicylic acid
amiodarone HCl
argatroban
acetylsalicylic acid
atenolol
atorvastatin
azithromycin
bivalirudin
capecitabine
cefamandole
cefazolin
cefoperazone
cefotetan
cefoxitin
ceftriaxone
celecoxib
cerivastatin
chenodiol
chloramphenicol
chloral hydrate
chlorpropamide
cholestyramine
cimetidine
ciprofloxacin
cisapride
clarithromycin
clofibrate
COUMADIN overdose
cyclophosphamide
danazol
dextran
dextrothyroxine
diazoxide
diclofenac
dicumarol
diflunisal
disulfiram
doxycycline
erythromycin
esomeprazole
ethacrynic acid
ezetimibe
fenofibrate
fenoprofen
fluconazole
fluorouracil
fluoxetine
flutamide
fluvastatin
fluvoxamine
gefitinib
gemfibrozil
glucagon
halothane
heparin
ibuprofen
ifosfamide
indomethacin
influenza virus vaccine
itraconazole
ketoprofen
ketorolac
lansoprazole
lepirudin
levamisole
levofloxacin
levothyroxine
liothyronine
lovastatin
mefenamic acid
methimazole
methyldopa
methylphenidate
methylsalicylate
ointment (topical)
metronidazole
miconazole (intravaginal, oral, systemic)
moricizine hydrochloride
nalidixic acid
naproxen
neomycin
norfloxacin
ofloxacin
olsalazine
omeprazole
oxandrolone
oxaprozin
oxymetholone
pantoprazole
paroxetine
penicillin G, intravenous
pentoxifylline
phenylbutazone
phenytoin
piperacillin
piroxicam
pravastatin
prednisone
propafenone
propoxyphene
propranolol
propylthiouracil
quinidine
quinine
rabeprazole
ranitidine
rofecoxib
sertraline
simvastatin
stanozolol
streptokinase
sulfamethizole
sulfamethoxazole
sulfinpyrazone
sulfisoxazole
sulindac
tamoxifen
tetracycline
thyroid
ticarcillin
ticlopidine
tissue plasminogen activator (t-PA)
tolbutamide
tramadol
trimethoprim/ sulfamethoxazole
urokinase
valdecoxib
valproate
vitamin E
zafirlukast
zileuton

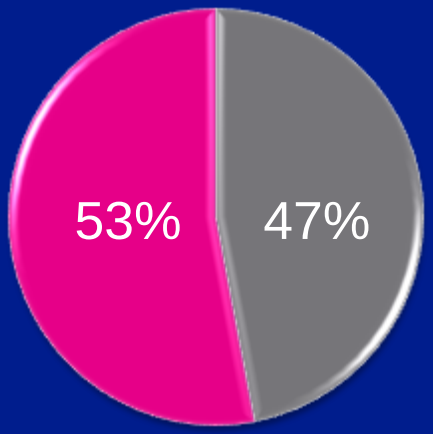
- Highlights
  - Atorvastatin, simvastatin
  - Esomeprazole, lansoprazole
  - Paracetamol, ASA, ibuprofen
  - Propranolol, naproxen
  - Chloramphenicol, clarithromycin, tetracycline, penicillin G, metronidazole …
  - Alcohol

www.rxlist.com/cgi/generic/warfarin_ad.htm

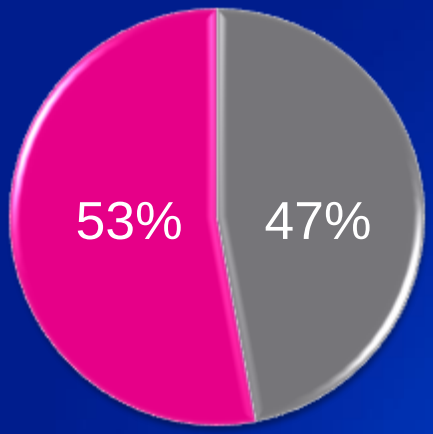
Underutilization of anticoagulation in AF*

Approximately half of high-risk patients with AF receive warfarin therapy

13 community hospitals



21 academic hospitals



Warfarin therapy

No warfarin therapy

*US population January–December 2002

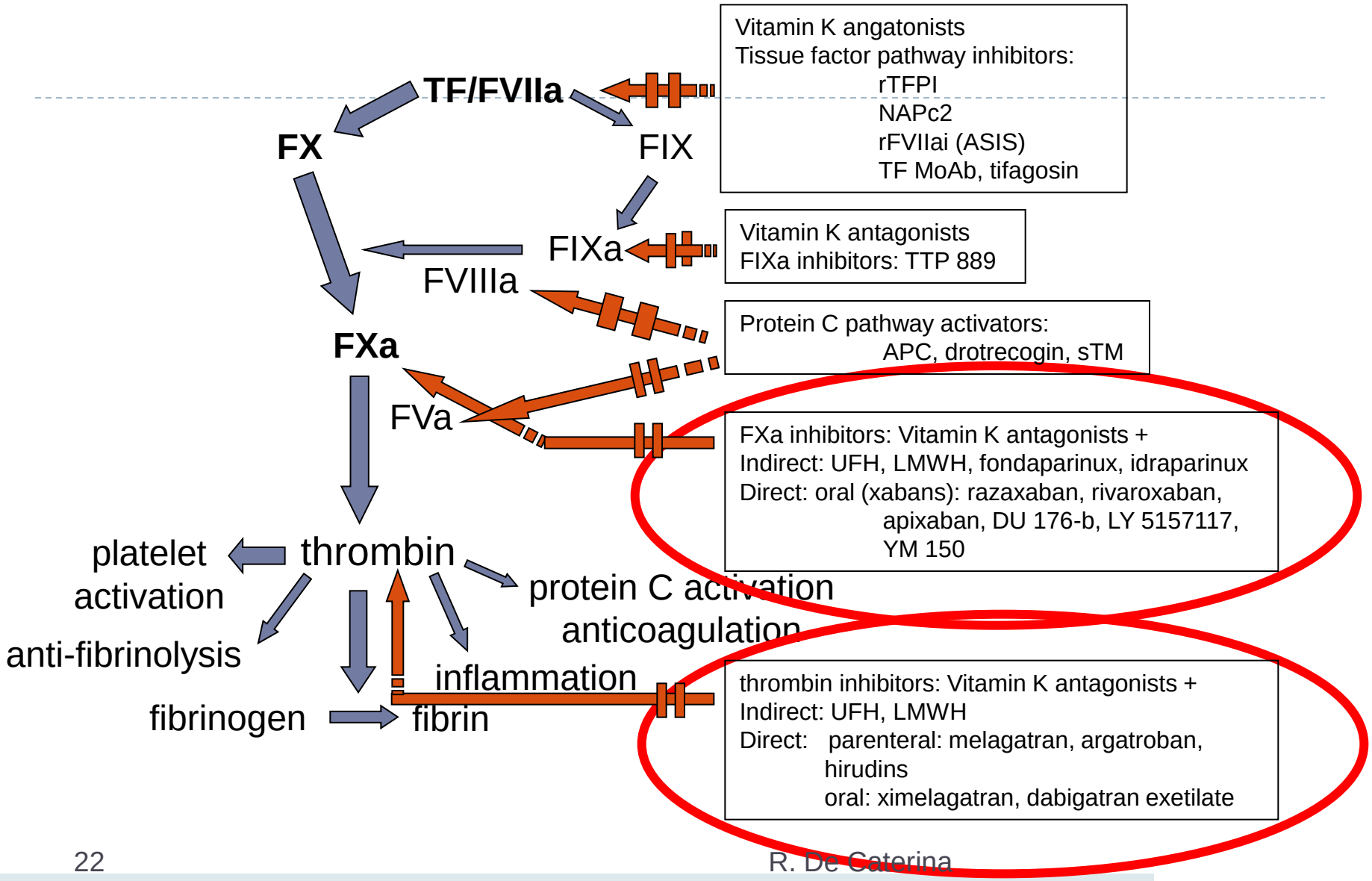
Waldo *et al*. *J Am Coll Cardiol* 2005

Therefore

- there was still a need for safe, effective, oral anticoagulants that do not require monitoring

Novel Vitamin K Antagonists

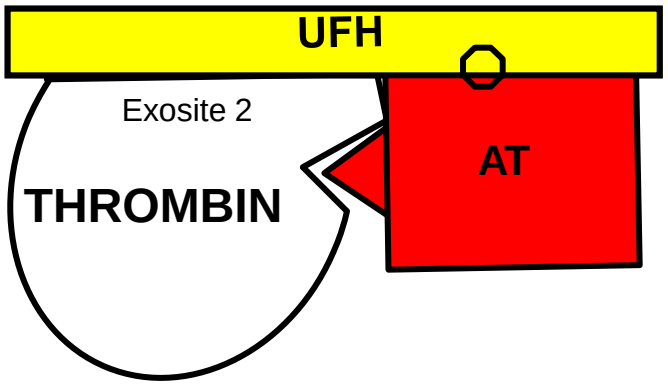
Agent	Route	Dosing	Half-life (hours)	Metabolism	Drug Interactions	Clearance	Phase of Development
ATI-5923 (Tecarfarin)	Oral	Variable, 1X daily	119	Cellular esterases	No P450 metabolism. Less or no drug interactions	100% liver	Phase II study completed



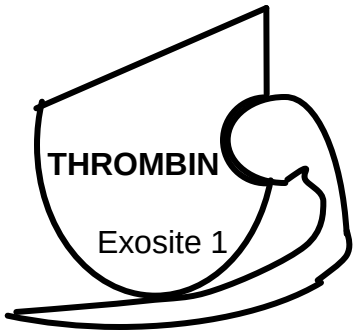
De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease – EHJ 2007; 28: 880-913

Thrombin inhibitors

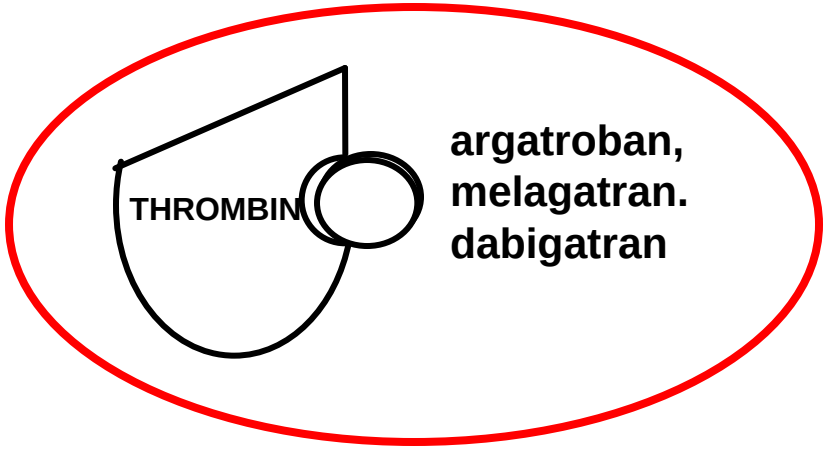
indirect



direct



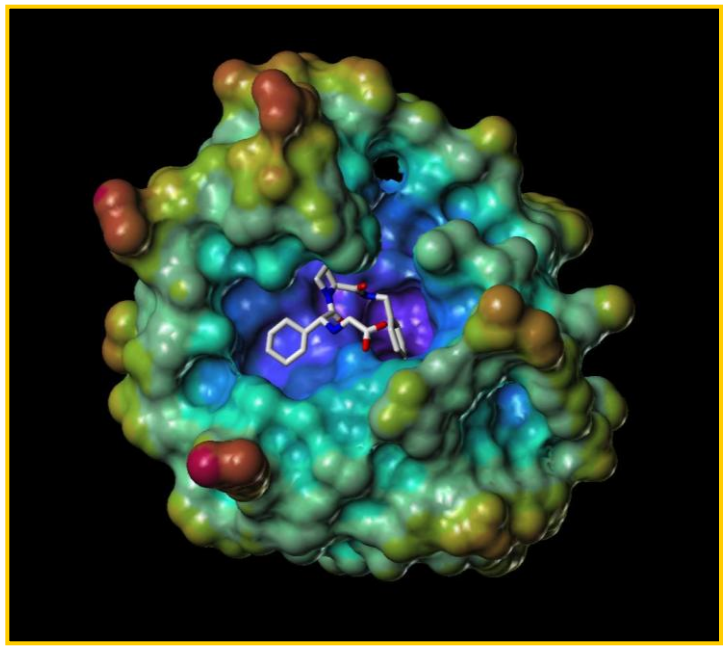
hirudin, bivalirudin



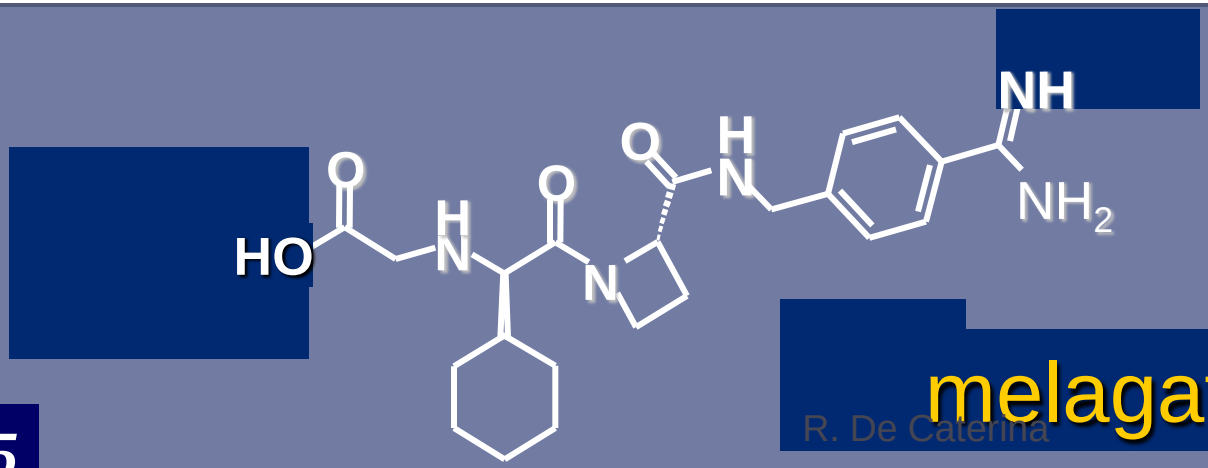
argatroban, melagatran. dabigatran

De Caterina et al. ESC WG 18 Task Force on Anticoagulants in Heart Disease – EHJ 2007; 28: 880-913

