MINISTERIO DE SANIDAD, POLÍTICA SOCIAL E IGUALDAD

agencia española de medicamentos y productos sanitarios

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Dose-finding in the cardiovascular therapeutic area: The novel oral anticoagulants

## EMA EFPIA Workshop on dose-finding and dose-selection
## 04-05 December 2014
## 30 Churchill Place, Canary Wharf, London E14 5EU

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# DISCLAIMER

This presentation might not be the view of the EMA-CHMP-CVSWP or AEMPS.

The ideas expressed here represent my personal view and do not bind the organisations mentioned above or any other party.

# GENERAL PRINCIPLES

- **ICH E8:** General considerations for clinical trials.

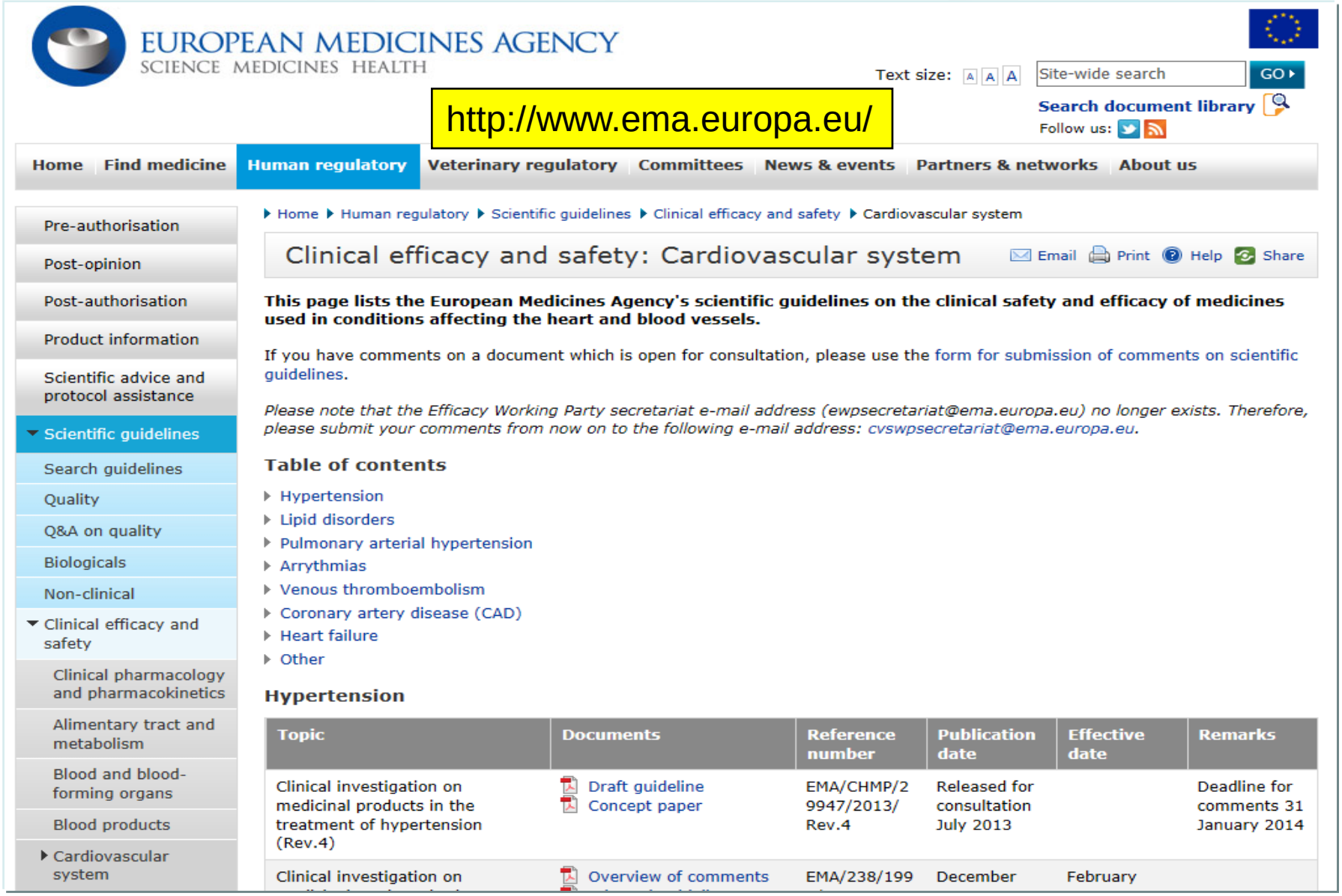
| *Type of Study* | *Objective of Study* | *Study Examples* |
|---|---|---|
| **Therapeutic Exploratory** | • Explore use for the targeted indication<br>• Estimate dosage for subsequent studies<br>• Provide basis for confirmatory study design, endpoints, methodologies | • Earliest trials of relatively short duration in well- defined narrow patient populations, using surrogate or pharmacological endpoints or clinical measures<br>• Dose-response exploration studies |

- **ICH-E4:** Dose-response information to support drug registration

**ICH E8:** http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E8/Step4/E8_Guideline.pdf
ICH E4: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E4/Step4/E4_Guideline.pdf

