The future of anticoagulation

lessons learned from vitamin K antagonists

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G|FK

A recent Clinical Case

- 84 year old lady admitted at the department of Internal medicine with pneumonia and congestive heart failure (treated with amoxycillin, furosemide, etc)
- Atrial flutter was recorded and the consulting cardiologist recommended *rivaroxaban* (15 mg)
- The kreatinin clearance was 30 ml/min; the next few days it was 22 and 20 ml/min

What would you do?

- Follow this advice?
- How to proceed
- Upon discharge: what kind of follow up?

NOACs and the revolution in anticoagulation

- New compounds welcome
- RCT's show good profiles of NOAC versus vitamin K antagonists (VKA)
- Switch towards simple and practical therapy is appealing to physicians and patients alike
- What will this bring along?

- Are we willing to proceed towards *unmonitored* anticoagulant therapy?
- Prevention of other CV diseases like diabetes, hypertension and dyslipidemia require some form of monitoring

ten Cate H. **New oral anticoagulants: discussion on monitoring and adherence should start now!** Thromb J. 2013 Jun 28;11(1):8.
ten Cate H. **Monitoring new oral anticoagulants, managing thrombosis, or both?** Thromb Haemost. 2012 May;107(5):803-5.

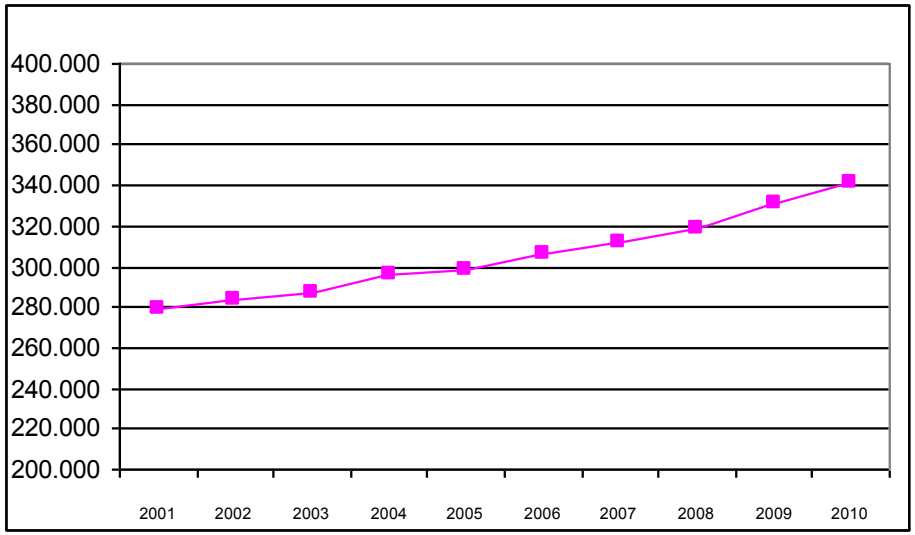
Summary annual reports FNT

Dutch Federation of Anticoagulation Clinics

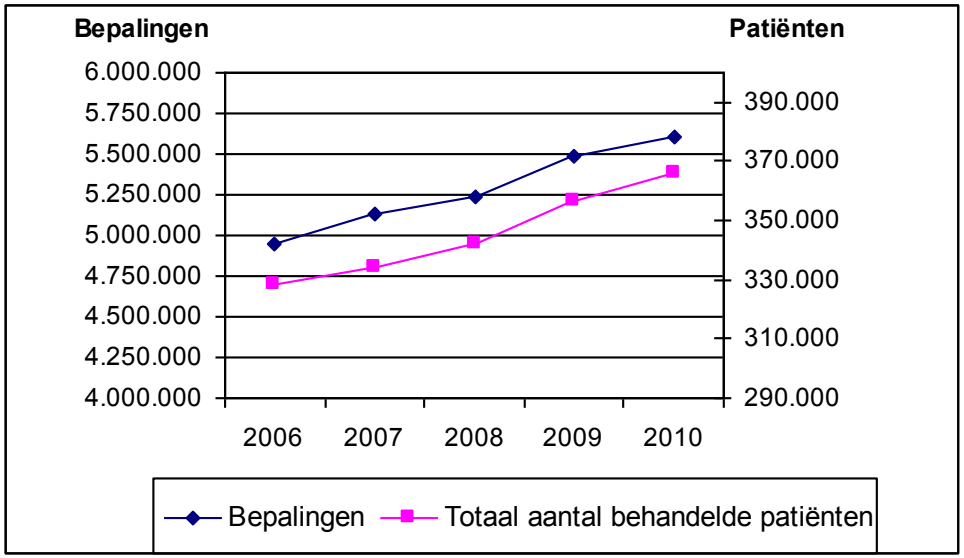
General AC clinic data 2013

- 58 AC clinics:
  - 460.000 patients
  - >6,0 million INR's
  - 40,3% blood collected at home
  - 81,1% acenocoumarol (8-97)

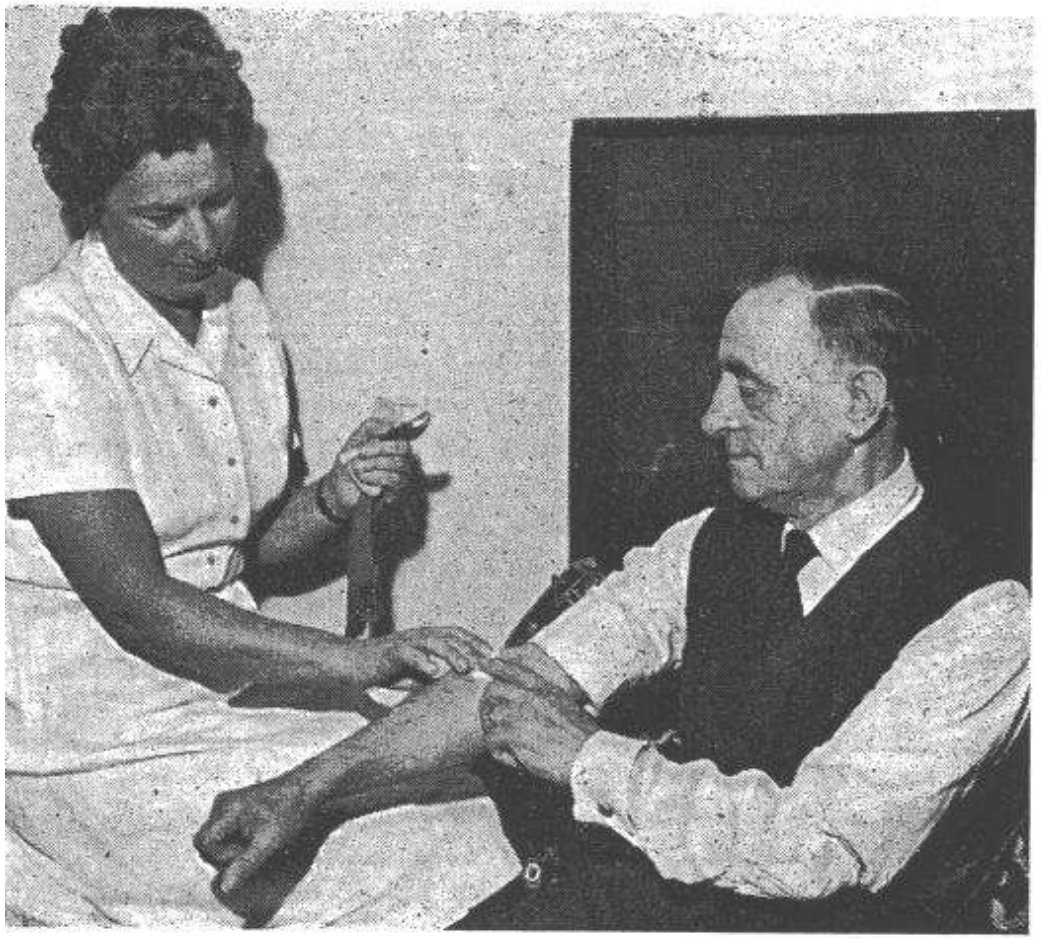
N of patients



N of pts and INR's



The Hague, 1952



Current anticoagulation practice

- Large population with AF, 50% > 75 years
- INR adjusted VKA (2.5-3.5); therapy is monitored, individually
- Side effects (bleeding) recorded
- Of course VKA are nuisance drugs!
- **Contact with patients!**

So why is this relevant?