Direct thrombin inhibition



- **Oral ximelagatran rapidly absorbed and biotransformed to the active form, melagatran**
  - **Renal excretion**
  - **Clinical studies demonstrate efficacy with bid dosing**
  - **No coagulation monitoring required**
  - **Low potential for drug/food/alcohol interaction**
  - **Fixed dosing and predictable response**

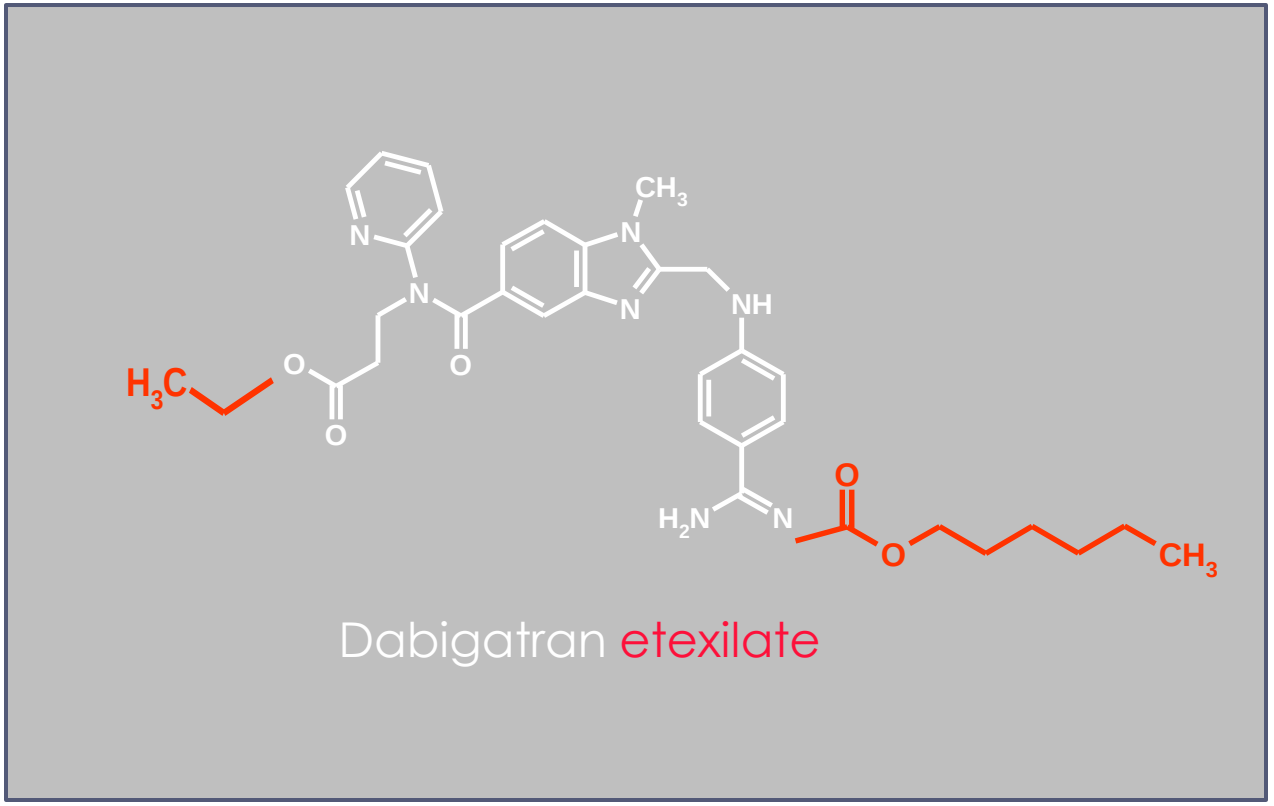


melagatran

ALAT > 3x ULN

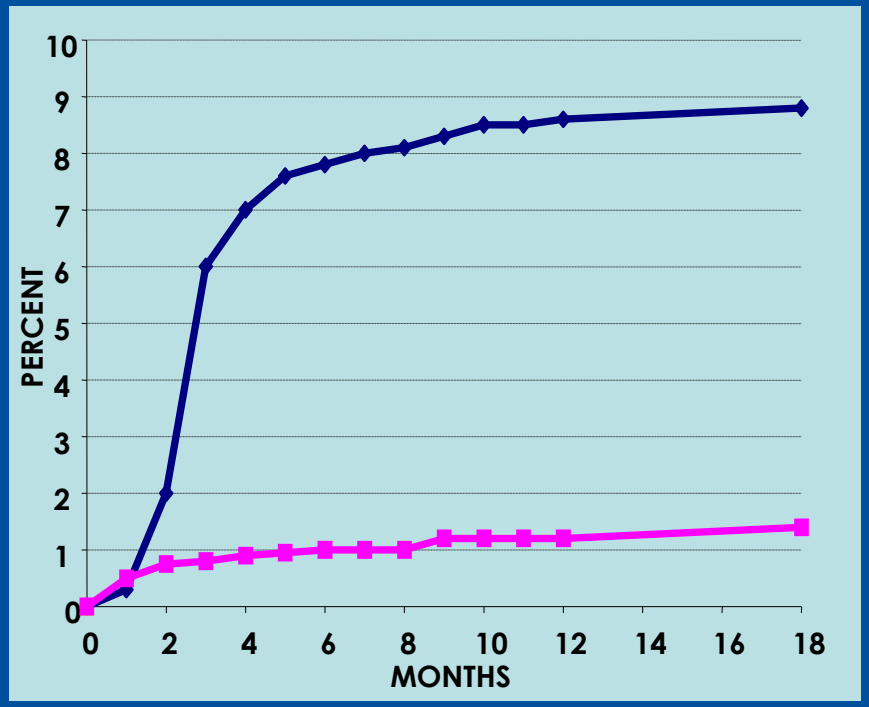

warfarin
ximelagatran
Incidence (%)
10
8
6
4
2
0
6.3%
6.0%
6.1%
0.8%
0.8%
0.8%
SPORTIF III
SPORTIF V
Pooled

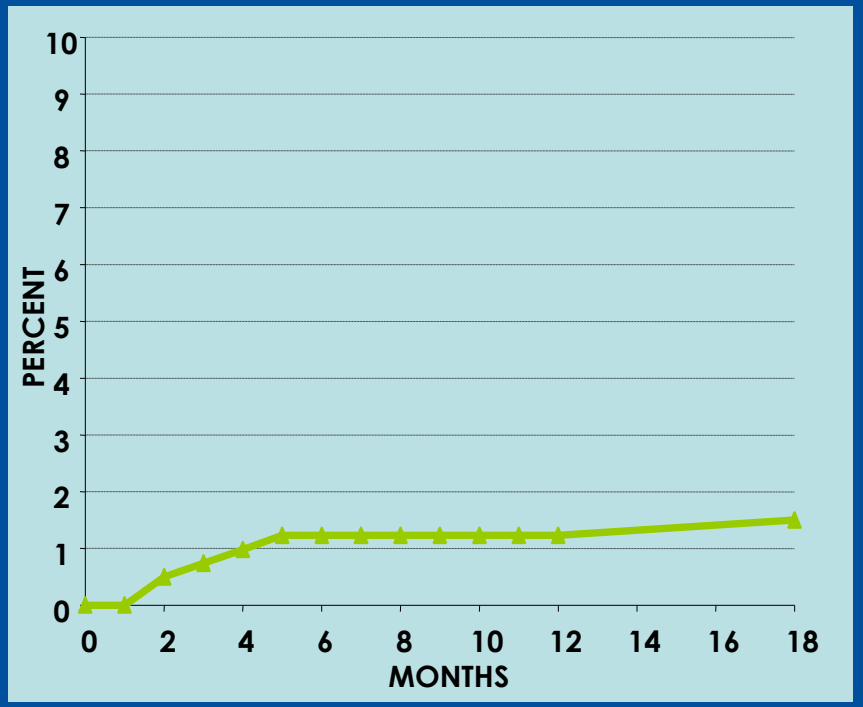
Dabigatran Etexilate:
A Novel Direct Thrombin Inhibitor



Liver Function Test

Cumulative risk of alanine aminotransferase greater than 3x the upper limit of normal vs. time after randomisation





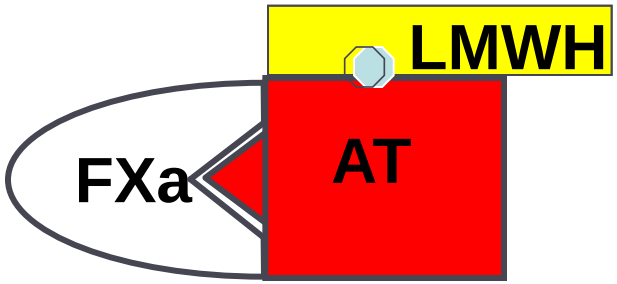
Ximelagatran
Comparator
Dabigatran

Ximelagatran and comparator data from Astra Zeneca Briefing Document for FDA Advisory Committee Meeting, Sept 10, 2004, page 128
Dabigatran data from PETRO and PETRO-Ex, data on file

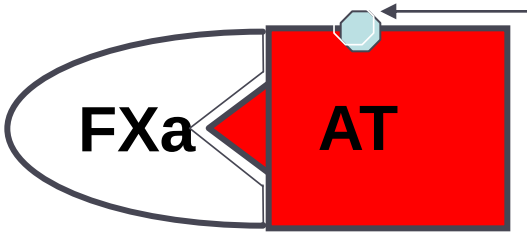
Oral FXa inhibitors, vs. LMWH vs. pentasaccharides