# EMA CARDIOVASCULAR GUIDELINES

- As for November 2014: 39 guidelines/concept papers

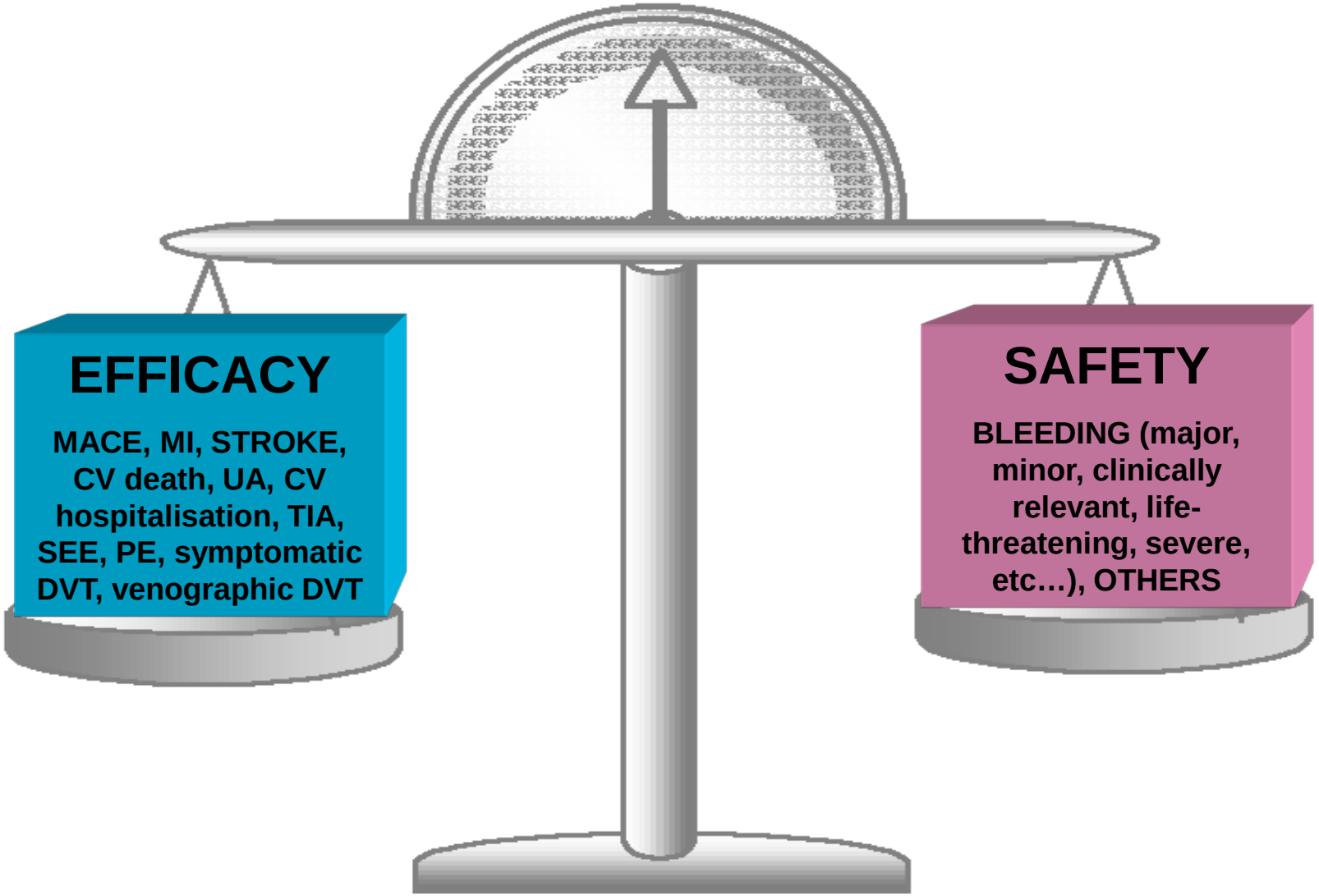


# EMA B/R Project: qualitative four-fold model of “benefits” and “risks”

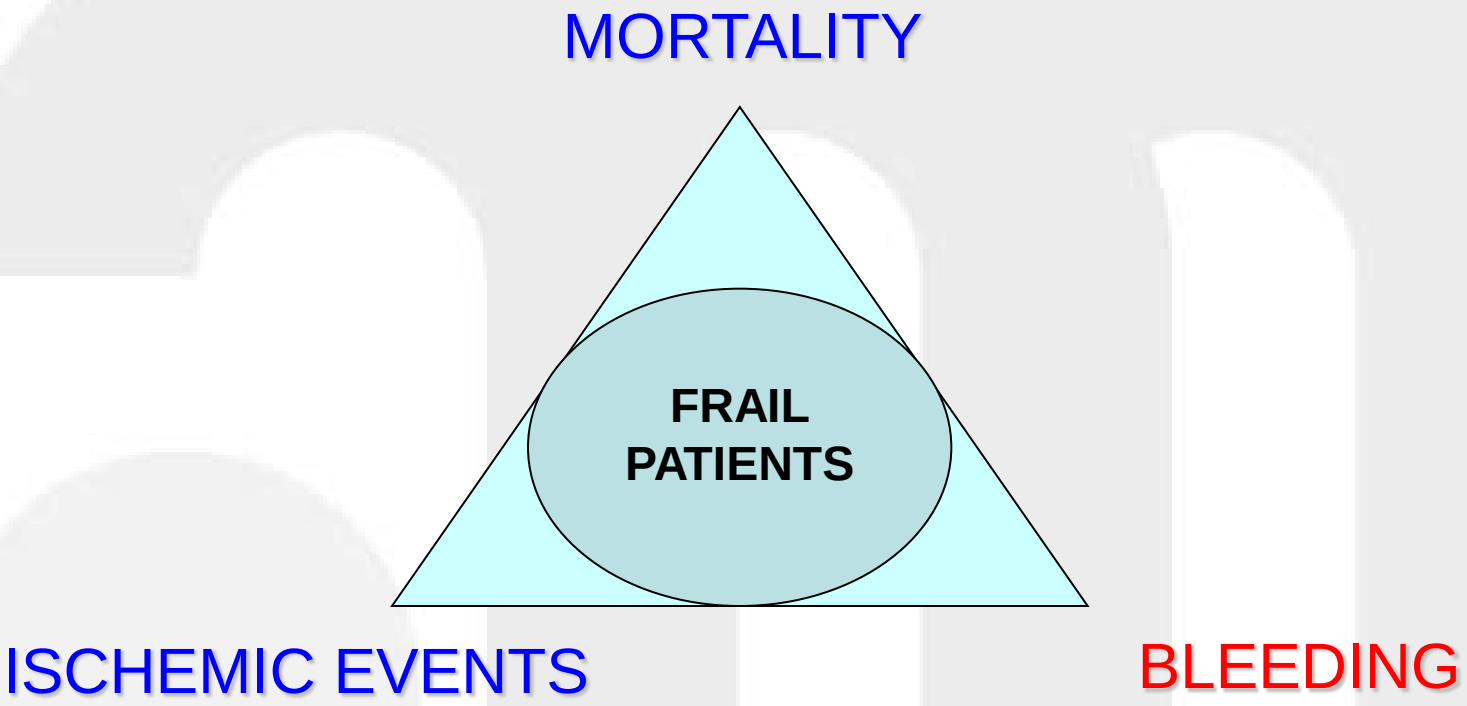
| | |
|---|---|
| Favourable Effects | Uncertainty of Favourable Effects |
| Unfavourable Effects | Uncertainty of Unfavourable Effects |

EMA (2010). Benefit-risk methodology project work package 2 report: Applicability of current tools and processes for regulatory benet-risk assessment. EMA/549682/2010.

# BENEFIT-RISK: ANTITHROMBOTICS



# RELATIONSHIP BETWEEN OUTCOMES



# PHASE II STUDIES: NOVEL ORAL ANTICOAGULANTS

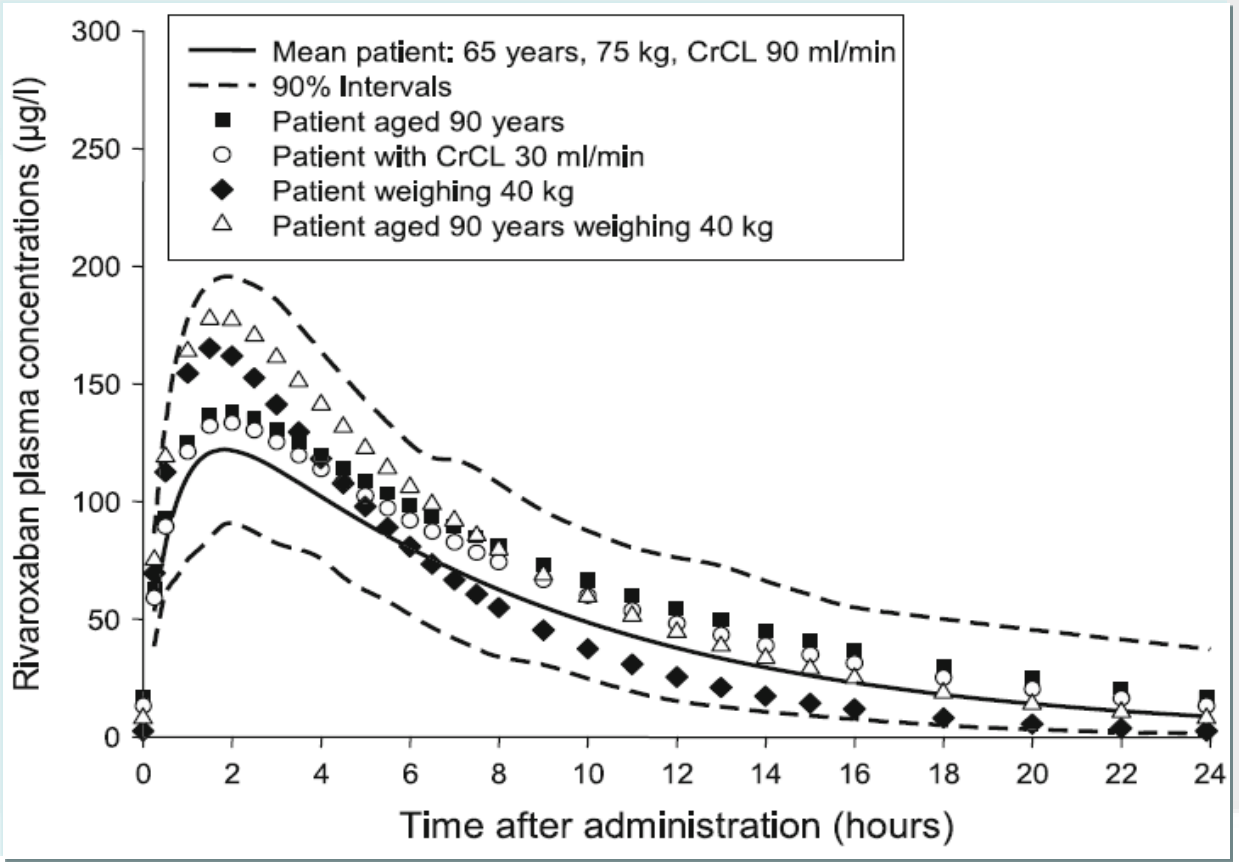
- **Target:** Choice of optimal dosing strategy (daily dose, administration interval, timing of administration). Balance between bleeding (and other AEs) vs. thrombotic risk.
- **Dose-exposure:** dose-exposure relationship (phase I-II) investigating intrinsic (e.g.: age, gender, weight, renal function) and extrinsic factors (e.g.: concomitant medications, PK/PD interactions).
- **Methods for assessing safety:** bleeding events of heterogeneous relevance (use of standardized definitions).
- **Methods for inferring efficacy:** a) surrogate imaging endpoints; b) Biomarkers (antithrombotic effect, bleeding risk): inhibition of factor Xa, thrombin, effect on coagulation tests (aPTT; PT; ECT; TAT complexes, etc).