- The existing AC network takes on responsibility for case management (on VKA)
- *With NOAC, specialists need to assume the case management role*
- With VKA, there were already (avoidable?) bleeding problems: **mainly due to lack of integrated care**

HARM (Hospital Admissions Related to Medication)

Table 1. Reasons for Potentially Preventable Medication-Related Hospital Admissions and the Associated Drugs

Reason for Admission	Preventable Admissions, No. (%) (n=332)	Associated Drugs (No. of Admissions[a])
Digestive system		
GI tract bleeding	48 (14.5)	Antiplatelets (34), NSAIDs (14), anticoagulants (12), oral corticosteroids (4)
GI tract symptoms (eg, diarrhea, constipation)	22 (6.6)	Oral antidiabetics (4), laxatives (4), diuretics (4), opiates (3), loperamide (3), statins (3), antibacterial drugs (3)
Circulatory system: cardiovascular symptoms (eg, dysrhythmias, heart failure)	35 (10.5)	β-Blockers (15), drugs affecting the RAAS (9), calcium antagonist (9), diuretics (9), anticoagulants (7)
Respiratory symptoms (eg, dyspnea)	26 (7.8)	Diuretics (12), respiratory drugs (6), β-blockers (6), NSAIDs (5)
Endocrine system: hypoglycemia or hyperglycemia	20 (6.0)	Insulin (18), oral antidiabetics (12), corticosteroids (3), diuretics (3)

Abbreviations: GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin angiotensin aldosterone system.
[a] An admission can be associated with more than 1 drug and is then mentioned more than once in the list.

Leendertse, A. J. et al. Arch Intern Med 2008;168:1890-1896.

ARCHIVES OF INTERNAL MEDICINE

Ministerie van Volksgezondheid,
Welzijn en Sport

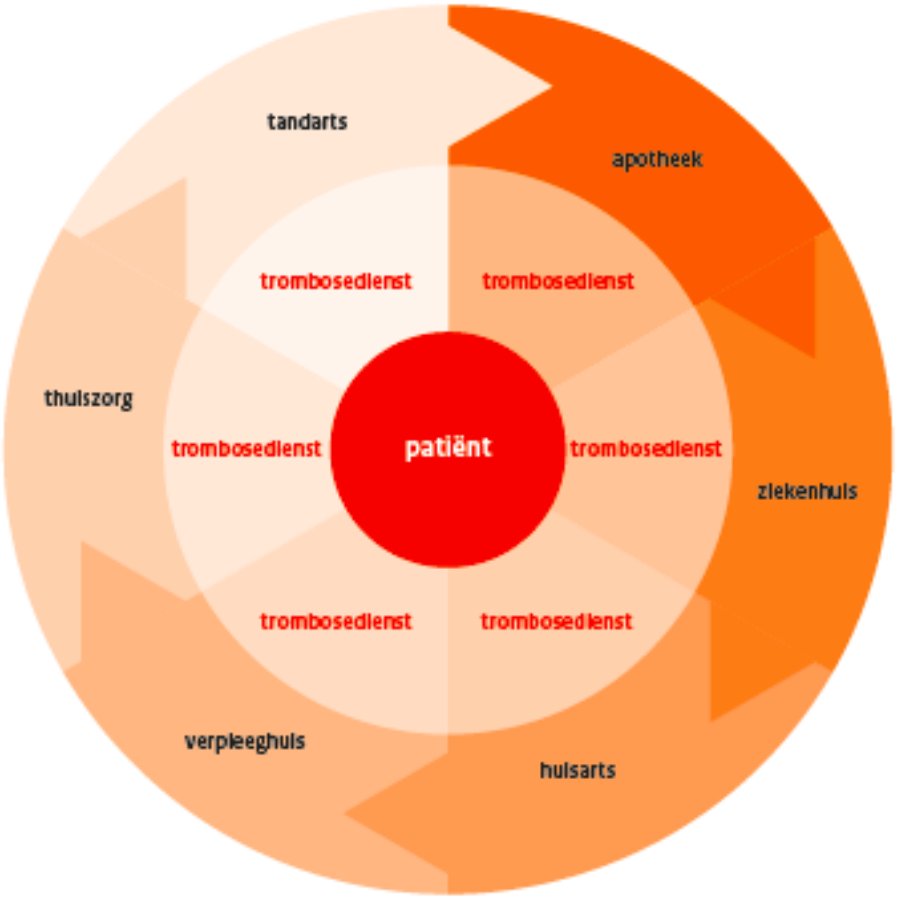
National Standard for Integrated Anticoagulation Care

Landelijke Standaard Ketenzorg Antistolling

voor de eerste- en tweedelijnszorg

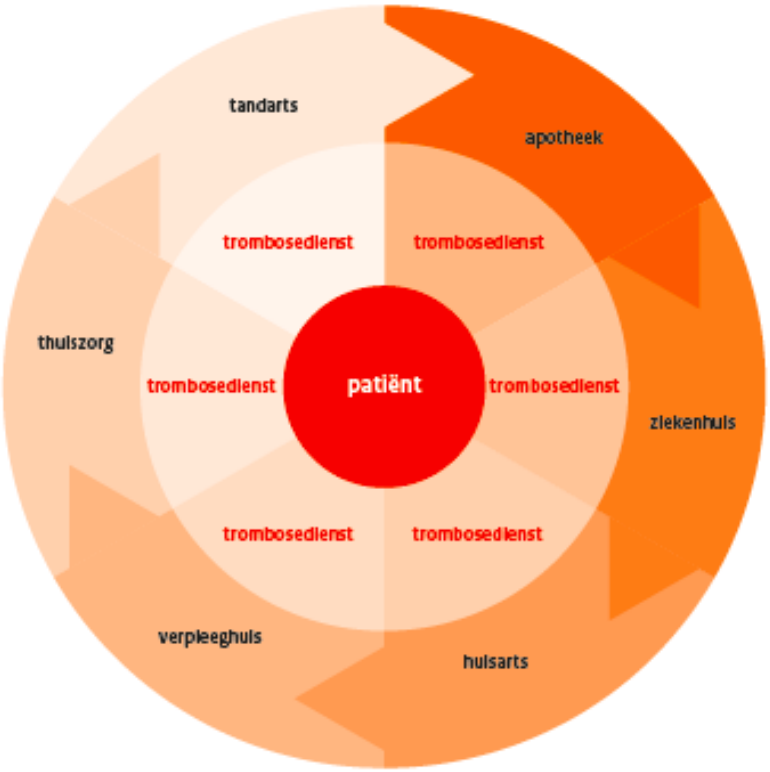
FNT, NVK, NIV, NMT, NHG, NVN, NVA, KNMP, NVZA, NVvC, NVvH, Verenso, De Hart&Vaatgroep