parenteral

oral

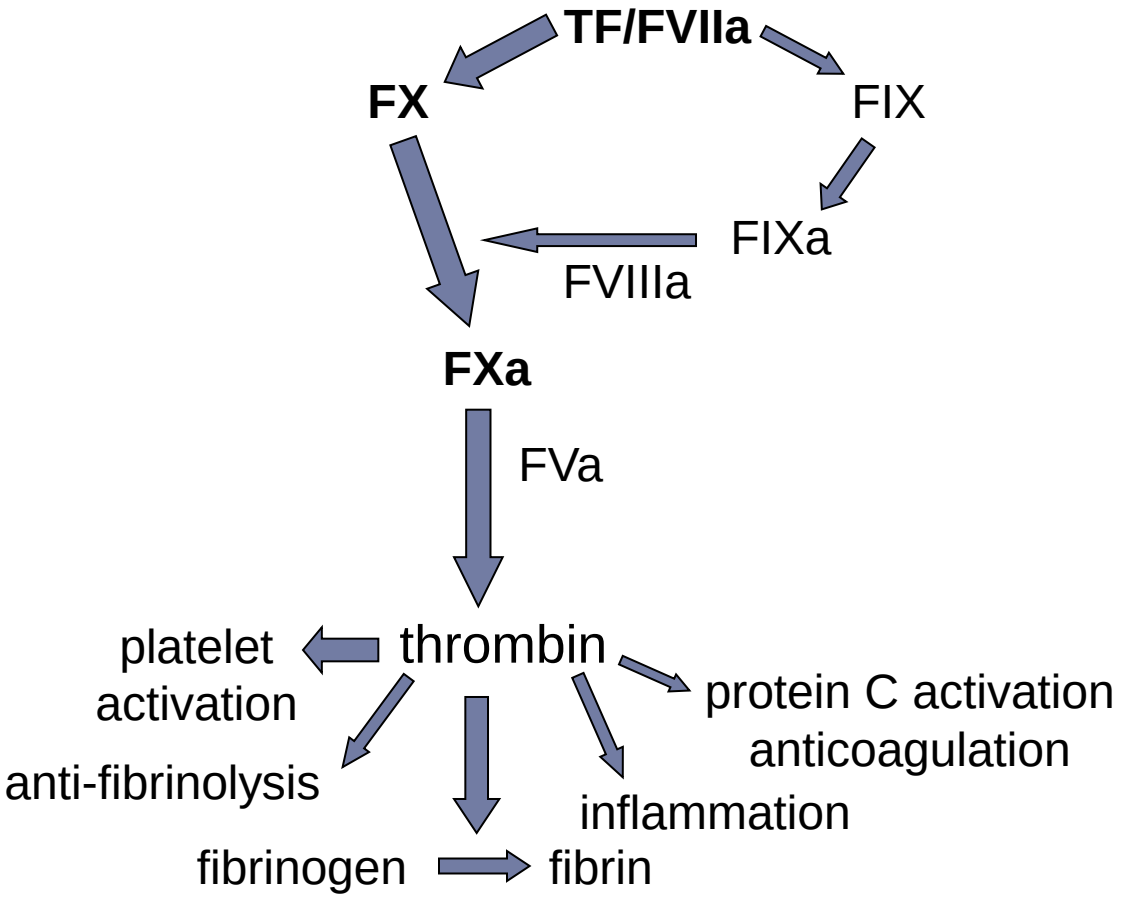


xabans



fondaparinux
idraparinux

Coagulation: an amplifying cascade



1 molecule of FXa

1000 molecules of thrombin

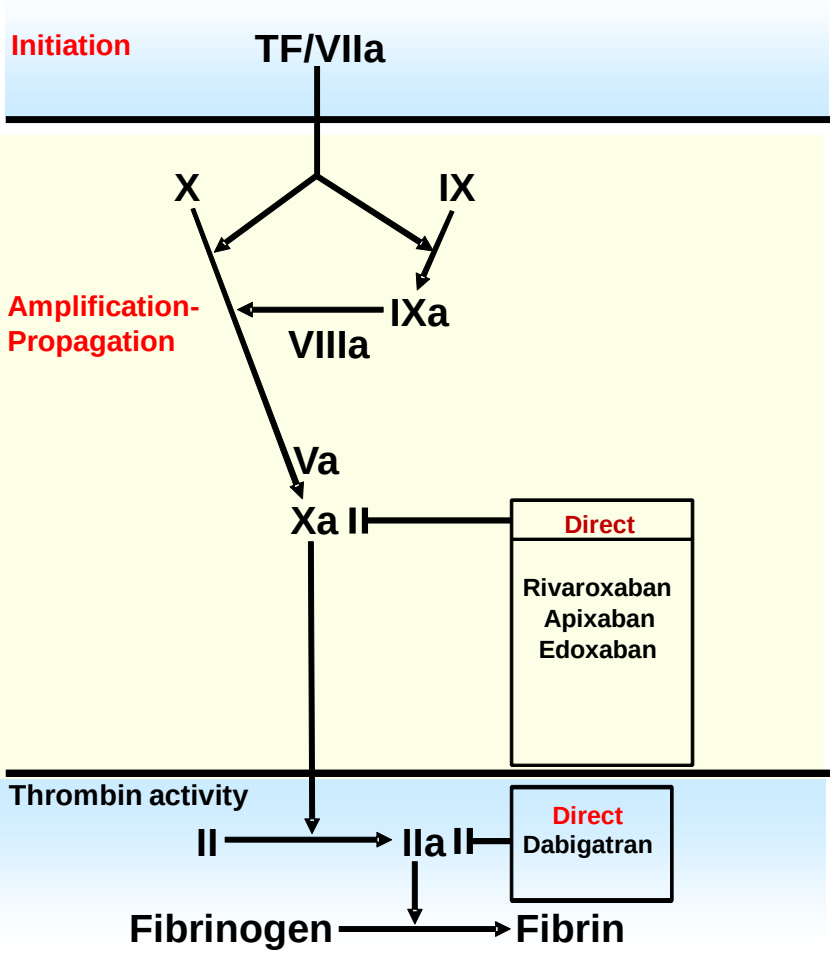
Mann KG, et al..J Thromb Haemost 2003; 1:1504–14.

Agenda

- The history of oral anticoagulation
- The NOAC revolution

General mechanisms of coagulation and targets of anticoagulants (Section I)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease



De Caterina R, Husted S, Wallentin L et al. Thromb Haemost, 2013, 109: 569–579

Features of novel oral anticoagulants

	Dabigatran[1]	Rivaroxaban[1,2]	Apixaban[1,3]	Edoxaban[4-6]
Target	IIa (thrombin)	Xa	Xa	Xa
Hours to Cmax	1.25-3	2-4	3-4	1-2
CYP metabolism	None	32%	Minimal	<4%
Bioavailability	6%	80%	60%	62%
Transporters	P-gp	P-gp/BCRP	P-gp/ BCRP	P-gp
Protein binding	35%	93%	87%	50%
Half-life	14-17 h	7-11 h	8-15 h	8-10 h
Renal elimination	80%*	33%#	25%#	35%#

BCRP, breast cancer resistance protein
CYP, cytochrome P450; P-gp, P-glycoprotein
NR, not reported

*Of absorbed substance

#Of ingested substance

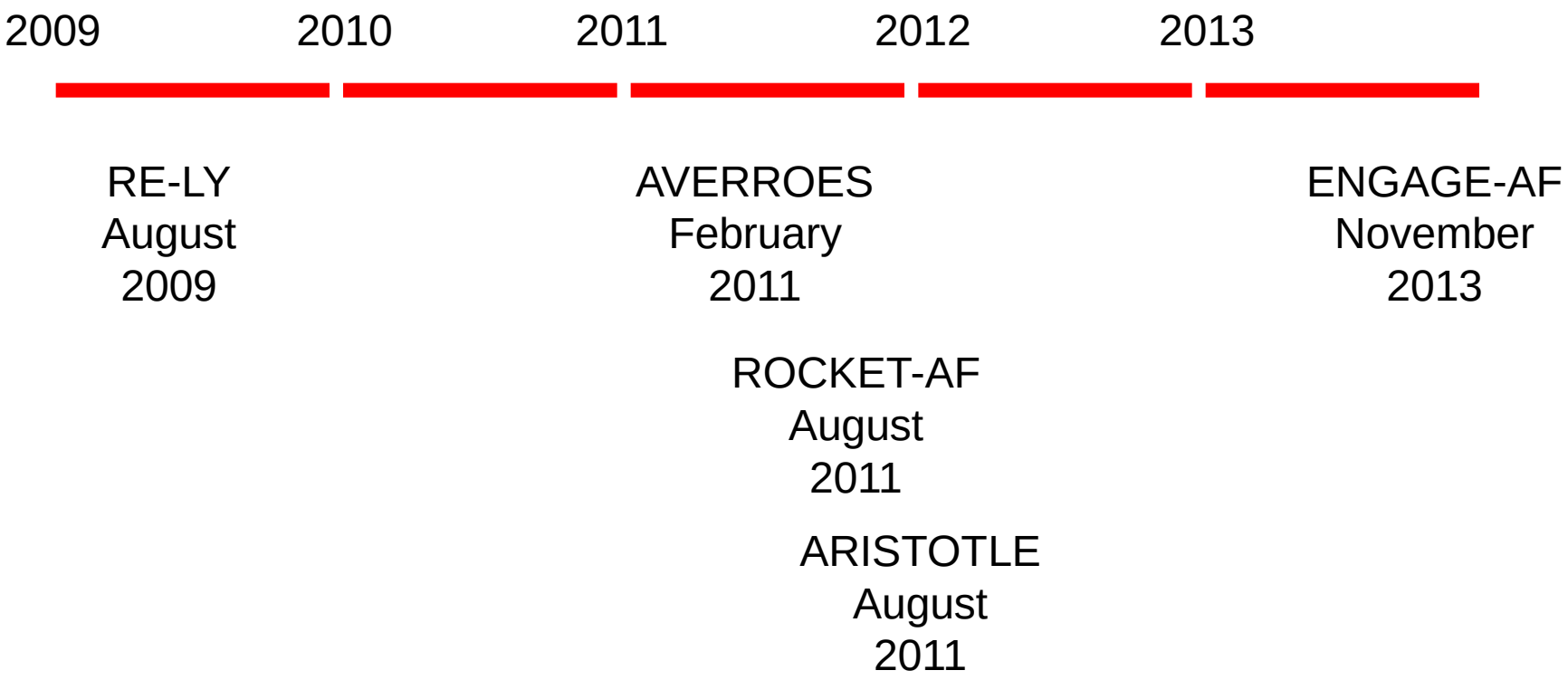
1. Eriksson et al. Clin Pharmacokinet 2009;48:1-22; 2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2011; 3. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK; 4. Ruff et al. Hot Topics in Cardiology 2009;18:1-32; 5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract; 6. Ogata et al. J Clin Pharmacol 2010;50:743-53

Having more effective or safer anticoagulants was not the original hypothesis for their development

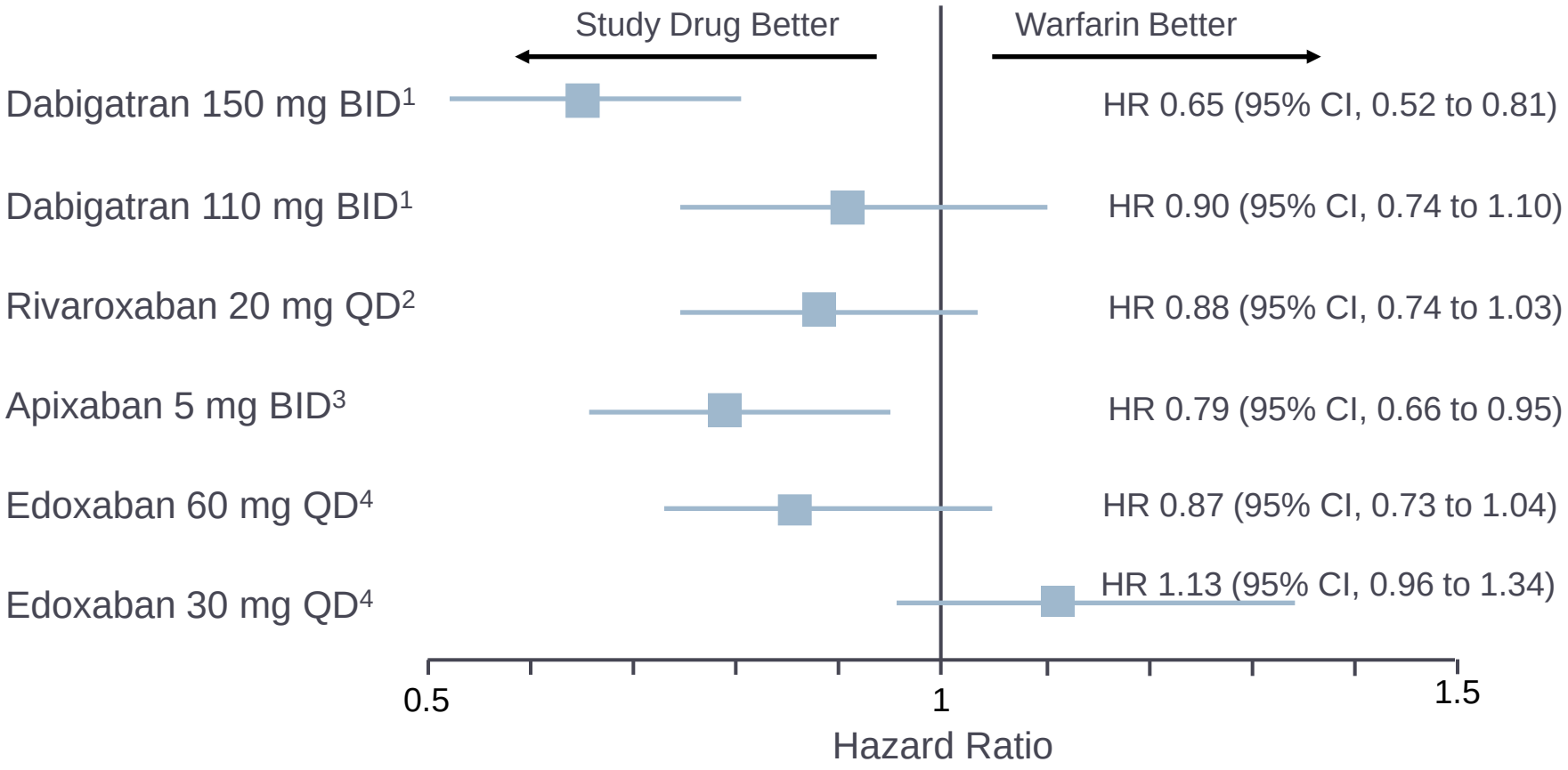
- the original hypothesis was to find “non-inferior” agents compared with warfarin, with **better acceptance because of the lack of need of frequent coagulation testing**

Can NOACs in SPAF offer a better risk-benefit profile?