aPTT = activated partial thromboplastin time; PT = prothrombin time; ECT = ecarin clotting time; TAT complexes: Thrombin-antithrombin complexes.

# Exposure: patients undergoing surgery

**Simulations of rivaroxaban plasma concentrations after a 10-mg once-daily dose in patients who have undergone hip replacement surgery.**

Patients who are elderly, have renal impairment, have low body weight, or are elderly with low body weight, have predicted average plasma concentrations that fall within the boundaries for the overall population (90%CI).

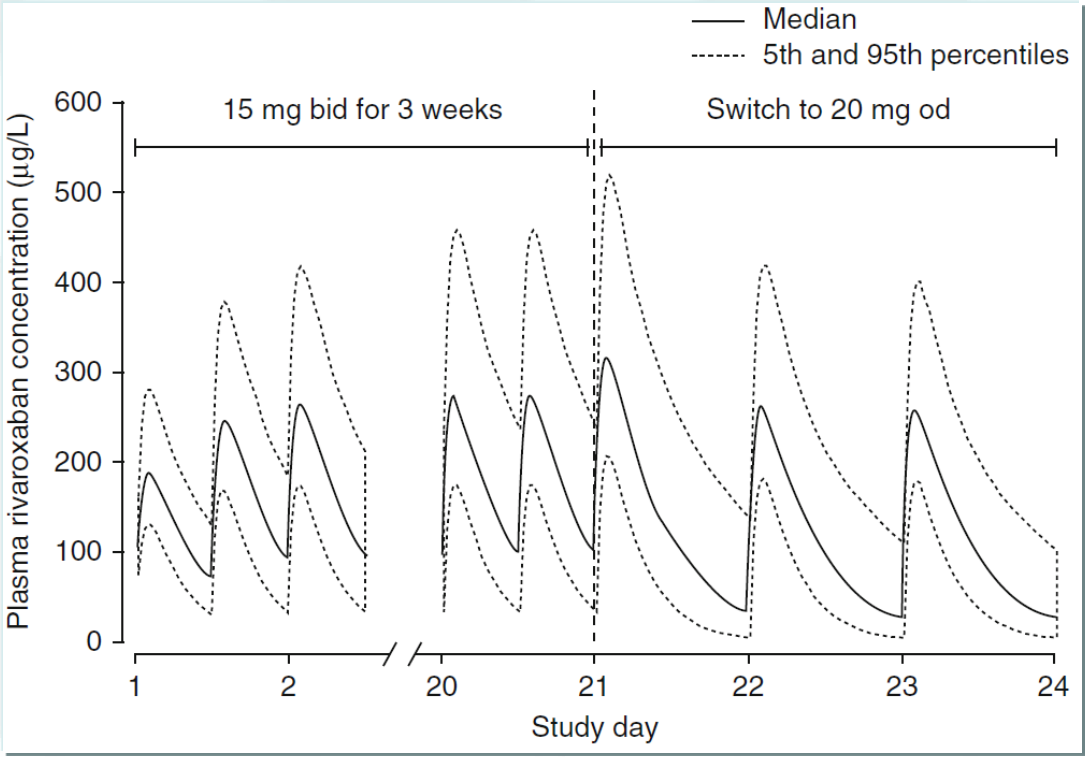



Mueck et al. Thromb Haemost. 2008;100:453–61.

# Exposure: Patients with acute VTE

**Simulated VTE treatment dosing regimen of rivaroxaban 15 mg bid for 3 weeks, followed by 20 mg od.**

Rivaroxaban exposure remains consistent during the transition, indicating that antithrombotic activity should be maintained. bid twice daily, od once daily

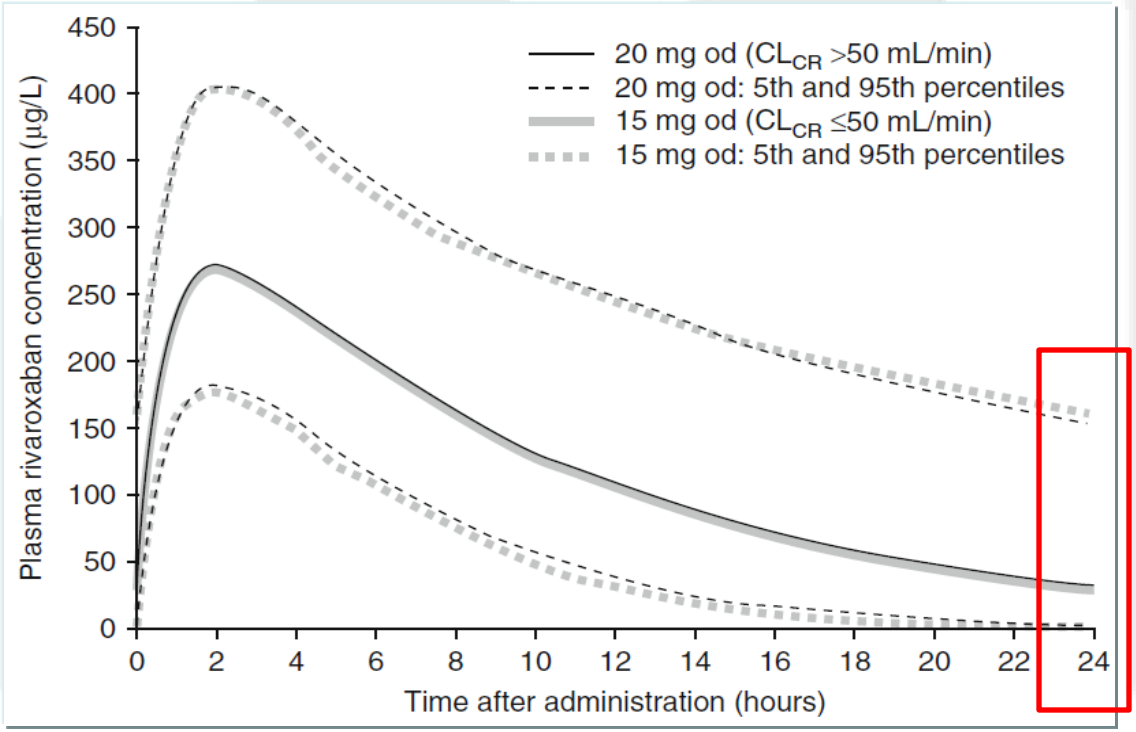



Mueck et al. Clin Pharmacokinet. 2011;50:675–86.