Projectrapportage in opdracht van het
Ministerie voor Volksgezondheid, Welzijn en Sport



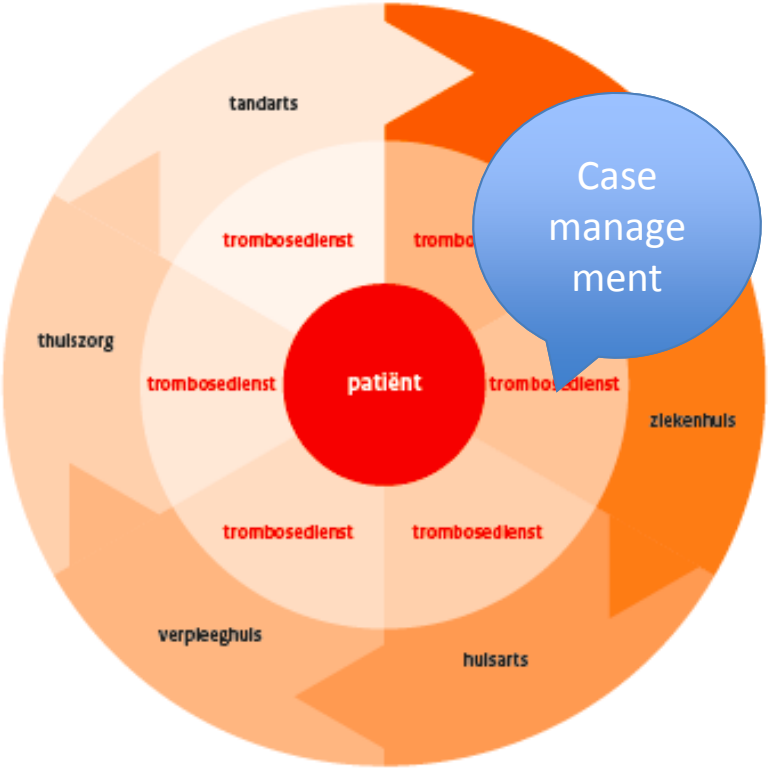
Organizes AC care in an integrated manner;
Patient in charge (central position)
AC clinic= case manager
Caretakers communicate!

Next step: patients on any kind of antithrombotic treatment is part of an integrated care chain



Accomplished May 2014

Next step: patients on any kind of antithrombotic treatment is part of an integrated care chain



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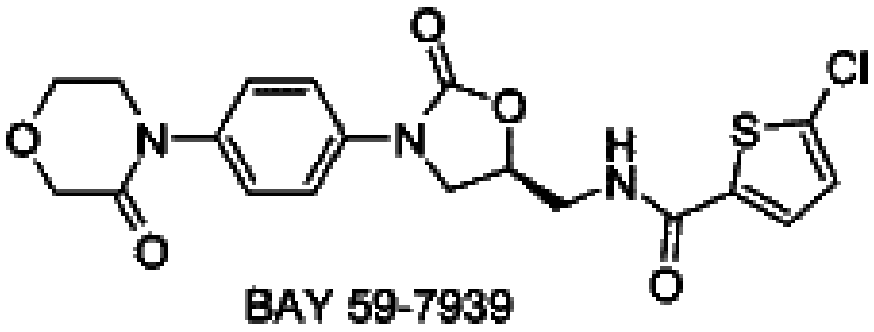
Landelijke Standaard Ketenzorg Antistolling

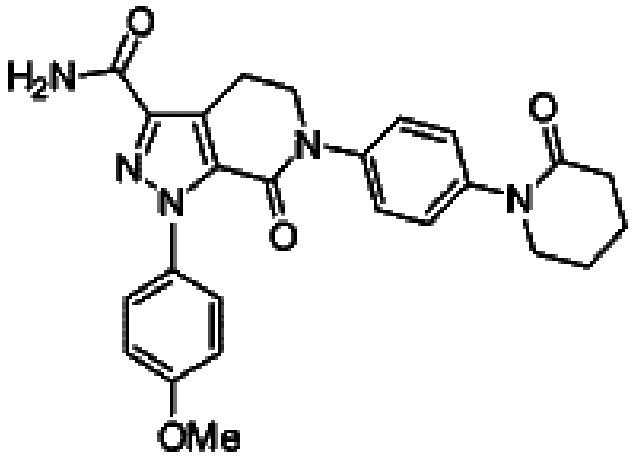
voor de eerste- en tweedelijnszorg

versie 2

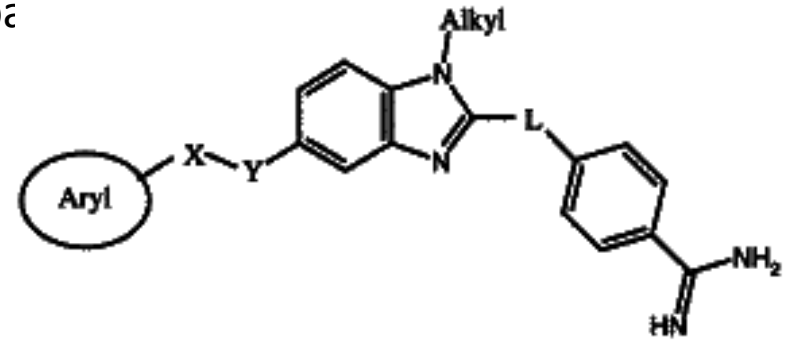
Non vitamin K dependent oral anticoagulants



rivaroxaba



apixaban



dabigatran

NOACs: unanswered questions

- Fixed dose “dogma”; no more monitoring necessary?
- Adherence issues in uncontrolled medication
- (how to monitor, reversal, thrombolysis, after recent stroke; when to resume; after ICH: when to resume; safe in multimorbid geriatric patients; is there a “therapeutic range”? Long term safety; *Hankey, Thromb Haemost 2014; 111: 808)*

Why a fixed dose?

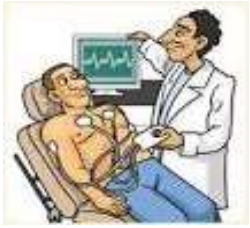
- To get rid of monitoring
- No biochemical basis
- Different with aspirin

Does fixed dose work?

- For VKA it failed
- Surprisingly: for NOACs, it works on average
- Larger therapeutic window, stable kinetics
- Nevertheless: interindividual variation; extreme concentrations will occur

Does one size fit all?