NOACs in atrial fibrillation - Timelines

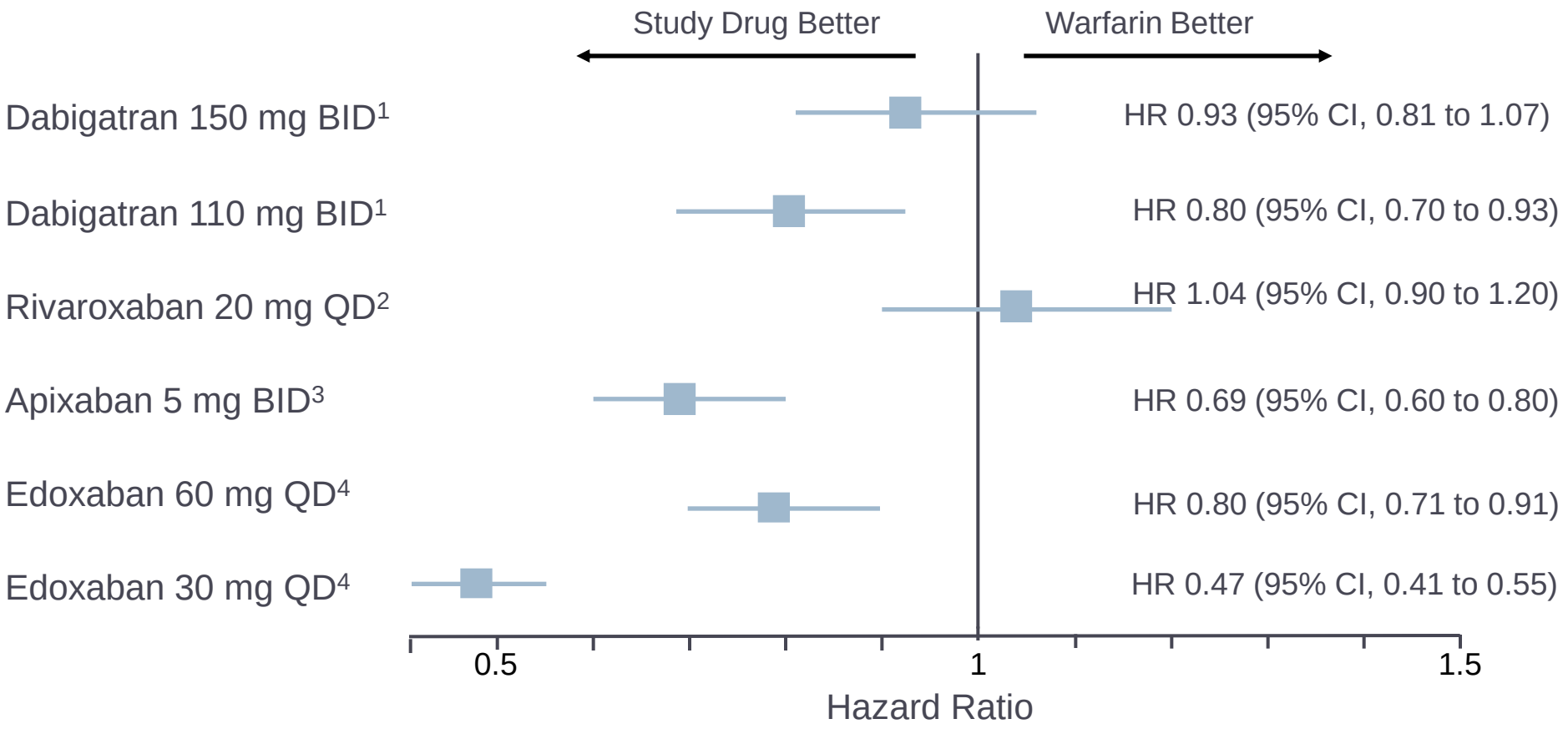


New Anticoagulant Therapies Compared to Warfarin: Stroke or Systemic Embolism



1. Connolly SJ et al. *N Engl J Med.* 2010;363:1875-1876.
2. Patel MR et al. *N Engl J Med*. 2011;365:883-891.
3. Granger CB et al. *N Engl J Med*. 2011;365:981-992.
4. Giugliano RP et al, for the ENGAGE-AF TIMI 48 Investigators; NEJM; 2013, doi: 10.1056/NEJMoa1310907

New Anticoagulant Therapies Compared to Warfarin: Major Bleeding



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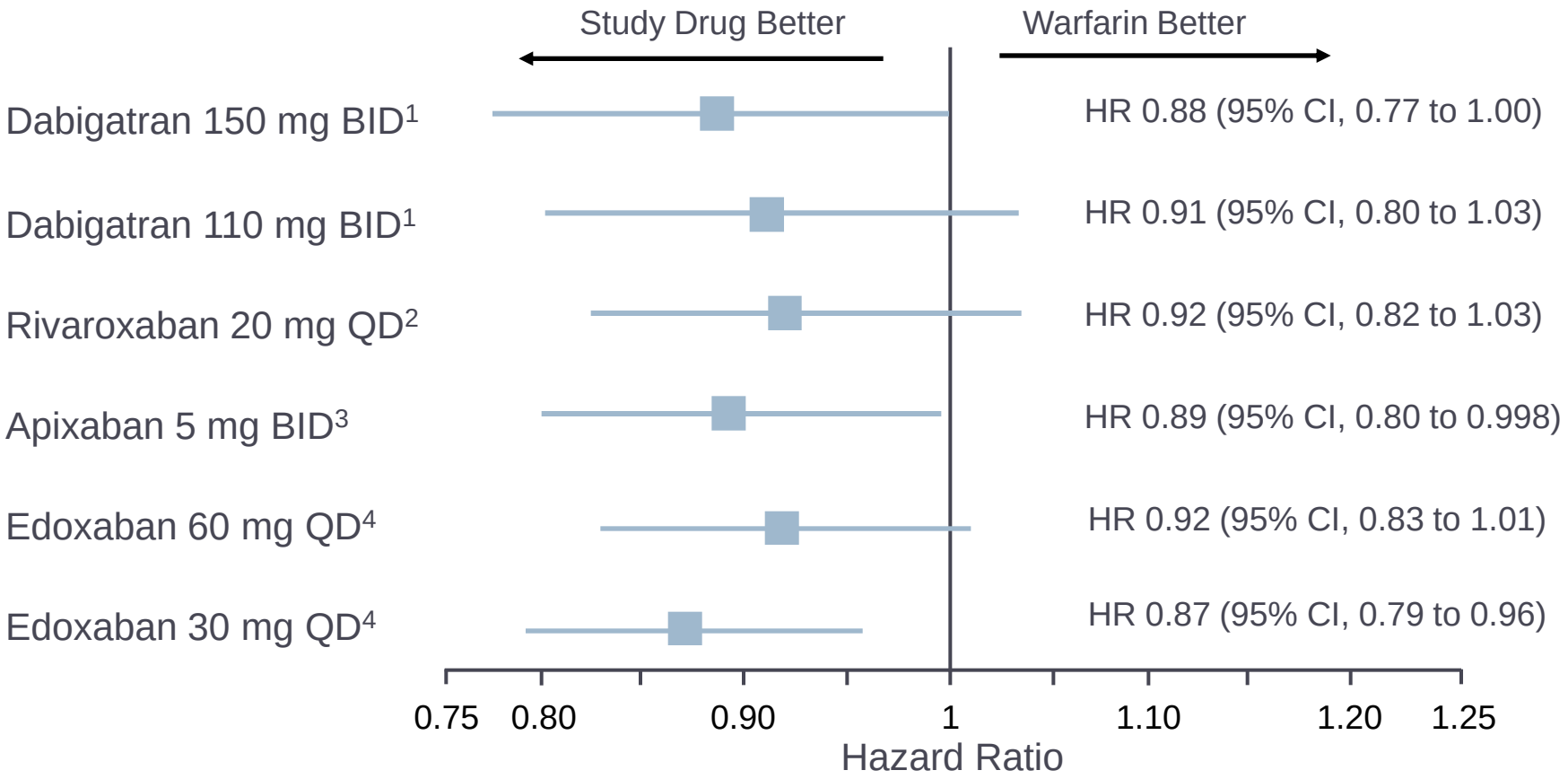
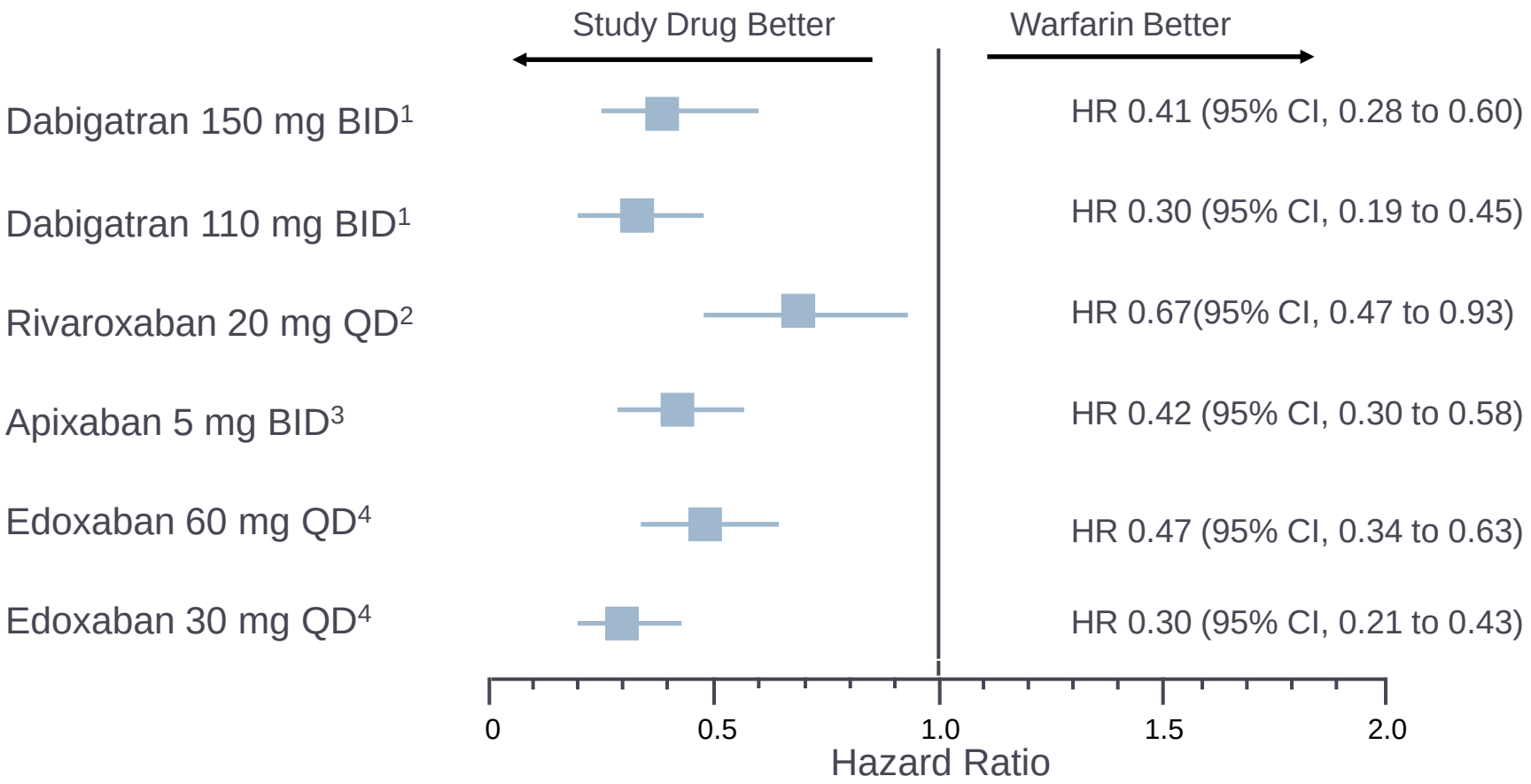
4. Giugliano RP et al, for the ENGAGE-AF TIMI 48 Investigators; NEJM; 2013, doi: 10.1056/NEJMoa1310907