# Exposure: Patients with Atrial Fibrillation

**Simulated rivaroxaban plasma concentration–time profiles for a virtual population of patients with atrial fibrillation.**

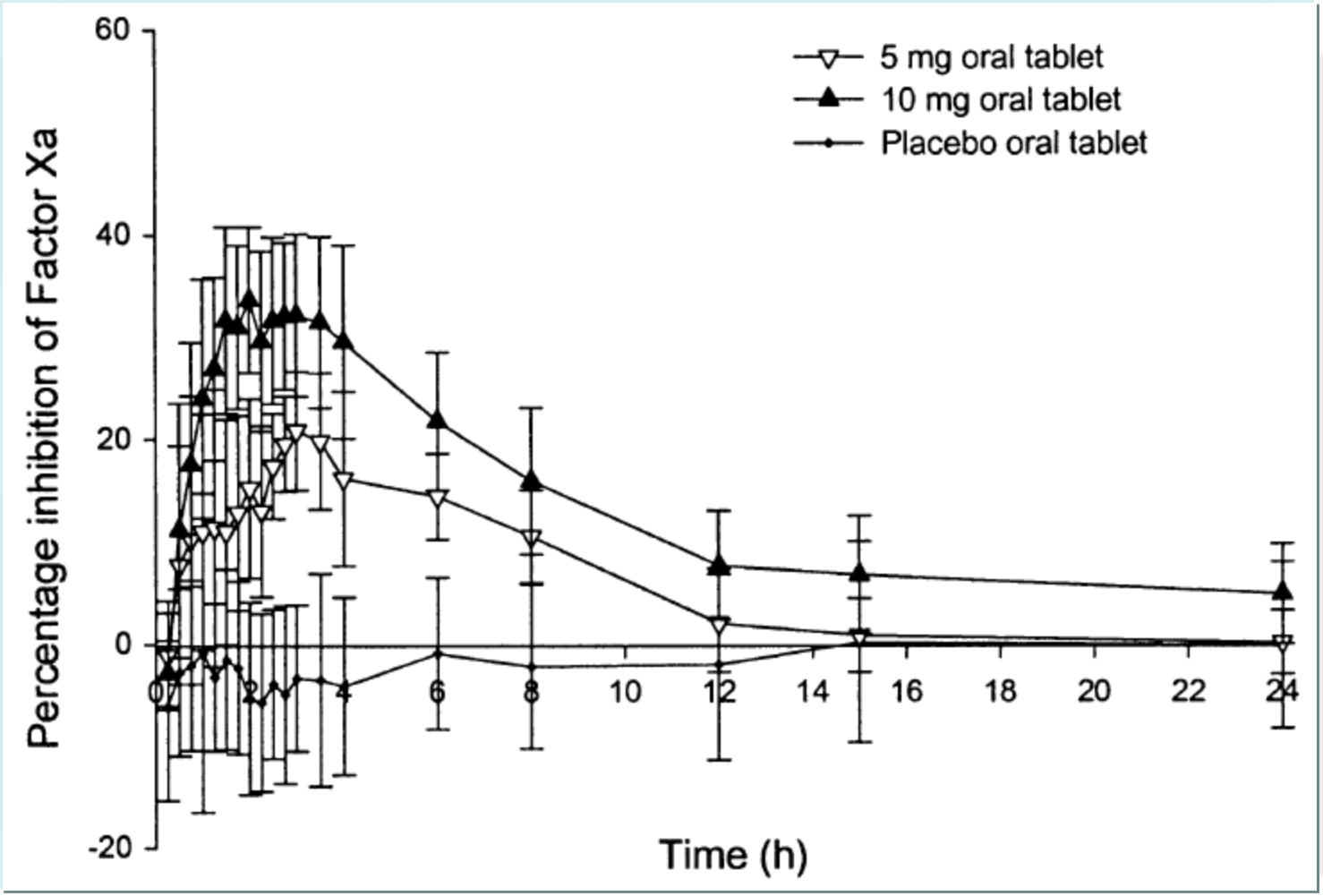
For patients with mildly impaired or normal CrCl (>50 mL/min), exposure is the same with a 20 mg od dose as for patients with moderate renal impairment (≤50 mL/min) with a 15 mg od dose.
CrCl creatinine clearance, od once daily




Mueck et al. Clin Pharmacokinet. 2011;50:675–86.

# Biomarkers

Median percentage change from baseline in Factor Xa inhibition after administration of rivaroxaban.




Mueck et al. Thromb Haemost. 2008;100:453–61.

# Methods for assessing safety

- Bleeding events.
- Overall and specific adverse events depending on the pharmacology of the new compound.

# BLEEDING DEFINITIONS

Rationale for the definition

↓

Definition

↓

Collection

↓

Assessment

**Do we need it?**

**Has it been validated?**

**How does it compare with other definitions?**

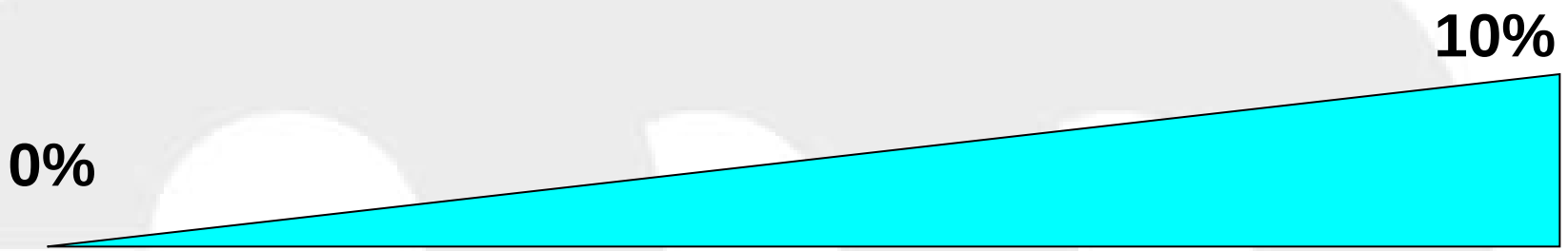
**Is it clinically relevant?**

**Is it associated to objective measurements of blood loss?**

**Does it overestimate or infraestimate bleeding risk?**

**Is it associated to a standardised method for collection?**

# BROAD RANGE OF MAJOR/SEVERE BLEEDING RATES DEPENDING ON DEFINITIONS




**ACS*:** COMMIT - TIMI – GUSTO – CURE – PLATO – ACUITY

**VTE**:** RECORD – ISTH – ISTF – EMA

**AF:** RE-LY – ISTH

*Quinlan et al. Eur Heart J. 2011; 32: 2256-65.