FU via anticoagulation clinic



start 1 month 3month 6month 12month

Referral + Consent

1 2 3 4 5

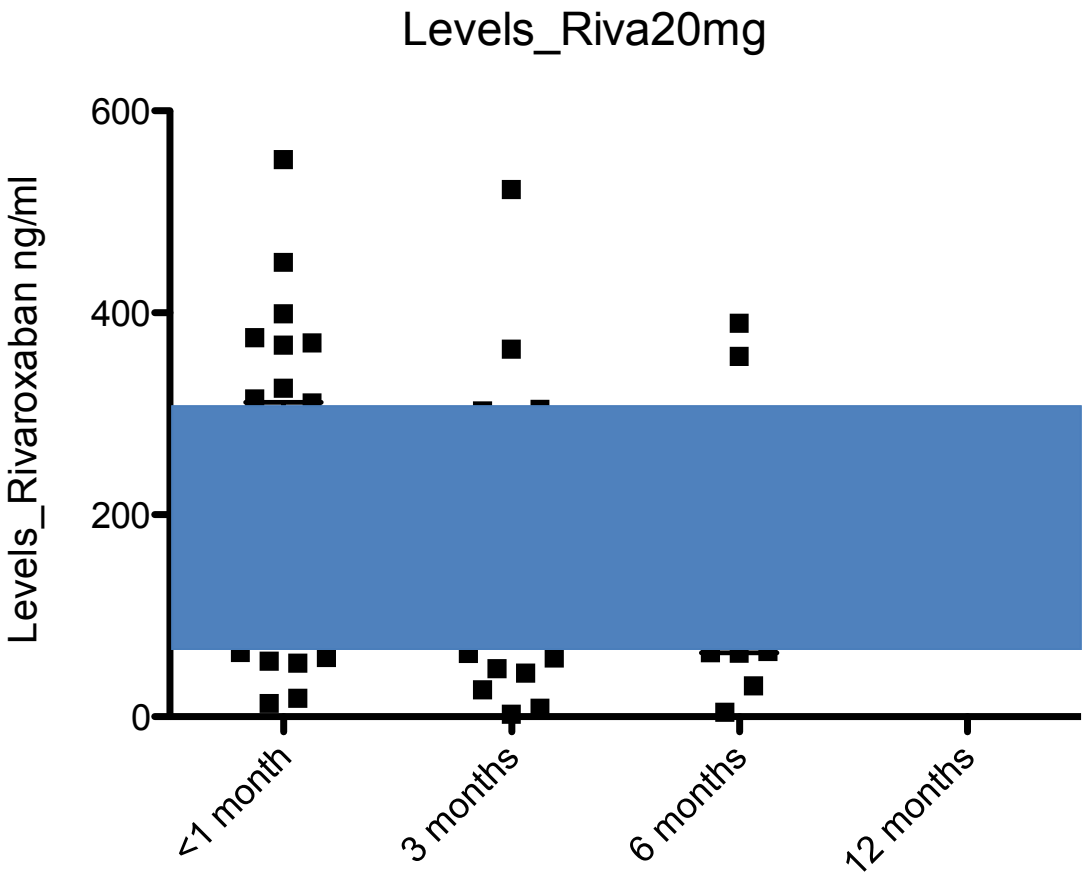
Lab tests MDRD | Lab tests | Lab tests MDRD | Lab tests | Lab tests MDRD

Complications + Morisky score | Complications + Morisky score | Complications + Morisky score | Complications + Morisky score

Observational " real life" study

ten Cate-Hoek et al, unpublished

Rivaroxaban



N=44

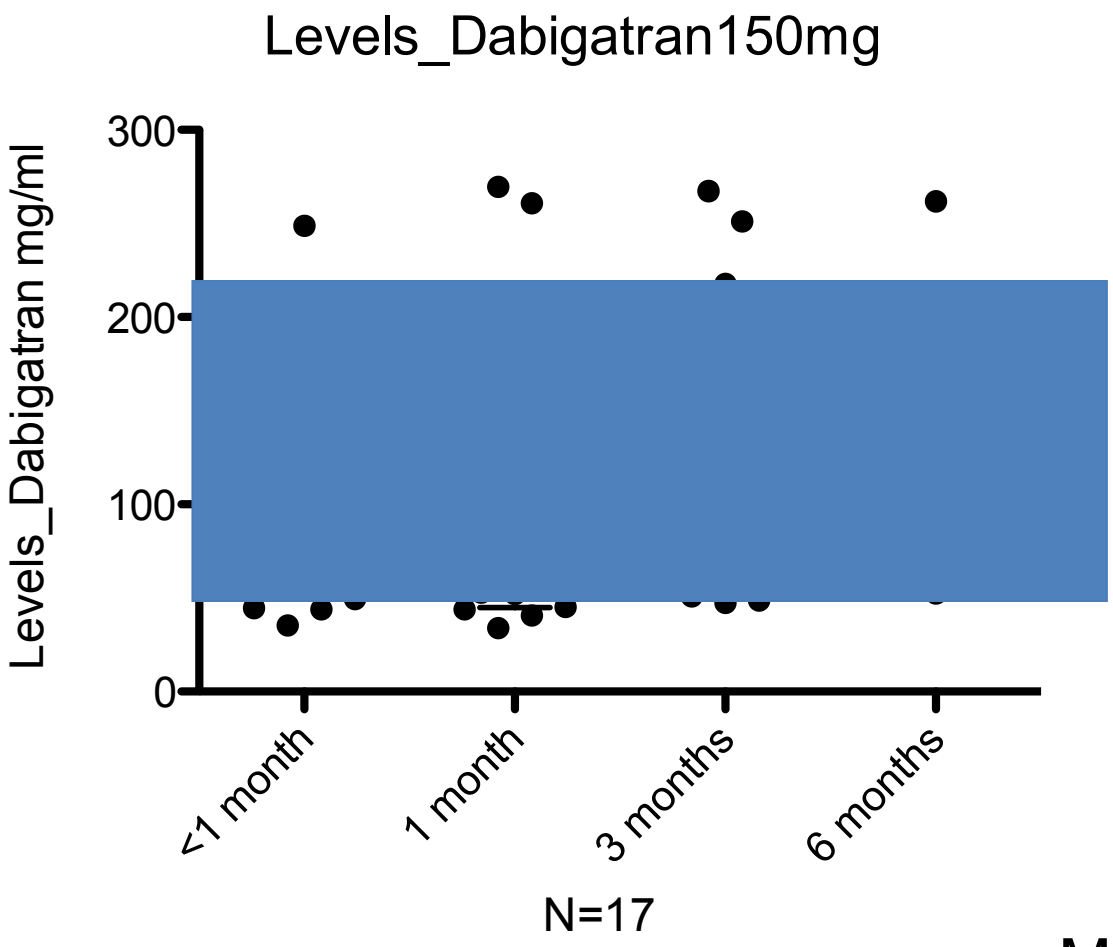
Median peak (IQR)

Timing and observed data

Timing	Plasma levels Rivaroxaban				
Evening n= 14	148(89-197)	128(94-246)	130(84-232)	176(63-286)	
Morning n= 30	194(76-347)	253(60-324)	109(35-284)	246(49-324)	261(167-283)

Blood sampling between 9.00 – 11.00 am

Dabigatran



Median peak (IQR)