New Anticoagulant Therapies Compared to Warfarin: All-Cause Mortality



1. Connolly SJ et al. *N Engl J Med*. 2010;363:1875-1876.
2. Patel MR et al. *N Engl J Med*. 2011;365:883-891.
3. Granger CB et al. *N Engl J Med*. 2011;365:981-992.
4. Giugliano RP et al, for the ENGAGE-AF TIMI 48 Investigators; NEJM; 2013, doi: 10.1056/NEJMoa1310907

New Anticoagulant Therapies Compared to Warfarin: Intracranial Hemorrhage



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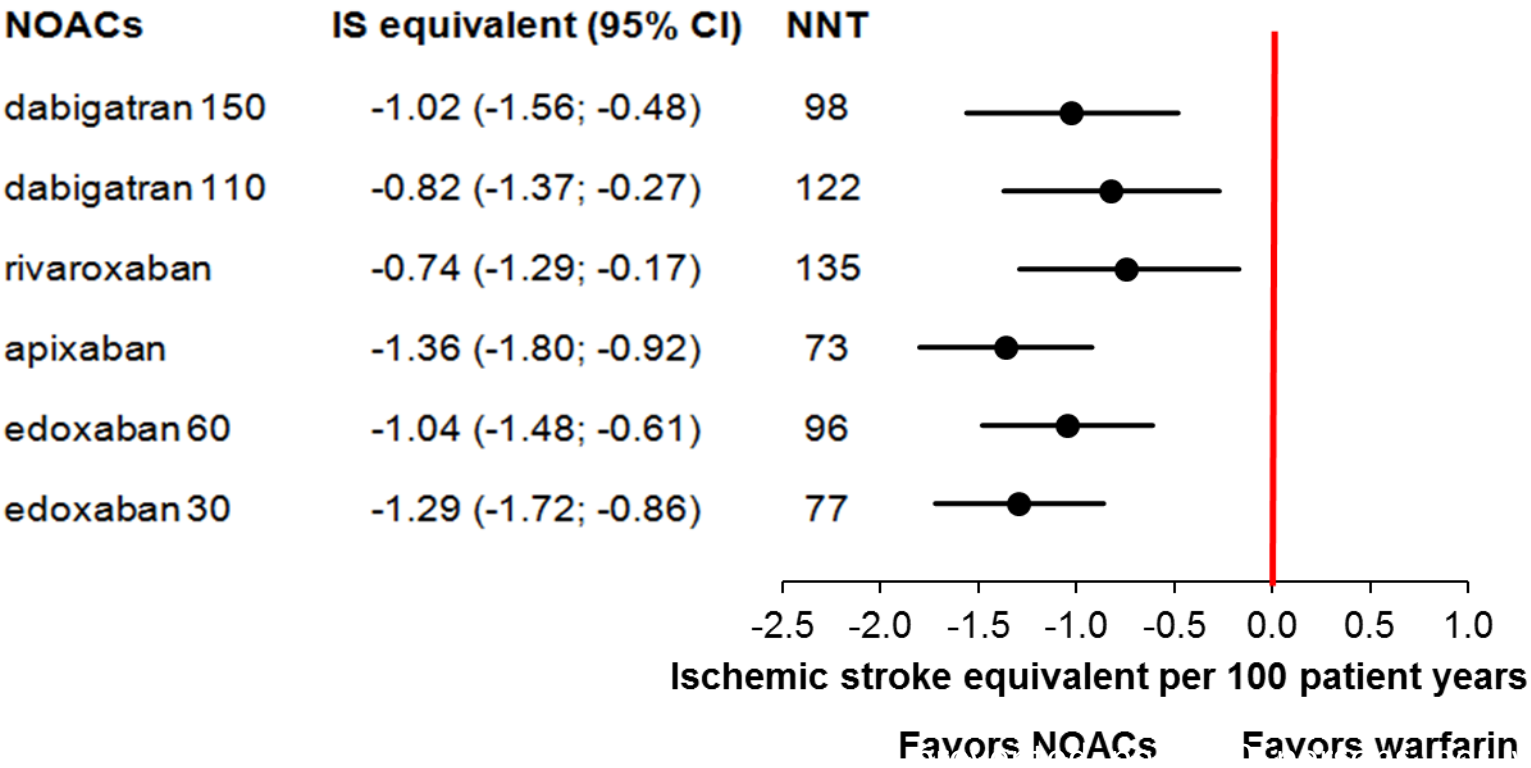
NCB (95%CI) of all treatment arms vs warfarin for the composite outcome including ischemic stroke + systemic embolism + myocardial infarction + hemorrhagic stroke + adjusted major bleeding



Renda G. et al. Am J Med 2015

Agenda

- The history of oral anticoagulation
- The NOAC revolution
- Highlights from clinical trials: from bedside to bench
  - Once day vs twice day

Once vs twice daily – an important choice!

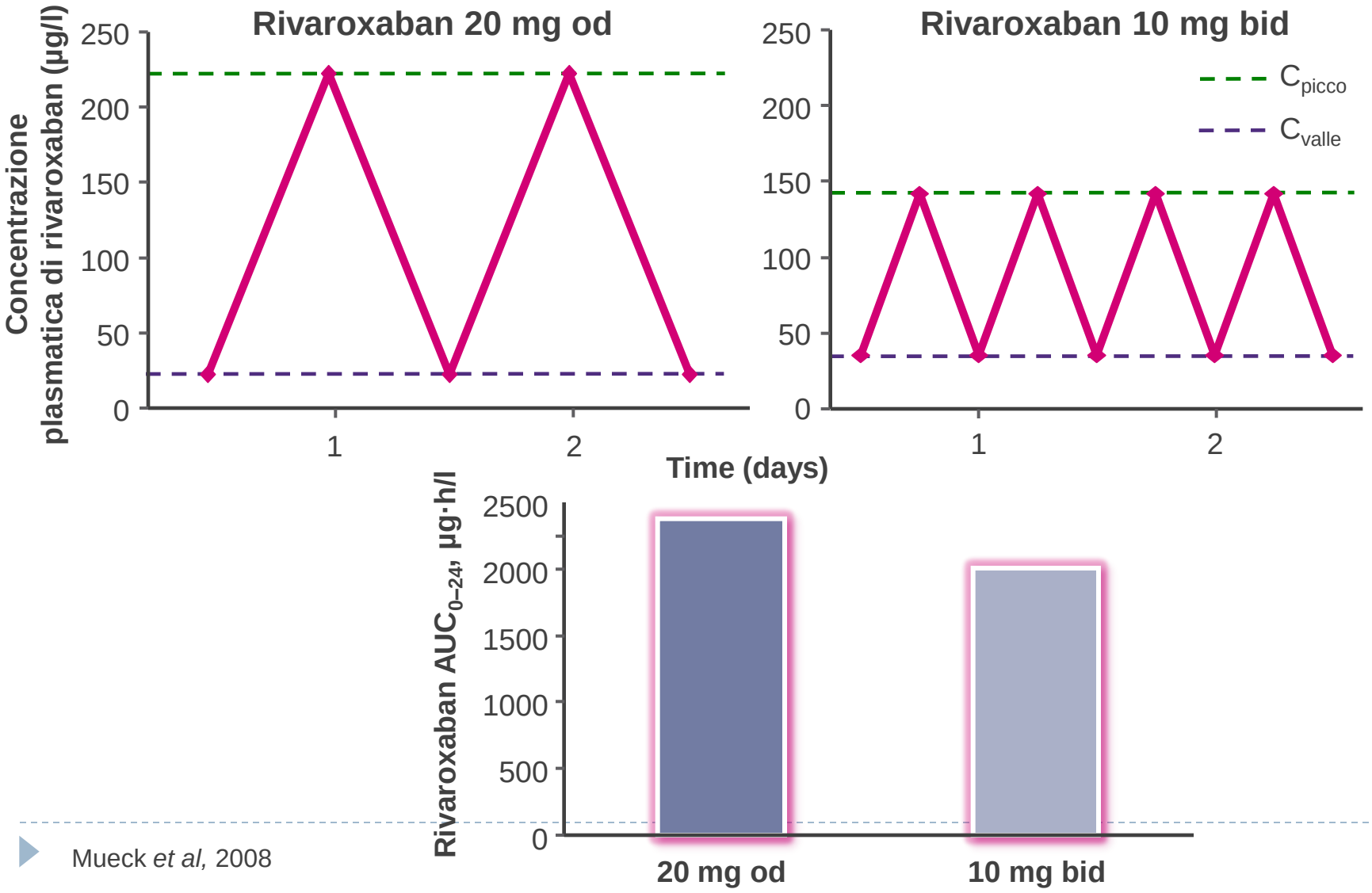
- The choice of the dose and regimen of administration is crucial in drug development
- Dose selection has to consider all elements maximizing efficacy while preserving safety
- It is selected in phase II studies – ideally, but not always – in the same patient population to whom the drug should be given
- Everything else being equal, patient's convenience (e.g., once daily dosing) is taken into account, as it increases adherence
- Adherence to the selected drug dosing is a major factor in the difference between a registration clinical trial and the actual post-marketing use of the drug

Influence of PK and PD parameters on dosing regimens

- The pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the new oral anticoagulants provide the opportunity for either od or bid dosing

- Determination of the optimal dosing regimen must be based on assessment of benefit (reduction in thrombotic events) versus risk (increase in bleeding events) in clinical studies

Rivaroxaban dosing od vs bid



Mueck *et al,* 2008

No doubts that in AF patients compliance to therapy is better with OD than with BID dosing

Adv Ther (2012) 29(8):675–690.
DOI 10.1007/s12325-012-0040-x

ORIGINAL RESEARCH

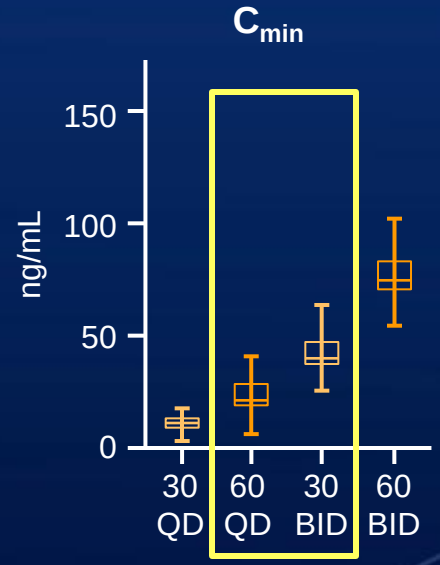
Impact of Daily Dosing Frequency on Adherence to Chronic Medications Among Nonvalvular Atrial Fibrillation Patients

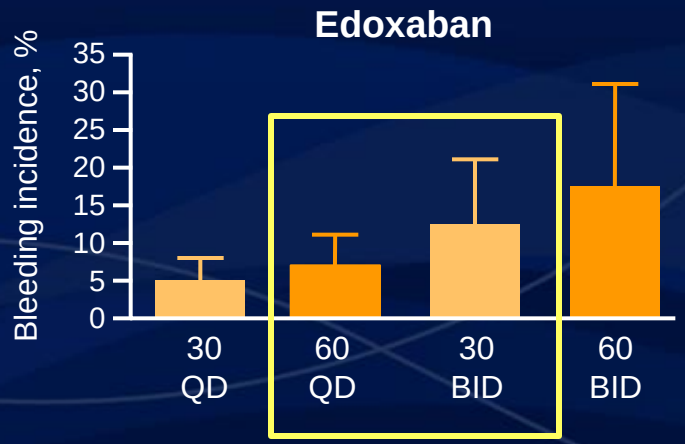
François Laliberté · Winnie W. Nelson · Patrick Lefebvre · Jeff R. Schein · Jonathan Rondeau-Leclaire · Mei Sheng Duh

CONCLUSION

This large population-based study of >10,000 patients, based on real-world data, indicates that nonvalvular AF patients treated with q.d. dosing regimens for chronic medications were associated with approximately a 26% higher likelihood of adherence compared with subjects on b.i.d. regimens. The findings were consistent across two methods of determining medication adherence.