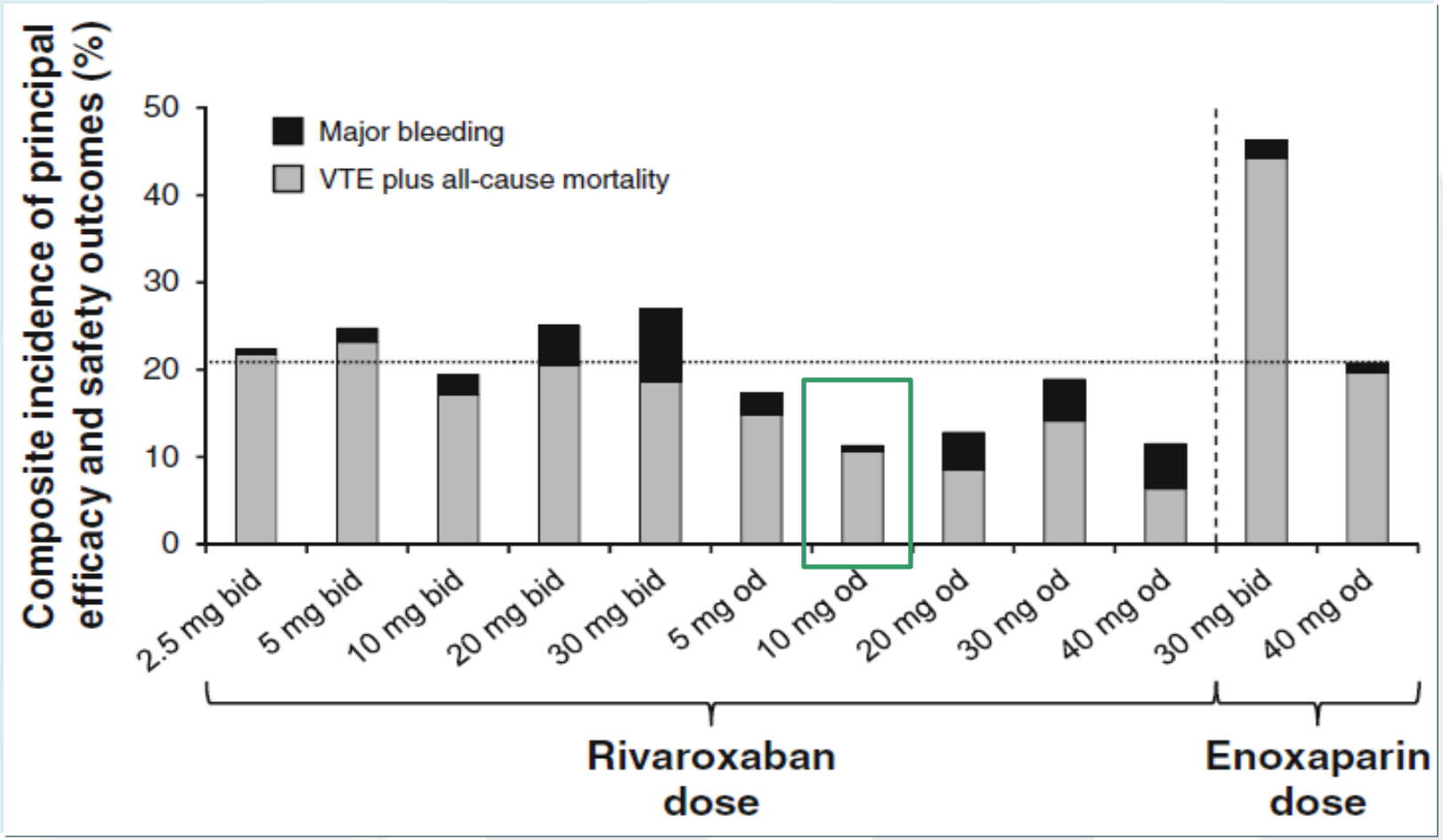
**Dahl et al. J Thromb Haemost 2010; 8: 1966–75.

# METHODS FOR INFERRING EFFICACY

- **Surrogate imaging endpoints**:
  - **Prevention of VTE after surgery:** Proximal/distal DVT detected by venography.
  - **Treatment of acute DVT/PE:** Change in thrombus burden at study endpoint versus baseline (DVT: Doppler/Venography: PE: lung scan, scintigraphy).
  - **Prevention of stroke and systemic embolism in A-Fib:** no surrogates. Phase II studies using clinical endpoints (stroke/SEE) in several hundreds of patients and additional investigations (PK/PD) or extrapolation from the treatment of acute VTE (same comparator).
  - **Acute coronary syndromes (ACS):** no surrogates. Phase II studies using clinical endpoints (MACE) in several hundreds of patients and additional investigations (PK/PD).

A-Fib = atrial fibrillation; DVT = Deep Vein Thrombosis; PE = pulmonary embolism; MACE = major adverse cardiovascular events; VTE = venous thromboembolism.

# PHASE II: THROMBOPROPHYLAXIS MAJOR ORTHOPAEDIC SURGERY*

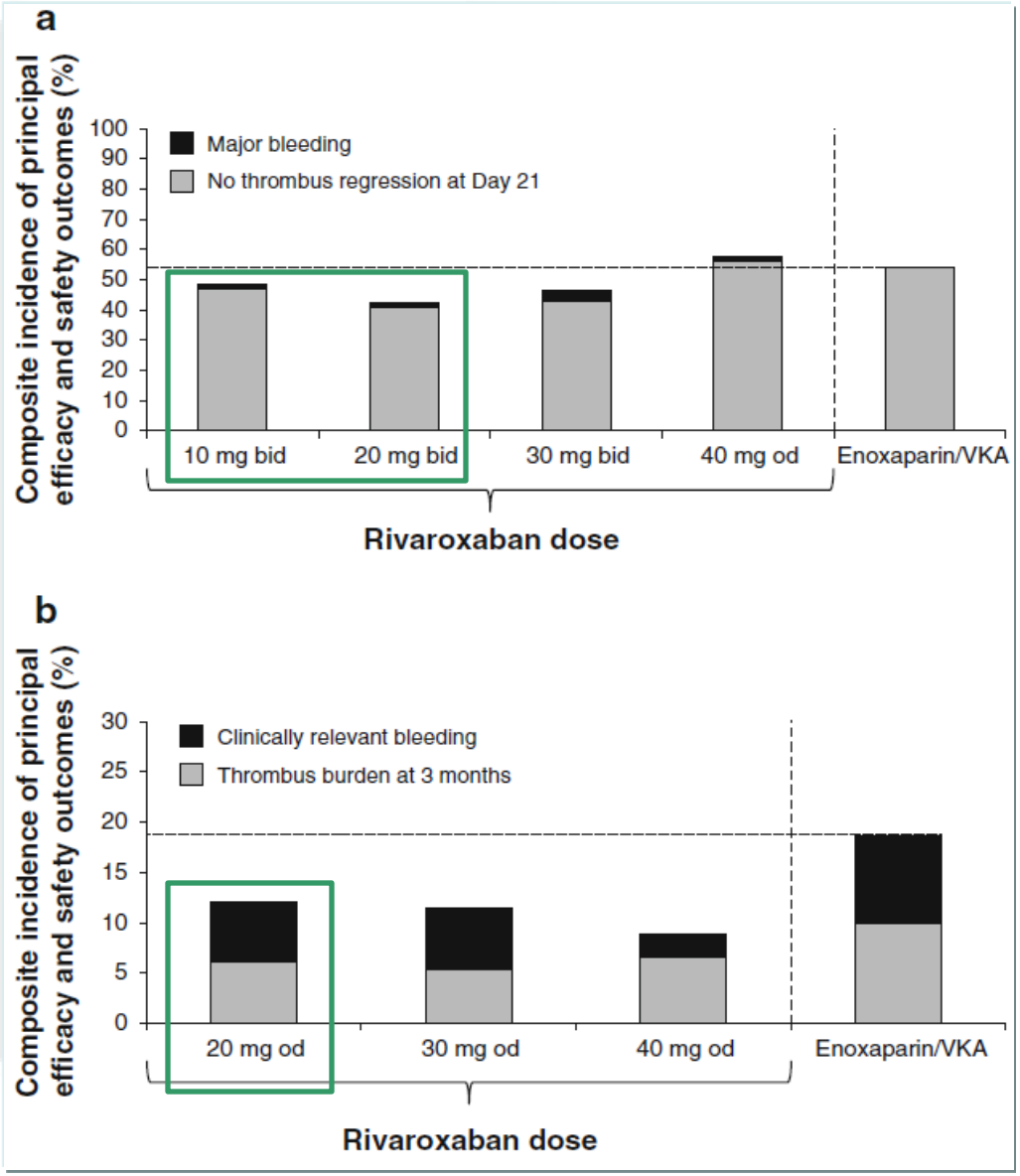



*The composite outcome depicted here was not a predefined endpoint of these trials.
Bid = twice daily; od = once daily; VTE = venous thromboembolism