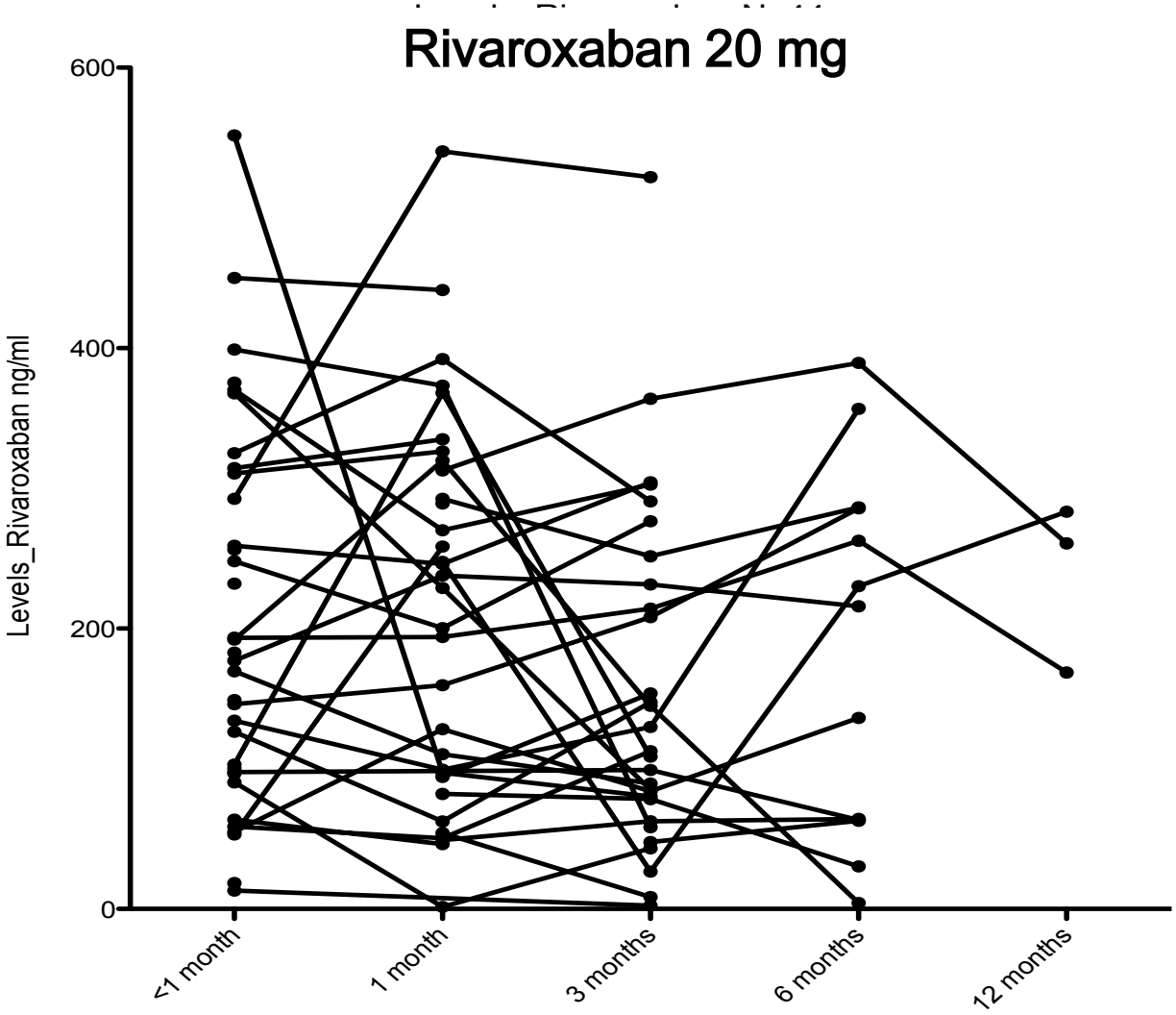
Published plasma concentrations

Drug	C peak (range)	C trough (range)
Rivaroxaban 20 mg od	215 ng/mL (22-535)	32 ng/mL (6-239)
Dabigatran 150 mg bid	175 ng/mL (117-275)	91 ng/ml (61-143)

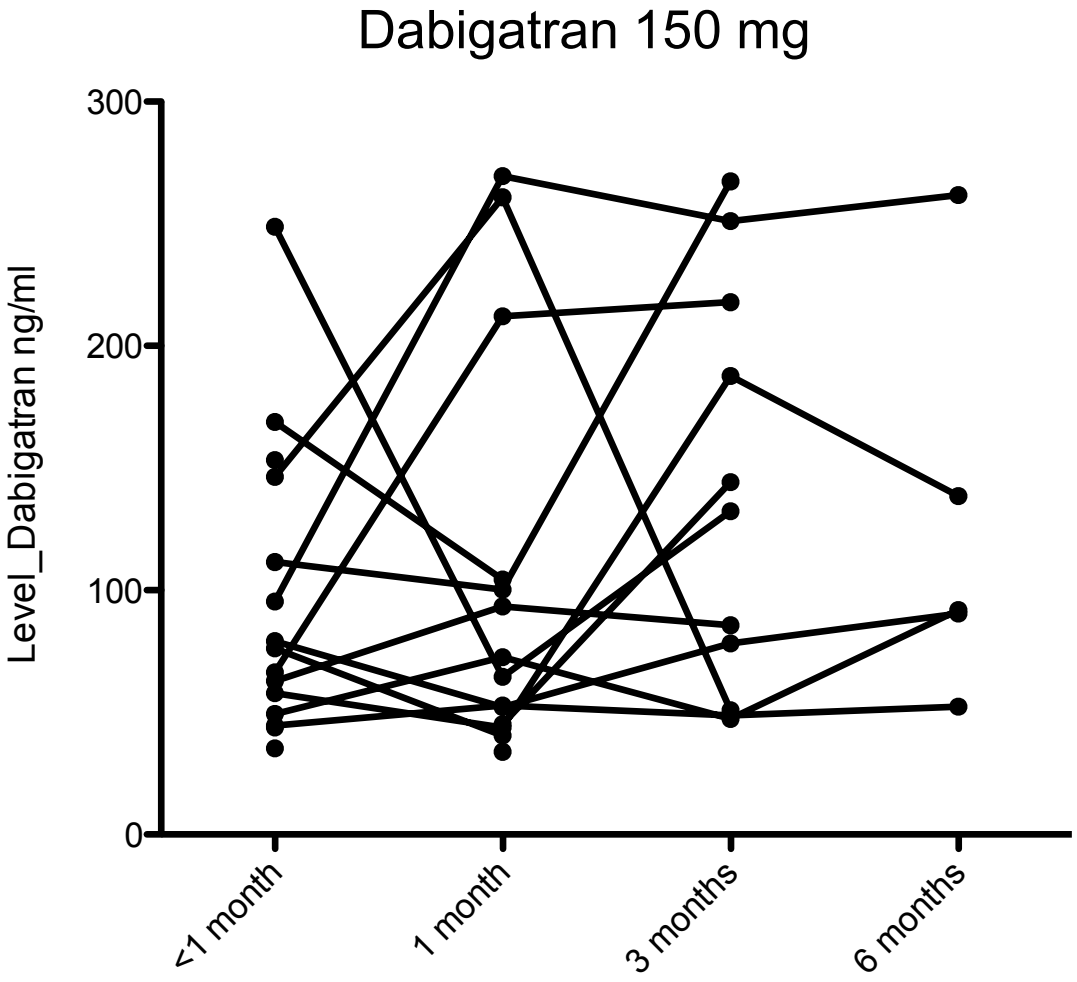
Peak 2 hours after ingestion,
troughs 24 and 12 hours respectively