Edoxaban phase II dose finding study in atrial fibrillation: exposure and bleeding

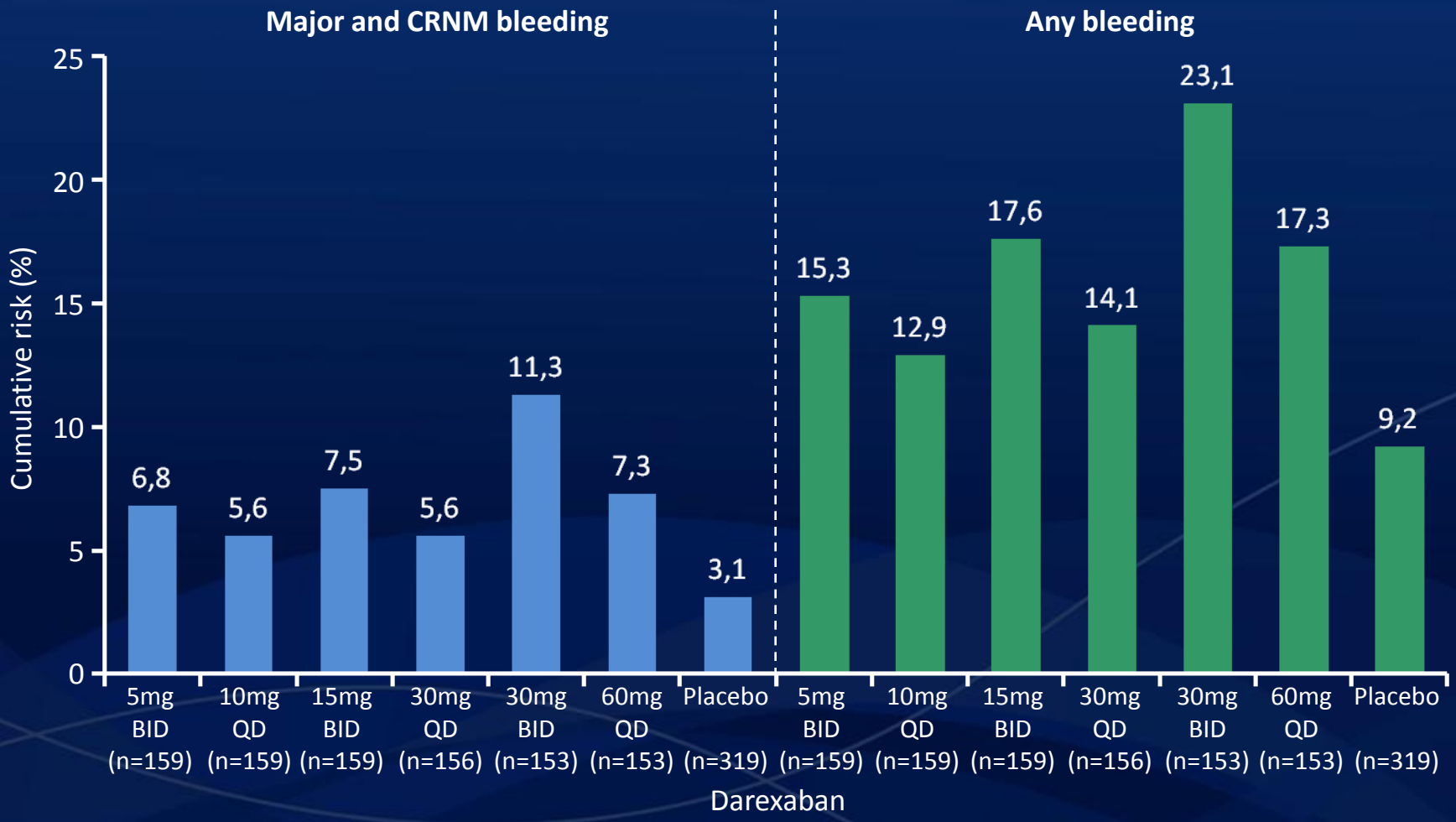




AUC, area under the plasma concentration-time curve from 0 to 24 hours at steady-state;
C_{max}, maximum steady-state plasma concentration;
C_{min}, minimum steady-state concentration;
QD, once daily;
BID, twice daily

Weitz et al. Thromb Haemost 2010;104:633-41

RUBY-1: cumulative risk of major and clinically relevant non-major bleeding and any bleeding events at 6 months (safety analysis set)



CRNM, clinically relevant non-major
BID, twice daily; QD, once daily

Steg et al. Eur Heart J 2011;32:2541–4

Therefore (conclusions):

- OD therapy in long-term stroke prevention in atrial fibrillation:
  - Appears to be as effective as BID
  - Appears to be as safe as BID
  - It might actually be safer than BID (indirect evidence from other anticoagulants)
  - It is certainly more appealing for the patient

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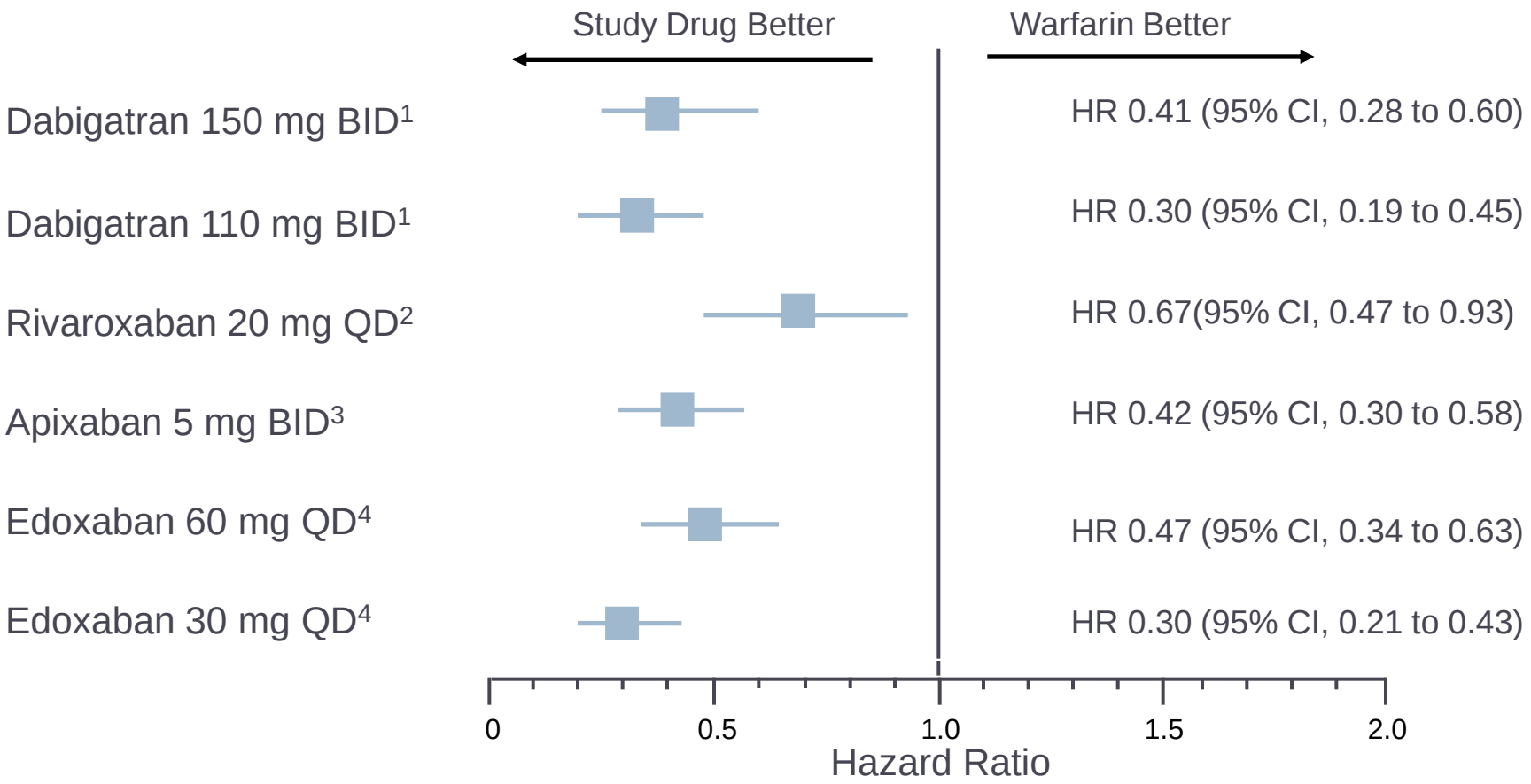
  - Intracranial hemorrhage

New Anticoagulant Therapies Compared to Warfarin: Intracranial Hemorrhage



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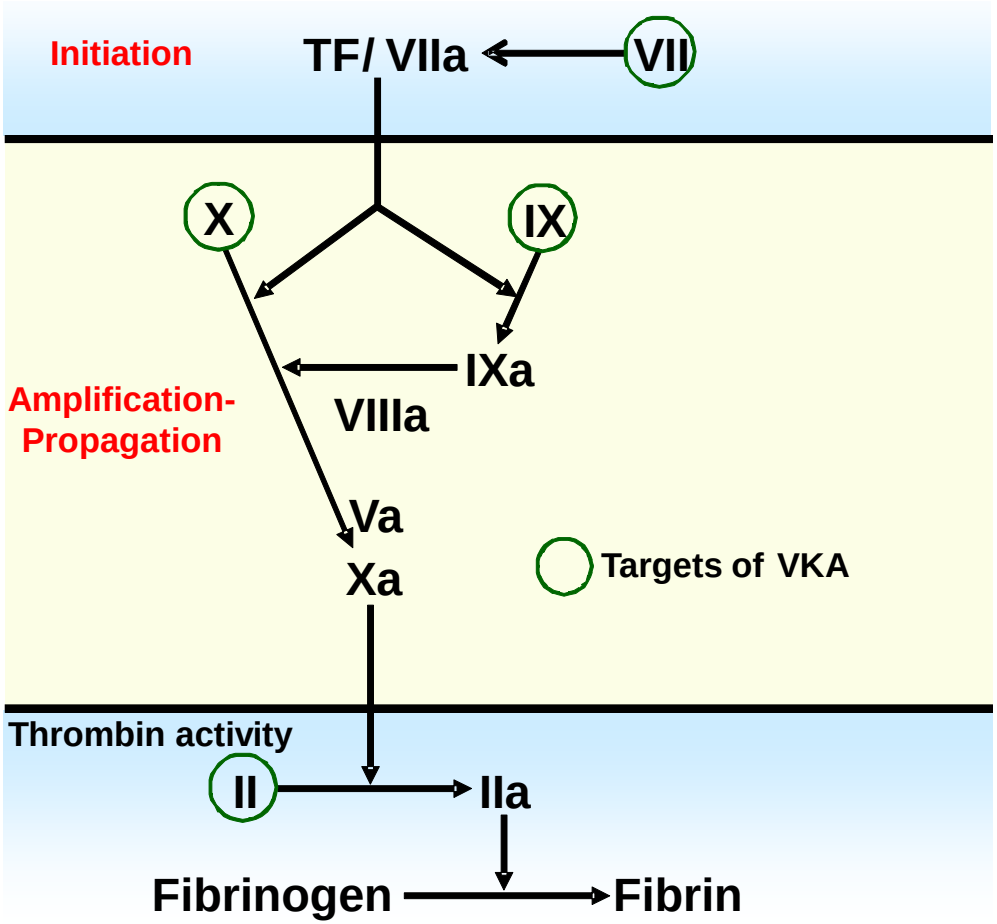
General mechanisms of coagulation and targets of anticoagulants (Section I)

Position Paper of the ESC Working Group on Thrombosis – Task Force on Anticoagulants in Heart Disease



De Caterina R, Husted S, Wallentin L et al. Thromb Haemost, 2013, 109: 569–579

Why is warfarin more dangerous than NOACs as to intracranial hemorrhage?

- Warfarin interferes with the formation of a gamma-carboxylated bioactive form of Factor VII
- Factor VII is a crucial mediator of tissue-factor initiated coagulation (the extrinsic pathway)
- The brain is extremely rich in tissue factor, possibly («teleologically») aimed at preventing the catastrophic occurrence of intracerebral bleeding
- By interfering with this pathway, warfarin has a high risk of intracranial hemorrhage, a risk not shared by NOACs

Agenda

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  - Intracranial hemorrhage
  - New treatment indications – coronary artery disease

A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B

European Heart Journal Advance Access published August 29, 2015

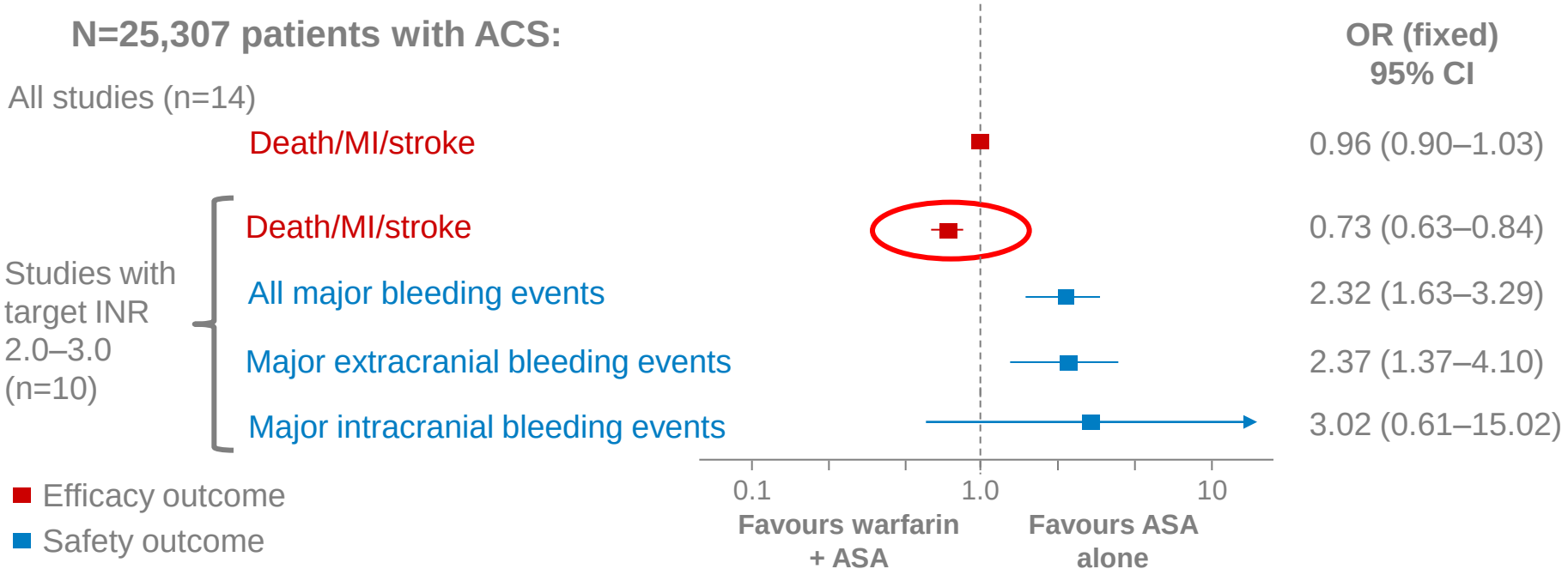
European Heart Journal
doi:10.1093/eurheartj/ehv320

ESC GUIDELINES

2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Why adding an anticoagulant long-term?