# PHASE II: TREATMENT OF DVT/PE ("TIME-VARYING" DOSE FINDING)

**a) D21:**
Major bleeding, thrombus regression

**b) 3 MONTHS:**
Clinically relevant bleeding, thrombus burden



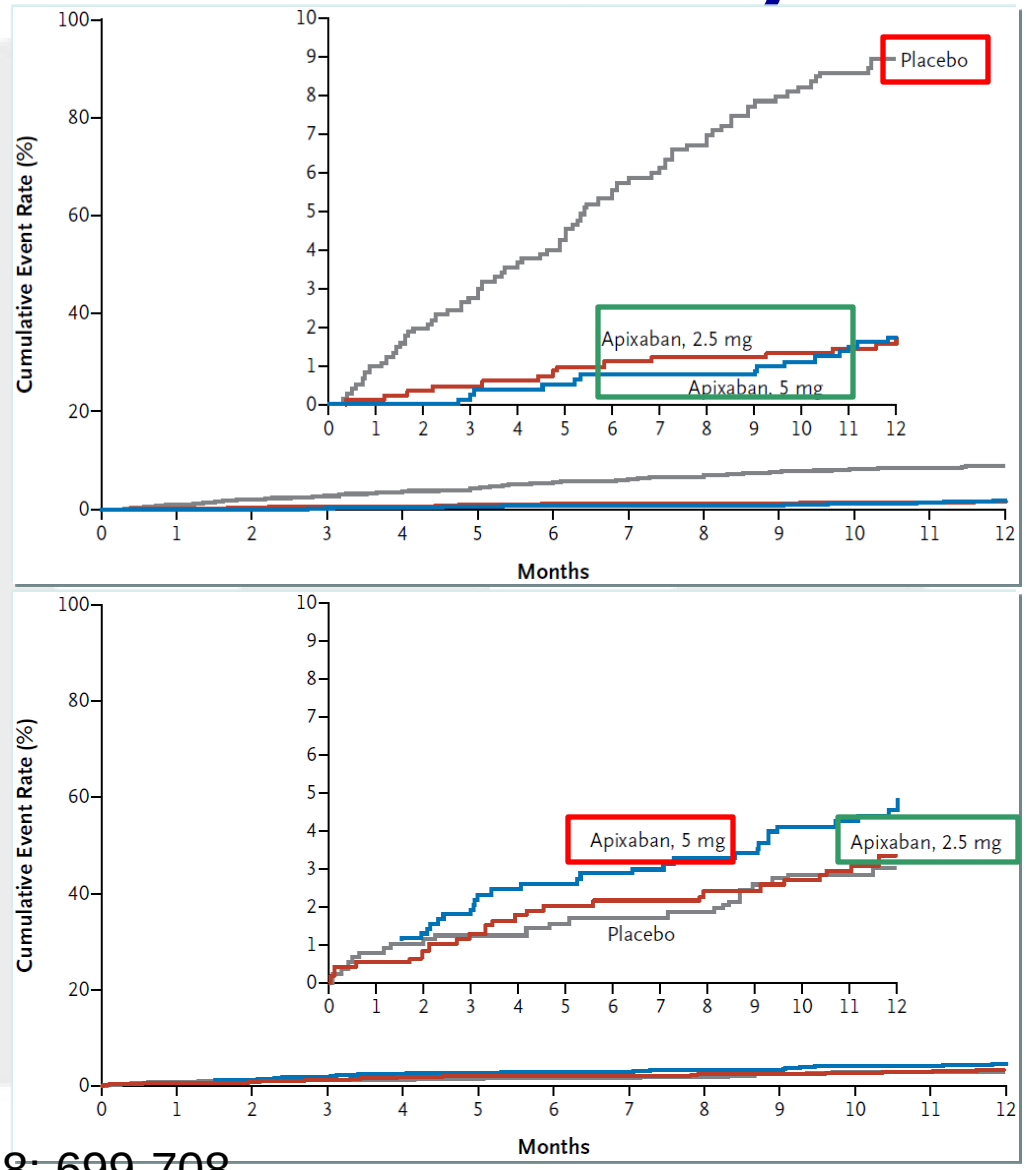

bid = twice daily; od = once daily;
VKA = vitamin K antagonist

# PHASE III: AMPLIFY-EXT (EXTENDED VTE TREATMENT)

**c) Extended treatment >6 mo.**

- Recurrent VTE

- Clinically relevant bleeding

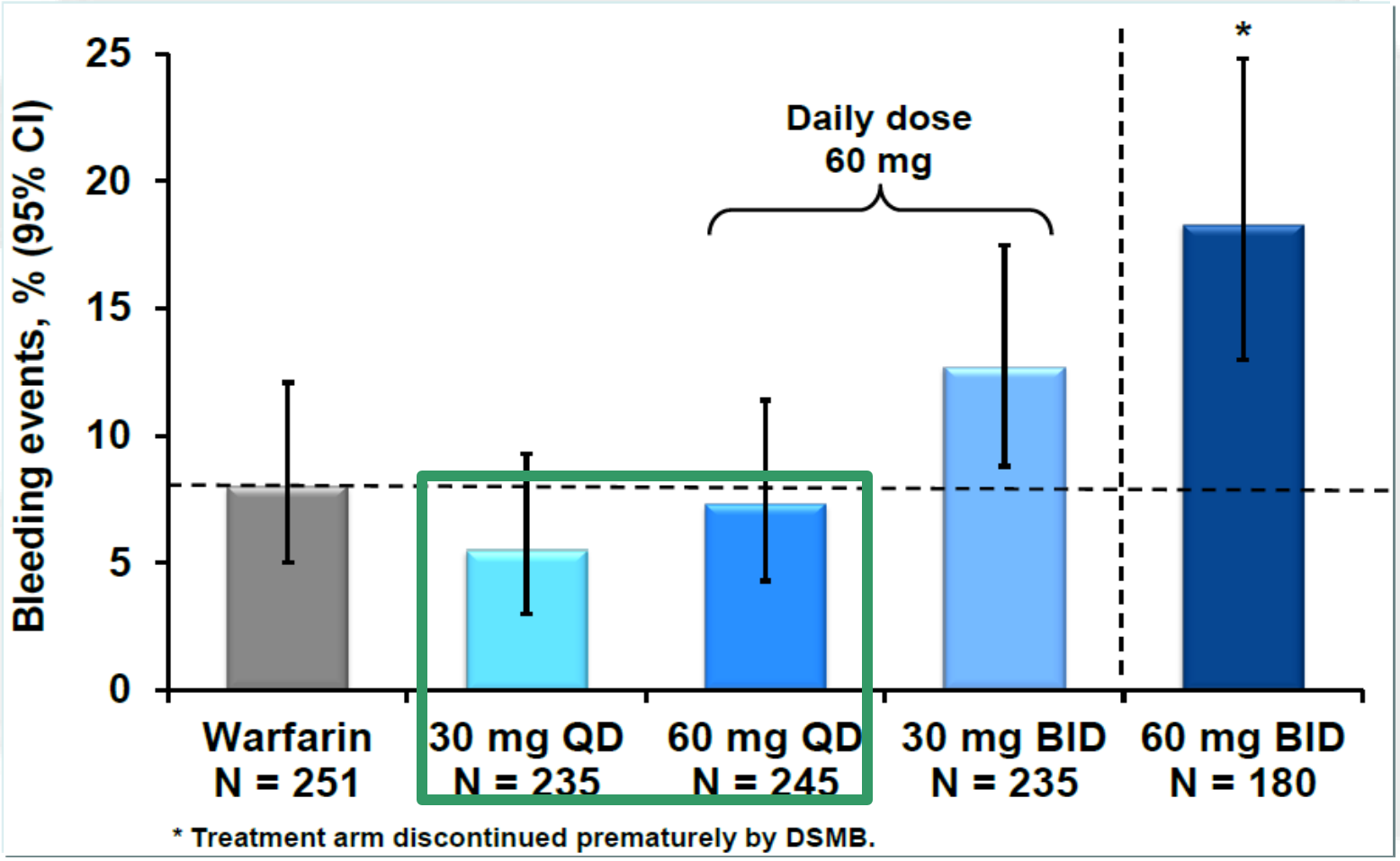



Agnelli G, et al. *N Engl J Med*. 2013; 368: 699-708.