Tripodi. Blood 2013 121:4032-35

Levels per patient over time



Levels per patient over time



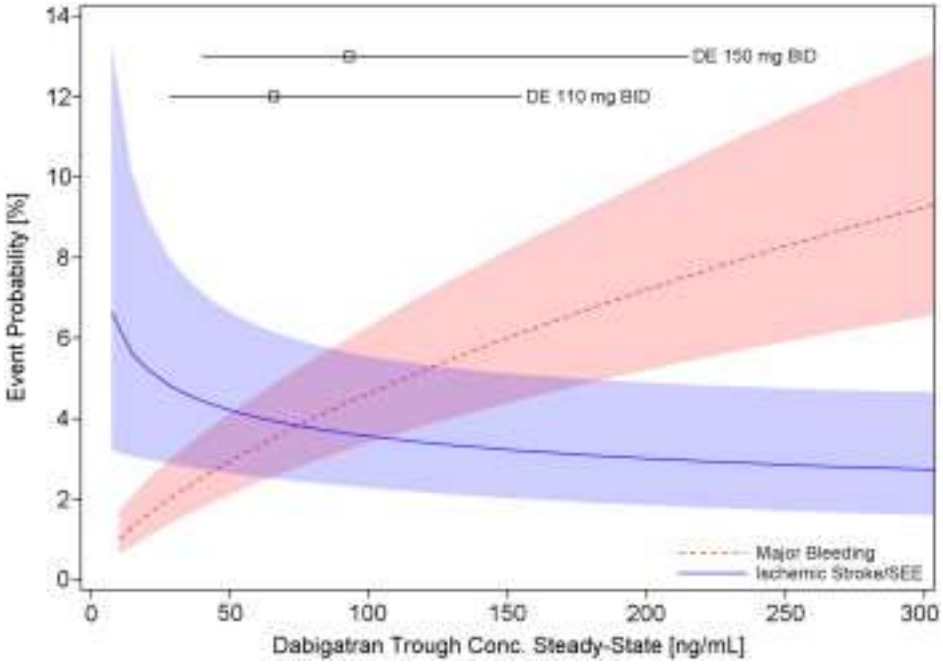


Figure 2 Probability of Major Bleeding Event and Ischemic Stroke/SEE Versus Trough Plasma Concentration of Dabigatran Calculated for 72-year-old male atrial fibrillation patient with prior stroke and diabetes. Lines and boxes at the top of the panel ind...

Paul A. Reilly , Thorsten Lehr , Sebastian Haertter , Stuart J. Connolly , Salim Yusuf , John W. Eikelboom , Micha...

The Effect of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients : The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy)

Journal of the American College of Cardiology, Volume 63, Issue 4, 2014, 321 - 328

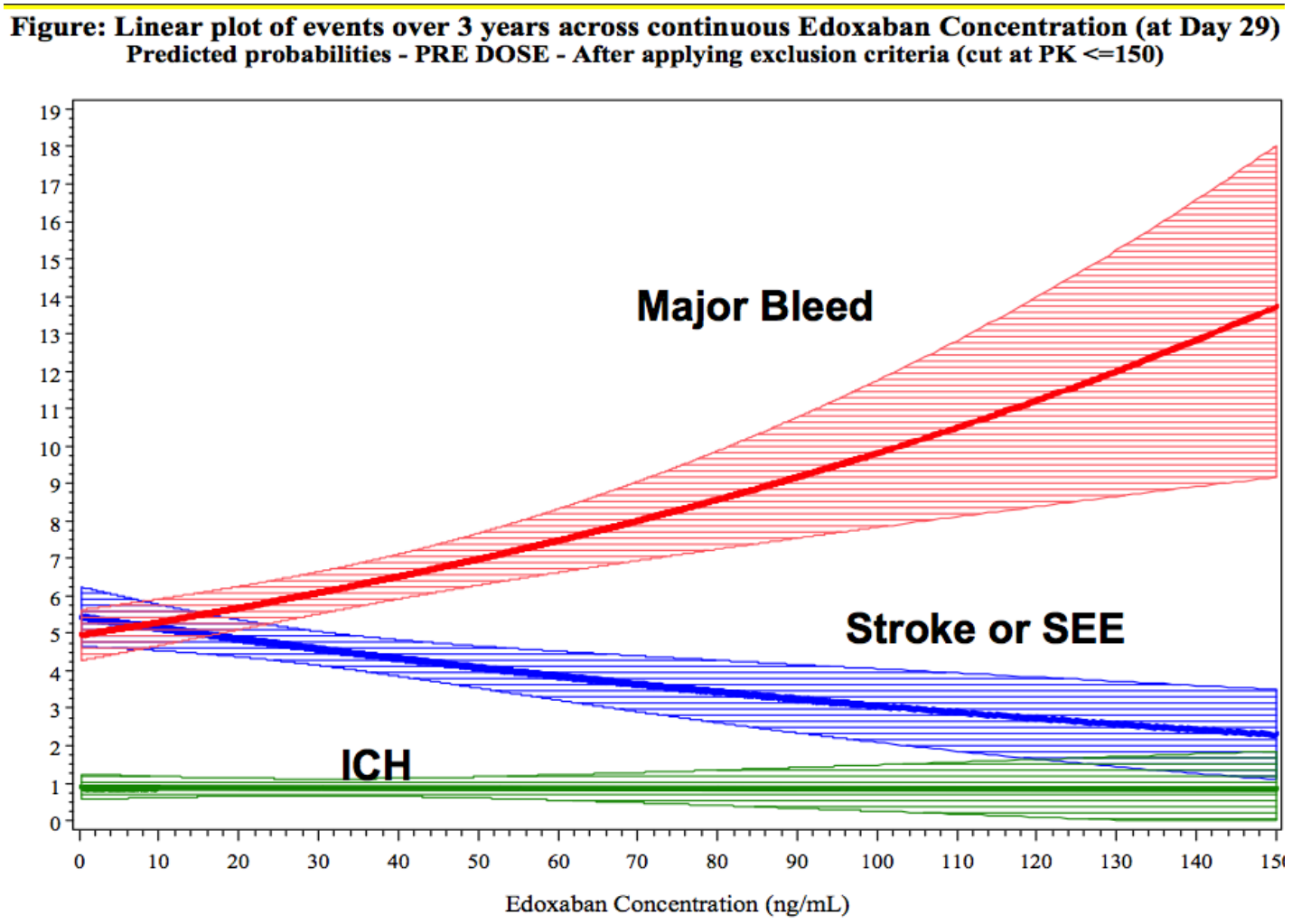
Levels & Patient characteristics

- Long-term FU RE-LY, 9183 pt, 112 isch. stroke (1.3%), 323 major bleed (3.8%)
- IS inversely related to trough ($p=0.045$),age and previous stroke ($p<0.0001$)
- Major bleed related to dabigatran overexposure ($p<0.0001$),age ($p<0.0001$) and ASA use ($p<0.003$) and diabetes ($p<0.018$)