Meta-analysis: ASA + warfarin reduced CV outcomes vs ASA alone

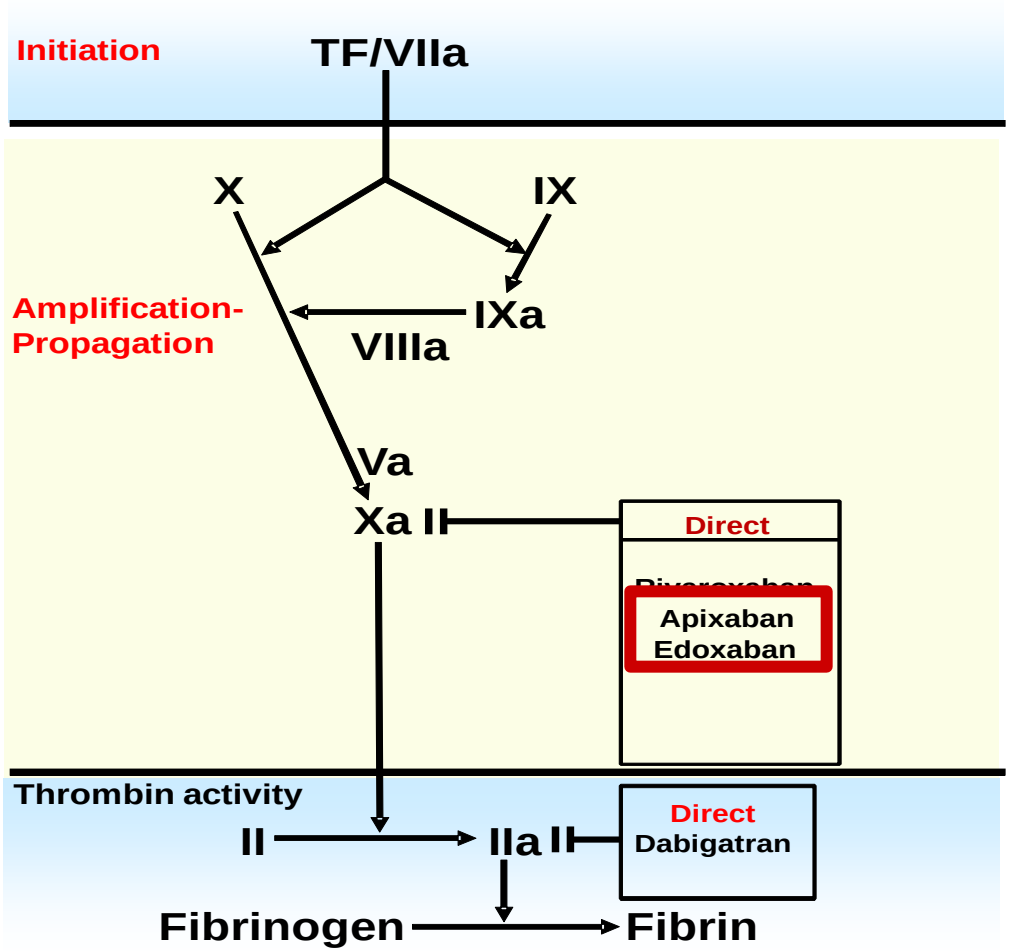


- Warfarin + ASA versus ASA alone:
  - Reduces death/MI/stroke only when the correct therapeutic dose is applied (INR 2.0–3.0)
  - Increases the risk of major bleeding events

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CI, confidence interval; CV, cardiovascular; INR, international normalized ratio; MI, myocardial infarction; OR, odds ratio.

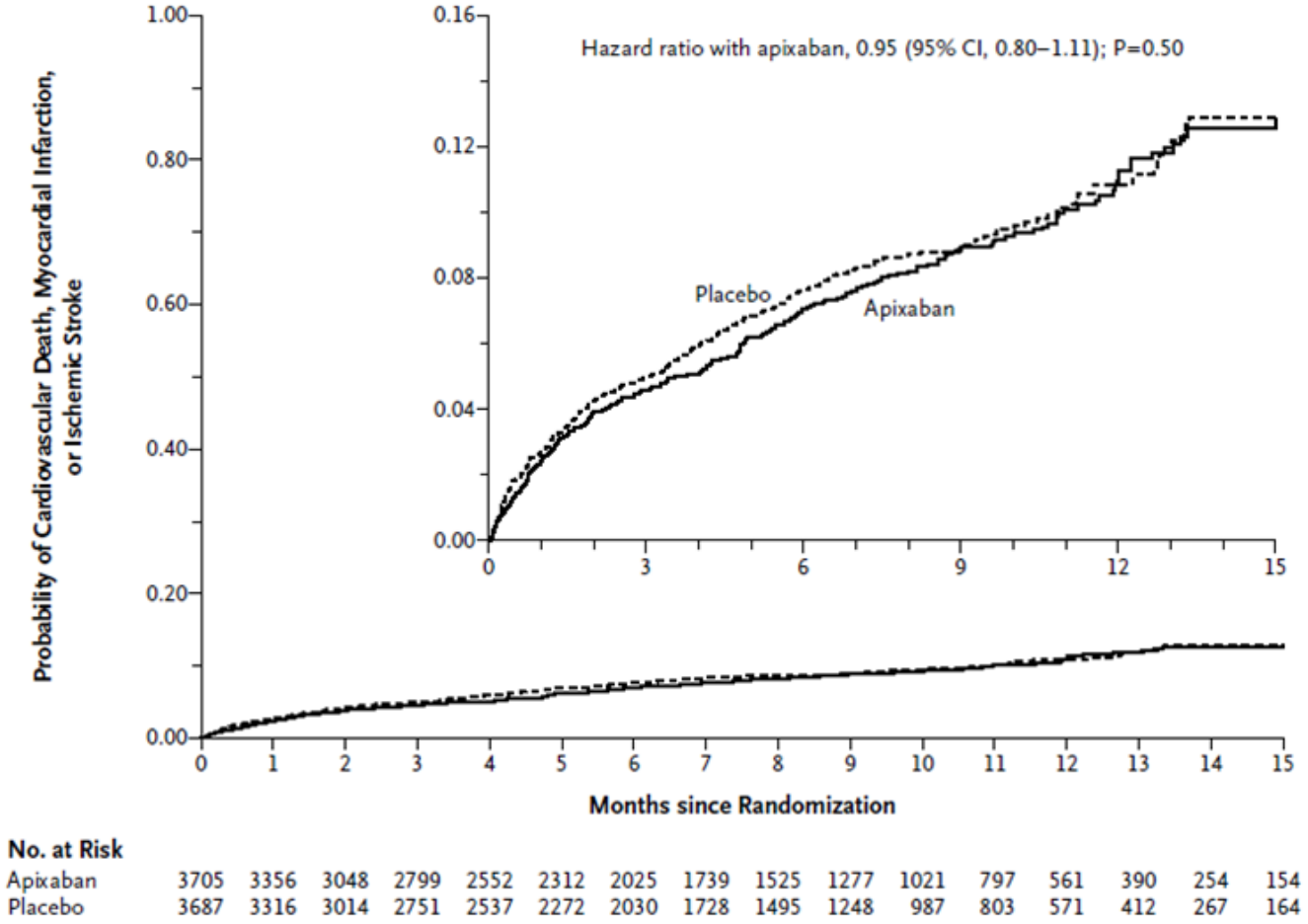
Andreotti *et al. Eur Heart J* 2006;27:519–26.

A new era in anticoagulation



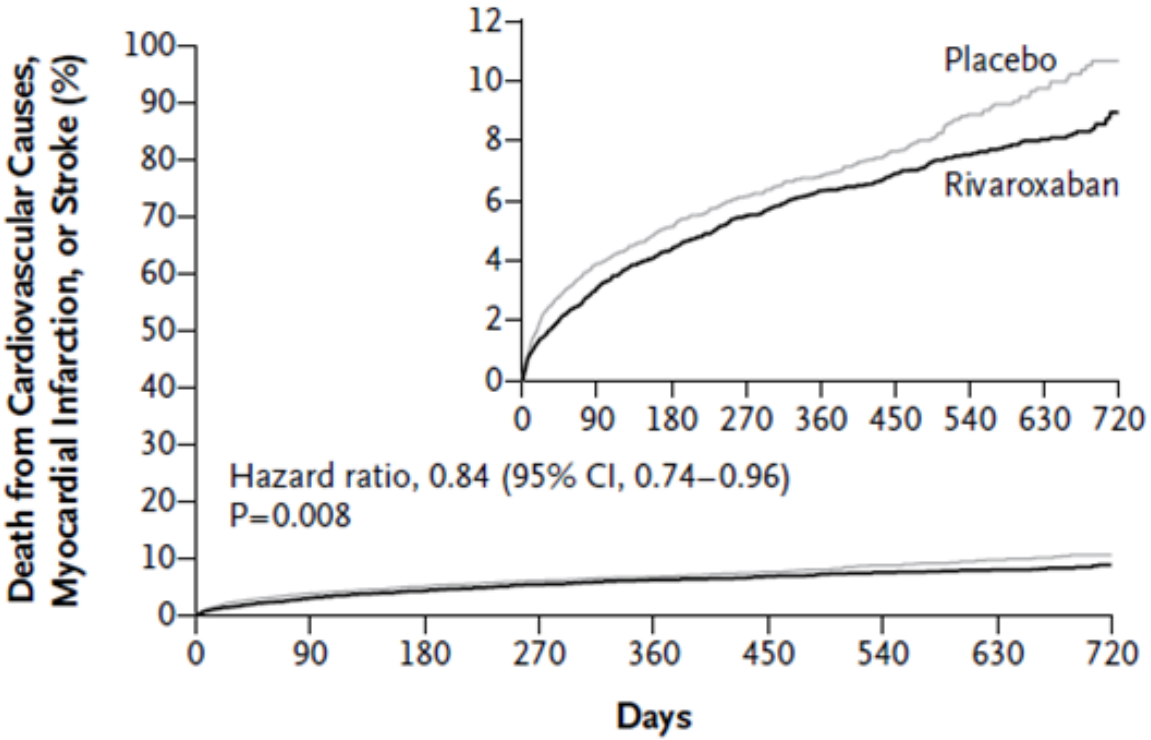
De Caterina *et al. Thromb Haemost* 2013;109:569–79.

APPRAISE-2: Primary efficacy outcome (CV death, MI, stroke)



Alexander *et al. N Engl J Med* 2011;365:699–708.