# Phase II: Prevention of Stroke/SEE

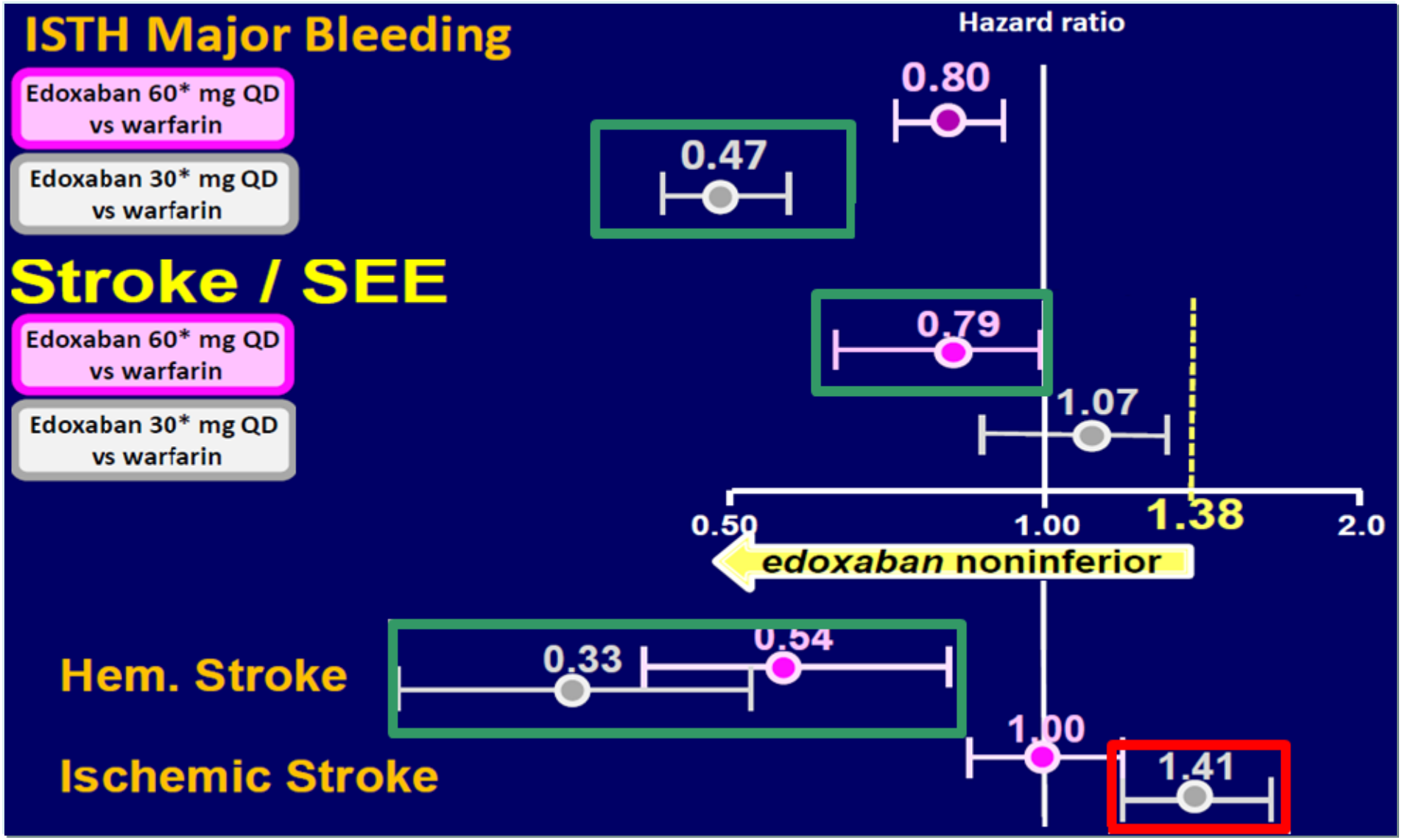
**Adjudicated bleeding: Phase II study, edoxaban vs. warfarin**

od = once daily; BID = twice-daily




Source: http://www.fda.gov/mwg-internal/de5fs23hu73ds/progress?id=nJ8qS-qqJok2oxKrSdR1L_VFako_8zm6v-2CcgI-ohM,&dl

# Phase III: Prevention of stroke/SEE




Giugliano RP, et al. *N Engl J Med*. 2013; 369: 2093-104.

# Phase II: Acute Coronary Syndromes

## MACE

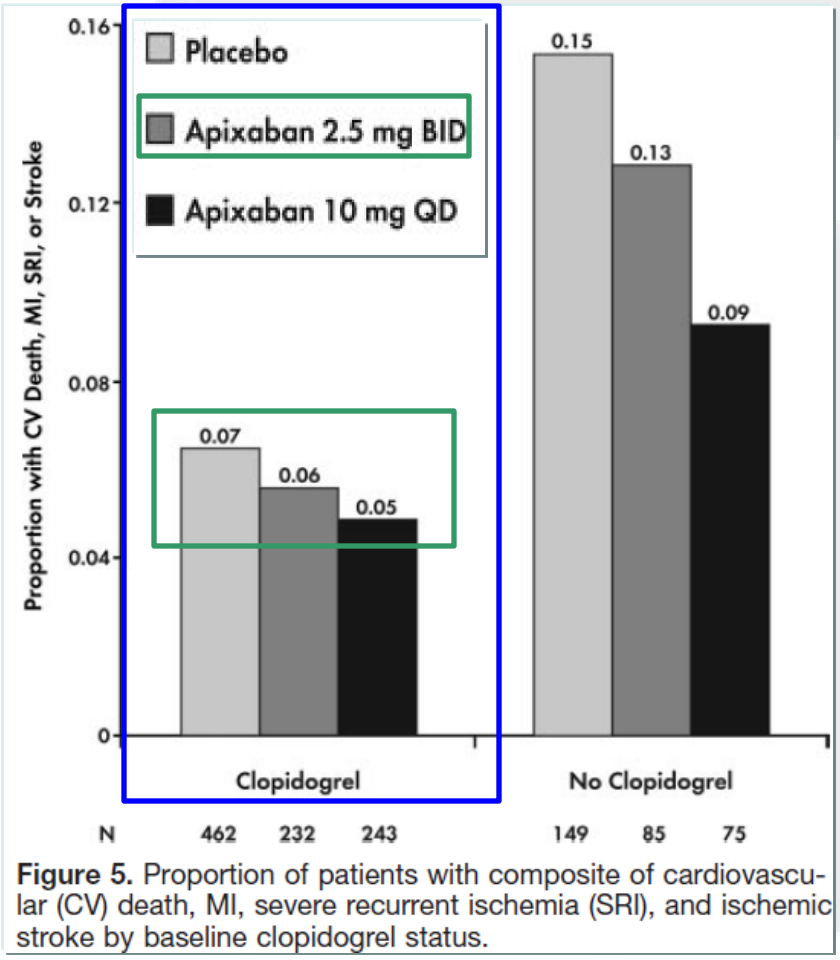



**Figure 5.** Proportion of patients with composite of cardiovascular (CV) death, MI, severe recurrent ischemia (SRI), and ischemic stroke by baseline clopidogrel status.