Reilly et al. J Am Cardiol 2014;63:321-8

Edoxaban trough & outcomes

Probability of events over 3 years

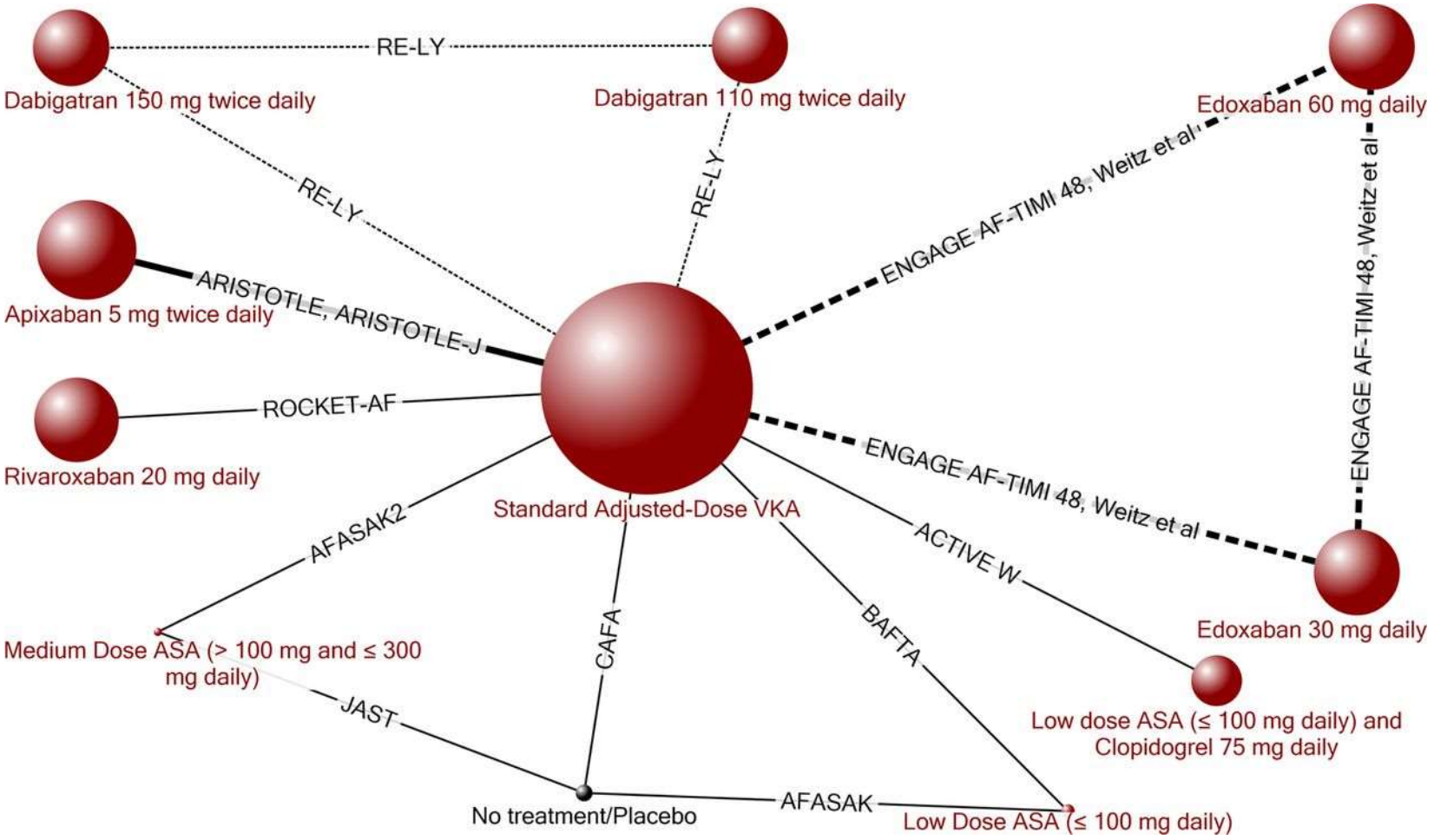


Engage AF, TIMI 48, presented at ESC 2014

Tailoring NOAC therapy?

- Select an anticoagulant (VKA or NOAC) on the basis of clinical criteria (age, morbidity, *eg* renal function; "frailty" (what is more important: robust efficacy or safety??), estimated adherence
- In case of NOAC, check PK in individual patient; at least trough (and peak?) value
- Consider switching therapy based on plasma activity (ideally knowing for all NOACS the therapeutic window)

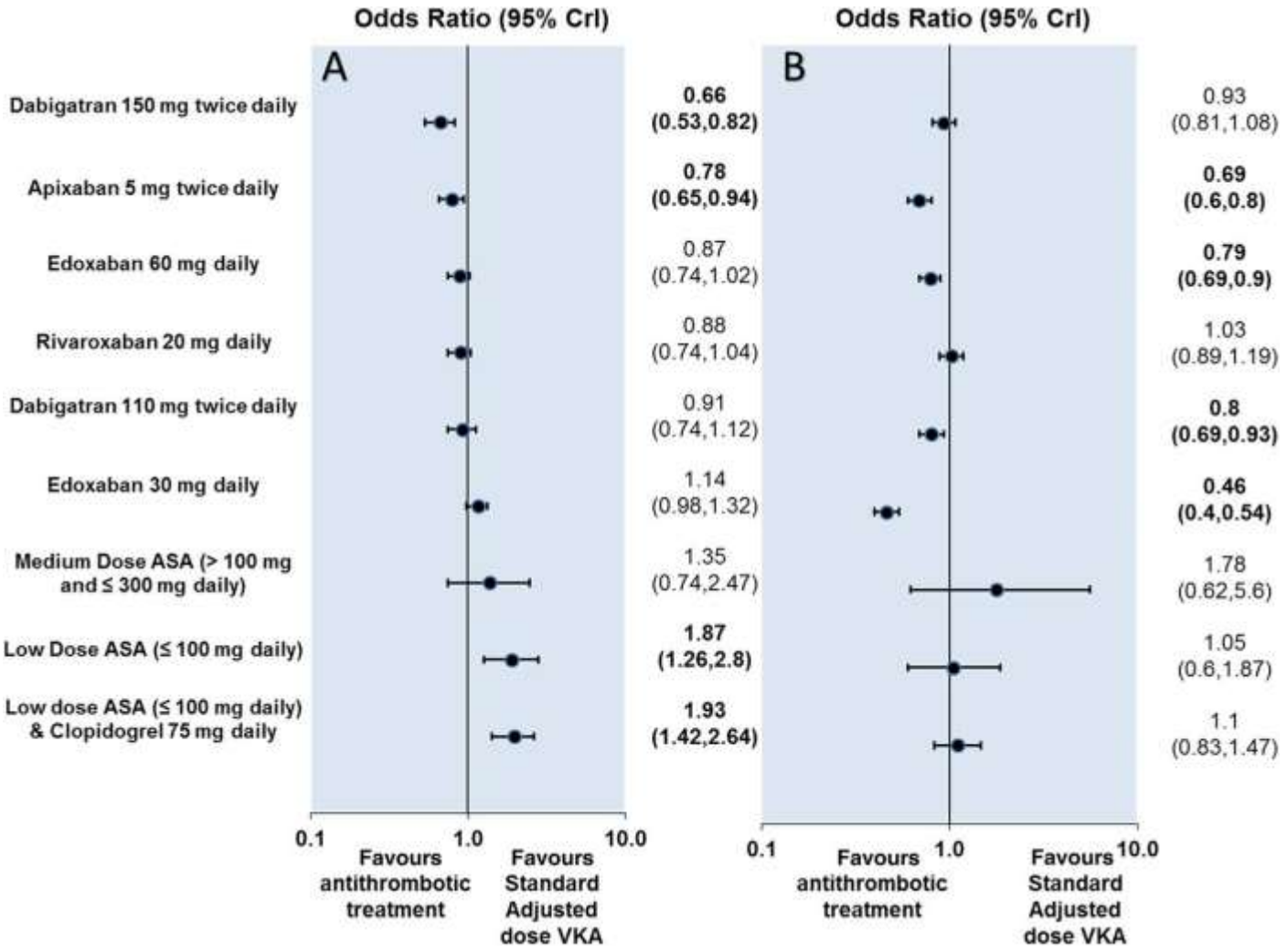
Evidence network for all-cause stroke or systemic embolism.



Cameron C et al. BMJ Open 2014;4:e004301

BMJ Open

OR for all-cause stroke or systemic embolism (A) and major bleeding (B) in Bayesian network meta-analysis versus standard adjusted dose VKA. CrI, credible interval; VKA, vitamin K antagonist.