ATLAS ACS 2–TIMI 51: Primary efficacy outcome (CV death, MI, stroke)

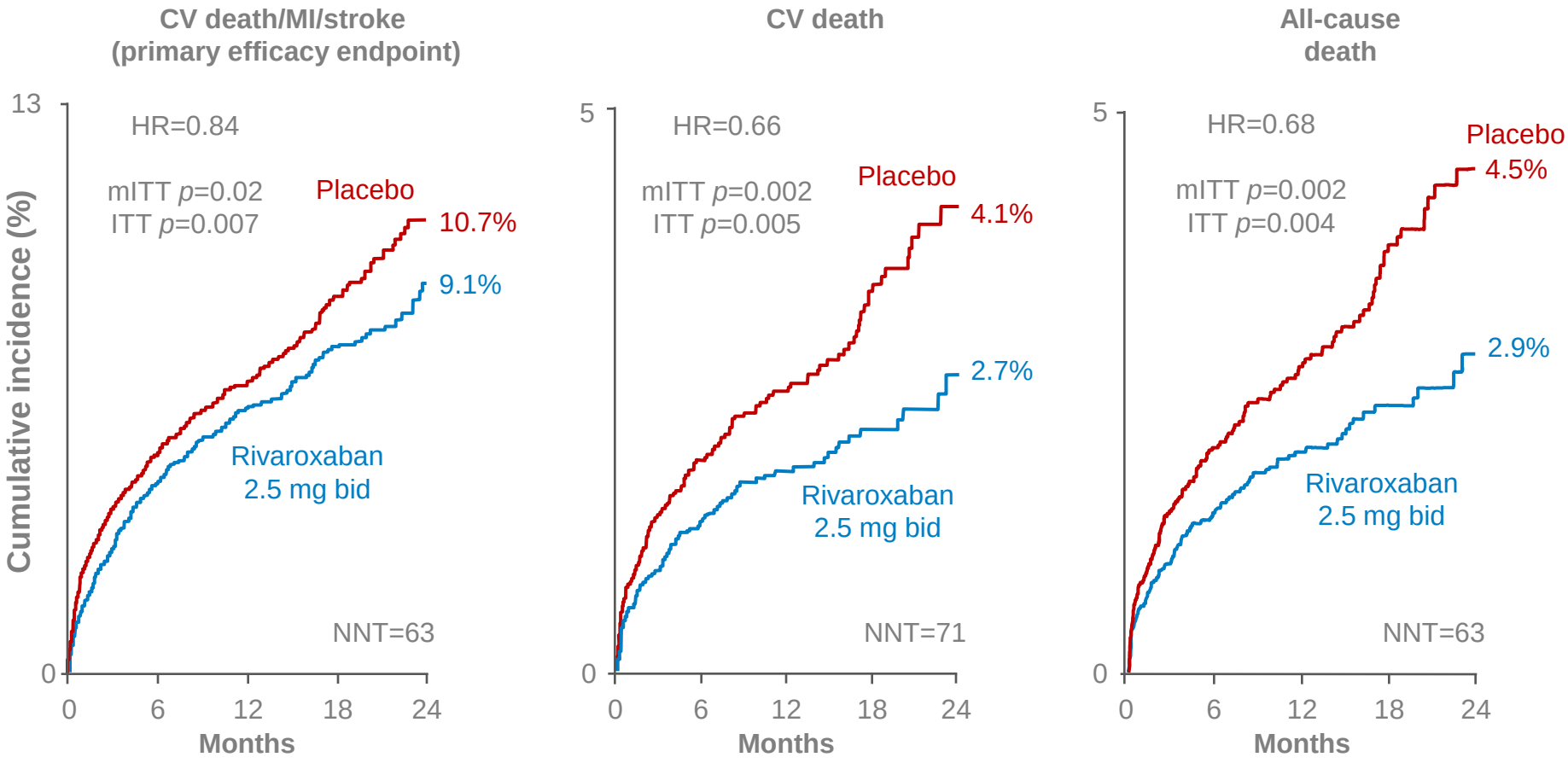


No. at Risk									
Rivaroxaban	10,229	8817	7797	6324	5137	3967	2830	1747	831
Placebo	5,113	4437	3974	3253	2664	2059	1460	878	421

Mega *et al. N Engl J Med* 2012;366:9–19.

ATLAS ACS 2–TIMI 51: rivaroxaban 2.5 mg bid significantly reduced CV events and death

The primary efficacy endpoint reduction was driven by reduced mortality



Both strata. bid, twice daily; CV, cardiovascular; HR, hazard ratio; ITT, intention to treat; MI, myocardial infarction; mITT, modified intention to treat; NNT, number needed to treat.

1. Mega *et al. N Engl J Med* 2012;366:9–19; 2. Gibson *et al. AHA* 2011 (www.clinicaltrialresults.org).

Rivaroxaban 2.5 mg bid in ATLAS ACS 2–TIMI 51 vs standard antiplatelet therapy showed…

- Greater efficacy, including fewer deaths and reduction in stent thrombosis (not shown)
- An important increase in bleeding, including intracranial haemorrhage (ICH), but without any increase in fatal bleeding or fatal ICH
- Even greater benefits in patients with elevated cardiac biomarkers and without previous stroke/TIA

De Caterina *et al. J Am Coll Cardiol* 2012;59:1413–25

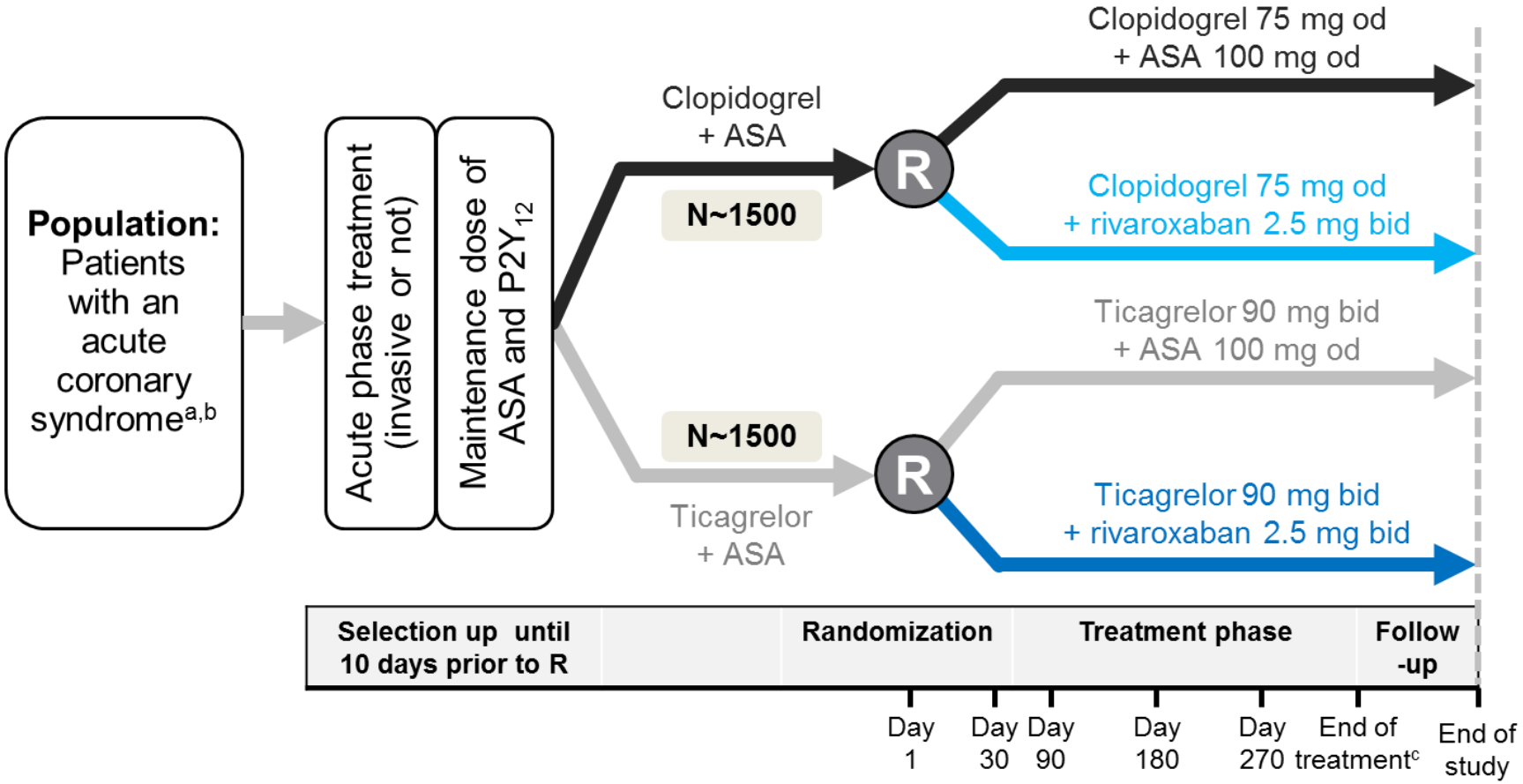
Difficulties in buying this concept

- Triple therapy in ACS is more complicated than DAPT using ticagrelor (or prasugrel)
- Identifying candidate patients is somewhat complicated
- Clopidogrel perceived as «an old drug»
- Is the lower mortality with rivaroxaban real? «*One swallow does not make spring*»
- Difficulties in accepting the much higher rates of bleeding

Can we then use rivaroxaban dropping aspirin in CAD?

GEMINI-ACS-1 Study Design

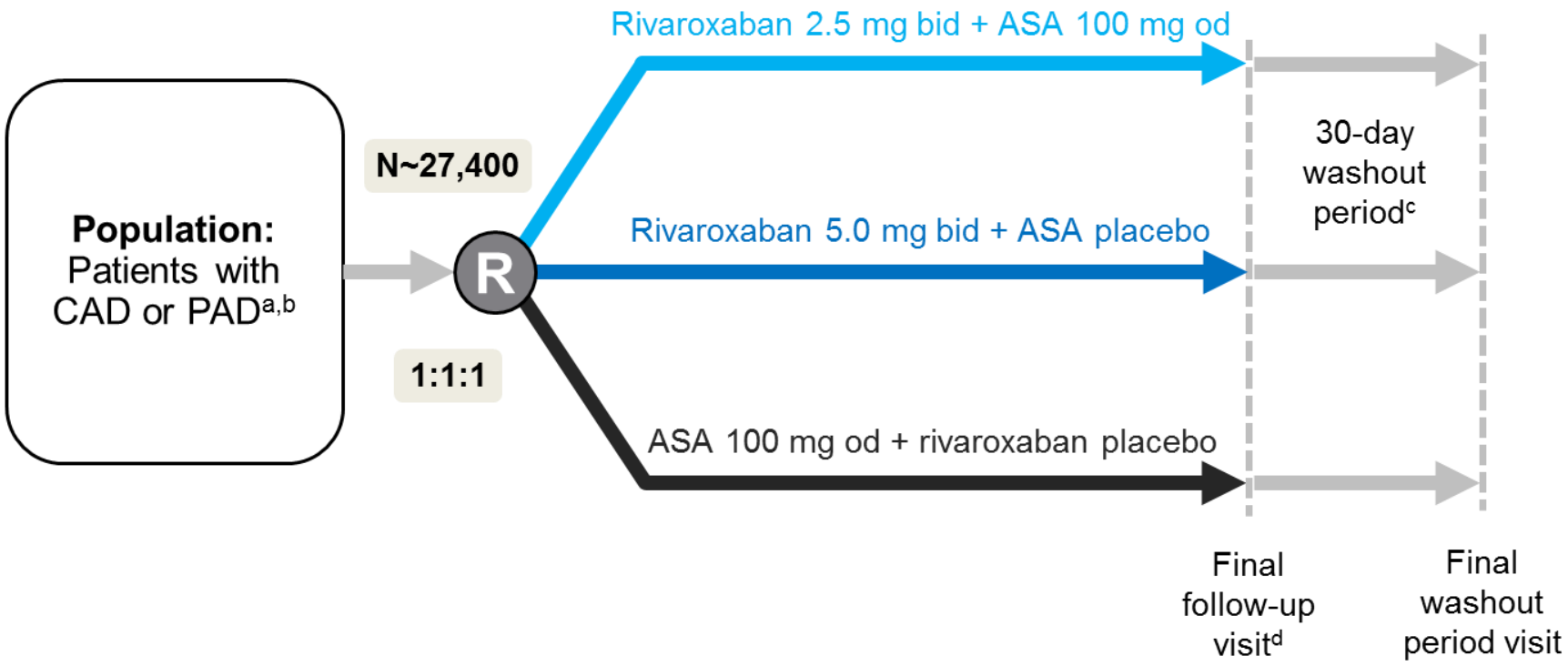
Objective: Safety of rivaroxaban versus ASA in addition to either clopidogrel or ticagrelor therapy in patients with a recent ACS



De Caterina R and Goto S, Vascul Pharmacol 2016; 81:1-14

COMPASS Study Design

Objective: Efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in patients with CAD or PAD



De Caterina R and Goto S, Vascul Pharmacol 2016; 81:1-14

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News Release

Not intended for U.S. and UK Media

Phase III COMPASS study with Bayer's Rivaroxaban in Patients with Coronary or Peripheral Artery Disease Shows Overwhelming Efficacy and Meets Primary Endpoint Early

08 Feb 2017

Conclusions

- A very exciting era in cardiology with NOACs, about 70 years after the patenting of warfarin as a rat poison!

Stay tuned!