## CLINICALLY RELEVANT BLEEDING (ISTH)

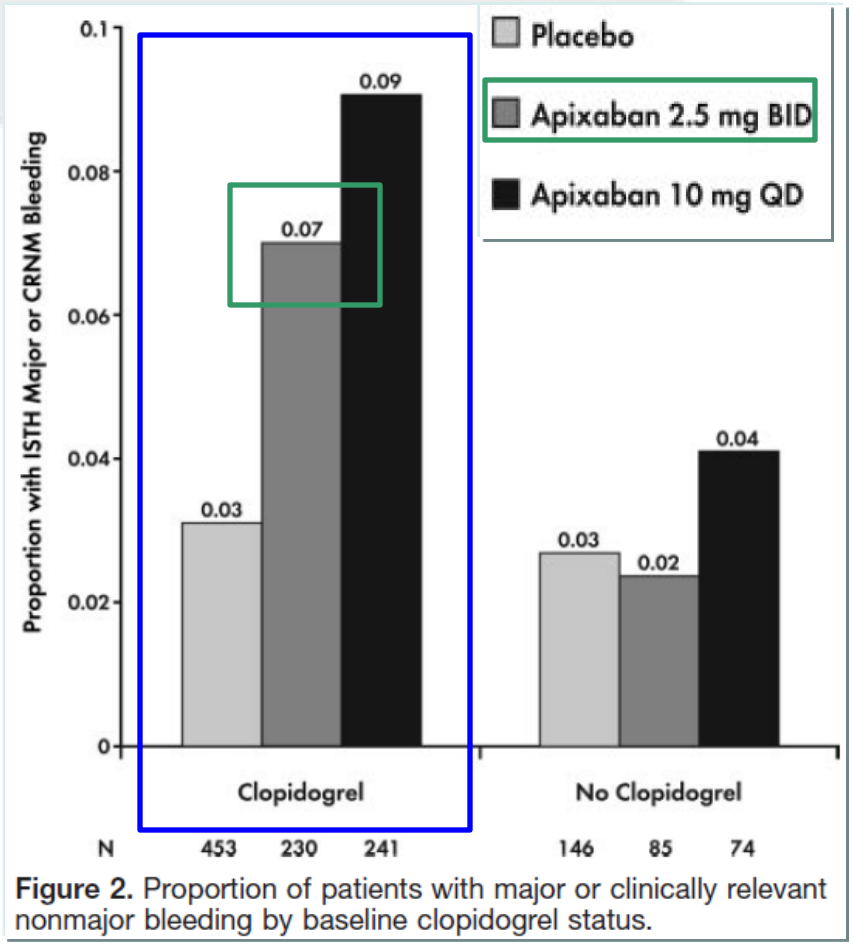



**Figure 2.** Proportion of patients with major or clinically relevant nonmajor bleeding by baseline clopidogrel status.

APPRAISE Steering Committee and Investigators. *Circulation*. 2009;119:2877-2885.

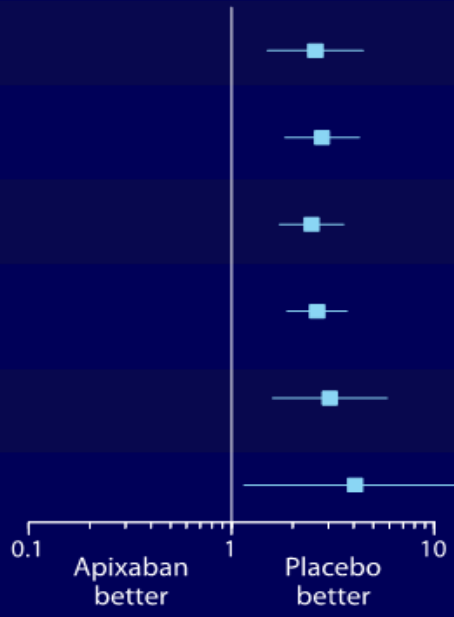
# Phase III: Acute Coronary Syndromes (APPRAISE: API 2.5 mg OD vs PBO)

- **MACE:** no benefit HR: 0.95; 95%CI: 0.80-1.11)
- **Major bleeding:** significant increase regardless scale, but…

**TIMI**: primary scale used in **phase III**

**ISTH**: primary scale used in **phase II**

| | Apixaban N=3705 | Placebo N=3687 | p-value |
|---|---|---|---|
| TIMI major | 1.3 | 0.5 | 0.001 |
| TIMI major or minor | 2.2 | 0.8 | <0.001 |
| ISTH major | 2.7 | 1.1 | <0.001 |
| ISTH major or clinically relevant non-major | 3.2 | 1.2 | <0.001 |
| GUSTO severe | 1.0 | 0.3 | 0.001 |
| Intracranial | 0.3 | 0.1 | 0.030 |




**Fatal bleeding: Apixaban = 5 vs. Placebo = 0**

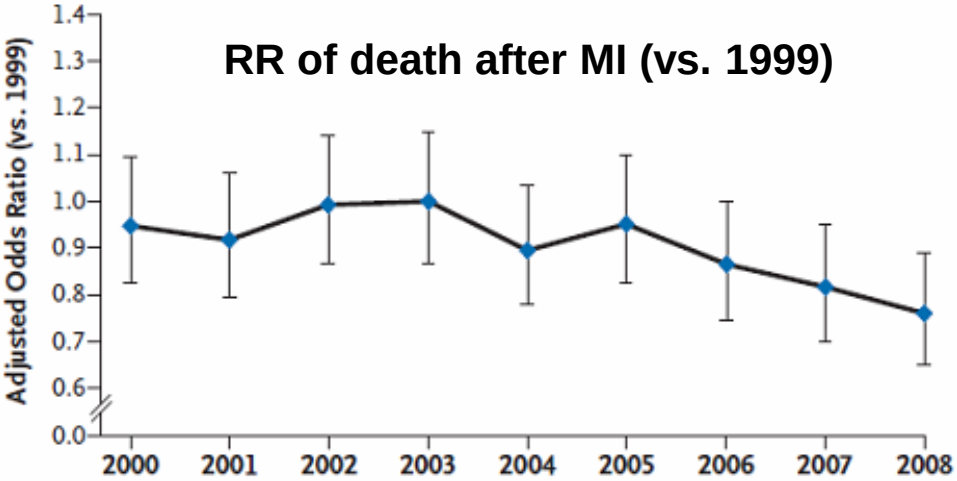
ISTH major bleeding = bleeding leading to death, occurring in a critical location, or associated with a ≥2 g/dL drop in hemoglobin or transfusion of 2 or more units of PRBC.

- **All-cause death:** 4.2% (155) vs. 3.8% (143)

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

# UNCERTAINTY ON CV MORBIDITY AND MORTALITY: NEED FOR LARGE CV OUTCOMES STUDIES

- Disasters with surrogate markers
- Progressively reduction in CV death (improvement in patients' care; dual antiplatelet therapy).
- Increased bleeding risk also associated to increased mortality.


Yeh et al, N Engl J Med 2010; 362: 2155-65.

# DOSE-SELECTION FOR PHASE III

- **Uncertainties at the end of phase II.**
  - Insufficient data on MACE, stroke/SEE all-cause/CV mortality.
  - Thromboembolism, bleeding and unexpected adverse events may result in increased mortality risk.

# RATIONALE FOR DOSE-SELECTION

- **Based on the totality of the data:** PK/PD, bleeding, biomarkers, surrogates, etc.
- **The more convenient dosing for the patient** (and for marketing purposes?):
  - **Once-daily:** favours compliance, less bleeding.
  - **Twice-daily:** more sustained, less fluctuating anticoagulation.
- **The effective dosing able to show superiority vs. standard treatment (or placebo):**
  - Unmet need is the decrease in TE. Some increase in bleeding may be acceptable: ACS, extended VTE treatment.
- **The effective dosing able to show non-inferiority vs. standard treatment and provision of an advantage in safety or administration (oral, unmonitored dosing):**
  - Mainly unmet need is the decrease in bleeding, unmonitored dose: acute VTE, AFib.

# OPTIMAL DOSING IDENTIFIED FROM PHASE II STUDIES

- **Reasonable body of evidence**: 1 dosing in phase III.
- **No clear optimal dose:** > 1 dosing in phase III.
- **Fixed vs. Adjusted:**
  - ***Intrinsic/extrinsic factors:*** renal function, inducers/inhibitors.
  - ***Time-varying risk of TE/bleeding****:* different dosing for initial, long-term, extended periods.

# CONCLUSIONS

- **Target:** Choice of optimal dosing strategy (daily dose, administration interval, timing of administration). Balance between bleeding vs. thrombotic risk.
- **Methods for assessing safety:** bleeding events of heterogeneous relevance (use of standardized definitions) complemented by overall and specific adverse events depending on the pharmacology of the new compound.
- **Methods for inferring efficacy**: surrogate imaging endpoints, biomarkers, etc.
- **Need for separate dose-finding studies in different clinical indications.** Extrapolations across indications may be suitable in some cases: a) similar pathophysiology; b) similar standard treatment.
- **Dose-selection:** based on the totality of the data. Test > 1 dose and/or adjusted-dose if significant uncertainty at the end of phase II.

# Thanks for your attention

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