Cameron C et al. BMJ Open 2014;4:e004301

BMJ Open

Adherence issues in uncontrolled medication

- CV medication: overall poor adherence
- What are the risk factors?
- NOACs: limited data

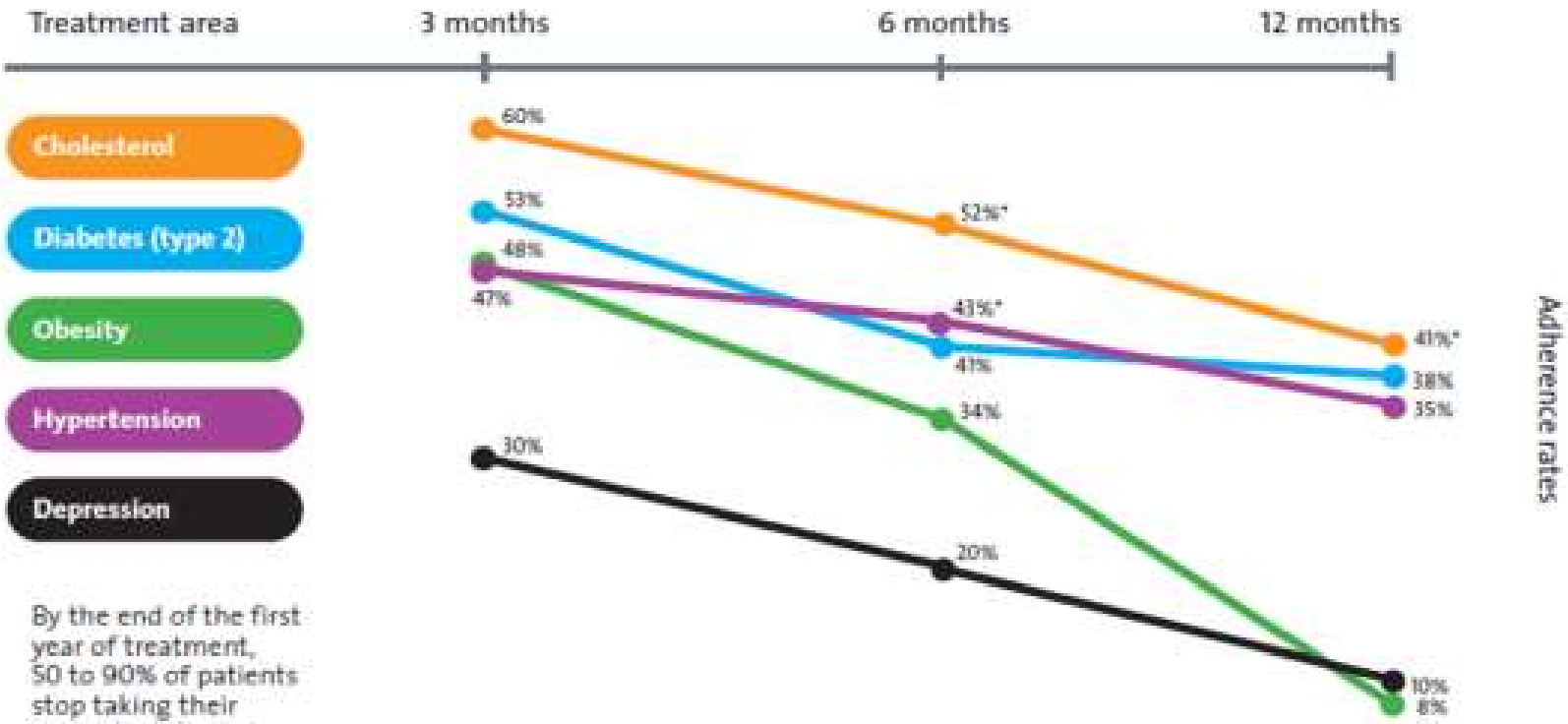
Adherence to medication: proper intake of medication when properly described

Maintenance: the extent to which a patient continues good health practices without professional supervision

Compliance: the extent to which a patient implements a prescribed remedy

Many patients stop taking their medications

Adherence rates plummet in just a few months



By the end of the first year of treatment, 50 to 90% of patients stop taking their prescribed therapies.

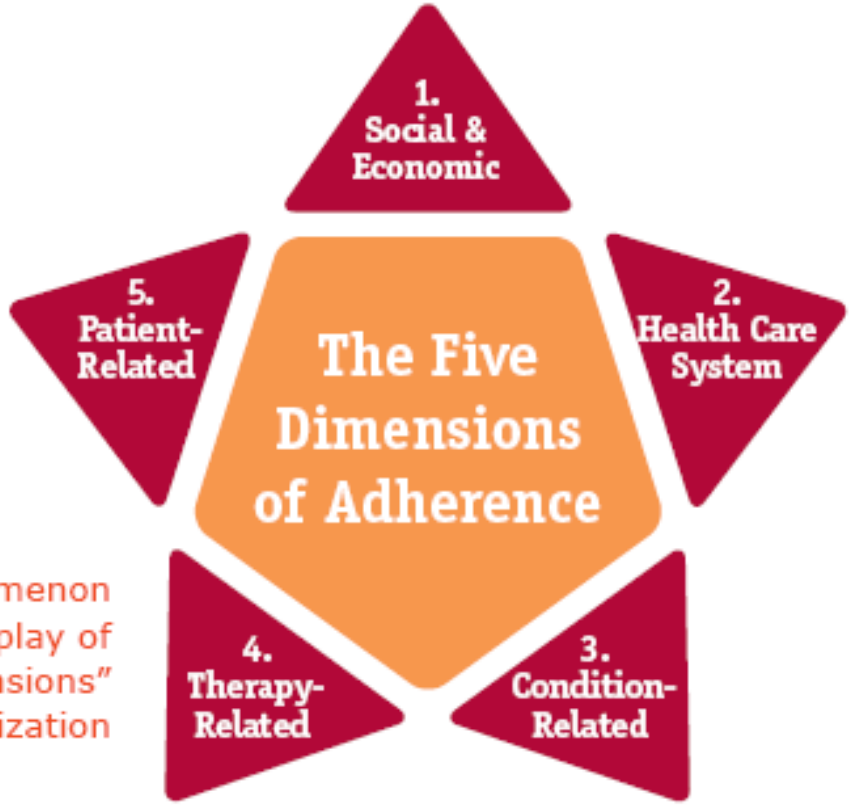
* Adherence rate ranges were averaged. **Source:** Various sources; A.T. Kearney analysis

Reasons for non-adherence

- Forgetfulness: 30%
- Other priorities 16%
- Personal decision to omit doses 11%
- Misunderstanding 9%
- Emotional factors 7%
- No reason provided ±27%

"Adherence is the extent to which a person's behavior [in] taking medication... corresponds with agreed recommendations from a health care provider"

(World Health Organization, 2003)



Adherence is a multidimensional phenomenon determined by the interplay of five sets of factors, termed "dimensions" by the World Health Organization

Recent data on adherence to NOAC (dabigatran)

- 70 pts, New Zealand; 24% discontinued *(Michel et al, Heart Lung Circ 2013)*
- 102 pts, New Zealand; 30% after 9 mo *(Thorne et al, Int Med J 2014)*
- 10,664 users; 25.7% discontinued < 6 mo; of those, a third switched to warfarin *(Jacevicius et al, abstract ASH 2013)*

- 17,691 pts: 39.9% were non persistent and the majority of those were not treated with warfarin upon discontinuation! *(Tsai et al, Am J Managed Care 2013)*

- 6256 cohort; 81% had a gap in therapy with a median of 2 gap days. Lower adherence was associated with a higher risk of death/stroke (HR 1.20 per 0.1 unit lower PDC, and HR 1.13 for stroke only) *(Shore et al, abstract ASH 2013)*

A possible way to go in NOAC management

- Structured, integrated care
- Frequent patient contacts
- Education, check on side effects, complications, proper drug intake
- Check NOAC activity level, renal (and liver?) function at least annually (first 2 years per 6 months)
- Expert centres for guidance, training, complex patient consultation etc

Thrombosis working group:
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Questions?

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