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HEALTH THROUGH KNOWLEDGE

INTERBLEED: An International Study of the Risk Factors for Gastrointestinal Bleeding and for Cardiovascular Events after Gastrointestinal Bleeding

Outline

- Importance of bleeding in patients with CV disease
- INTERBLEED design

Global challenge of CV disease

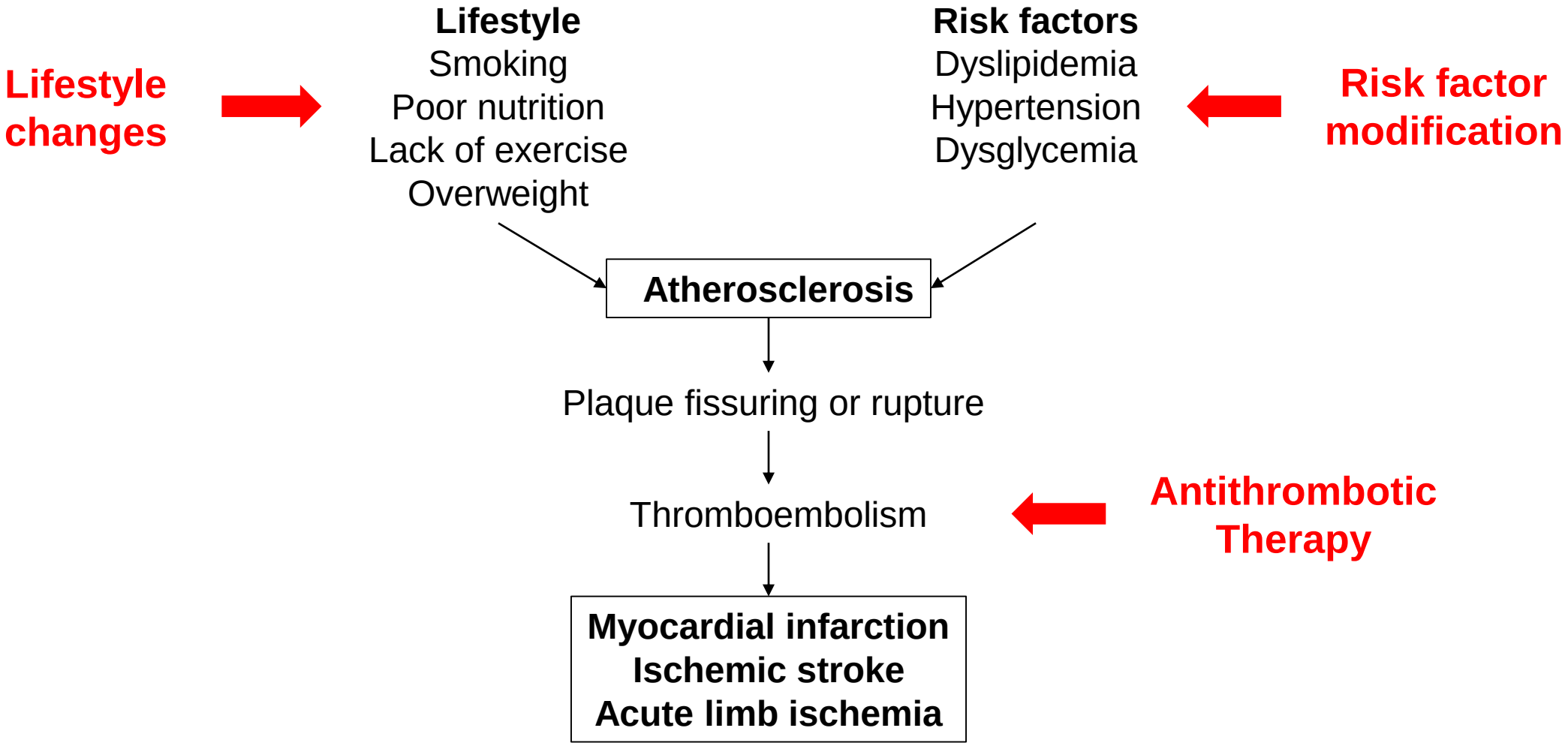
- Still the single most common cause of death (17 million deaths per year, 1 in 3 deaths)
- Affects 300 million persons (4% or 1 in 25 of the world population)
- Growing burden in developing countries due to increasing risk factors and survival of persons with risk factors

Joseph P, et al. *Circ Res* 2017; 121: 677-94. World Heart Federation factsheet. Cardiovascular Diseases 2016

Why is bleeding important in patients with cardiovascular disease?

- Common (single most common adverse outcome in most antithrombotic trials)
- Predicts subsequent cardiovascular events and mortality (similar prognostic importance as MI)
- Association potentially modifiable
- Important knowledge gap re potentially modifiable associations
- Understudied

Antithrombotic therapy in cardiovascular prevention



Bleeding and subsequent adverse outcomes

Modifiable?

Modifiable?

Antithrombotic drugs → **Bleeding** → **Cardiovascular events and mortality**

Risk factors for bleeding

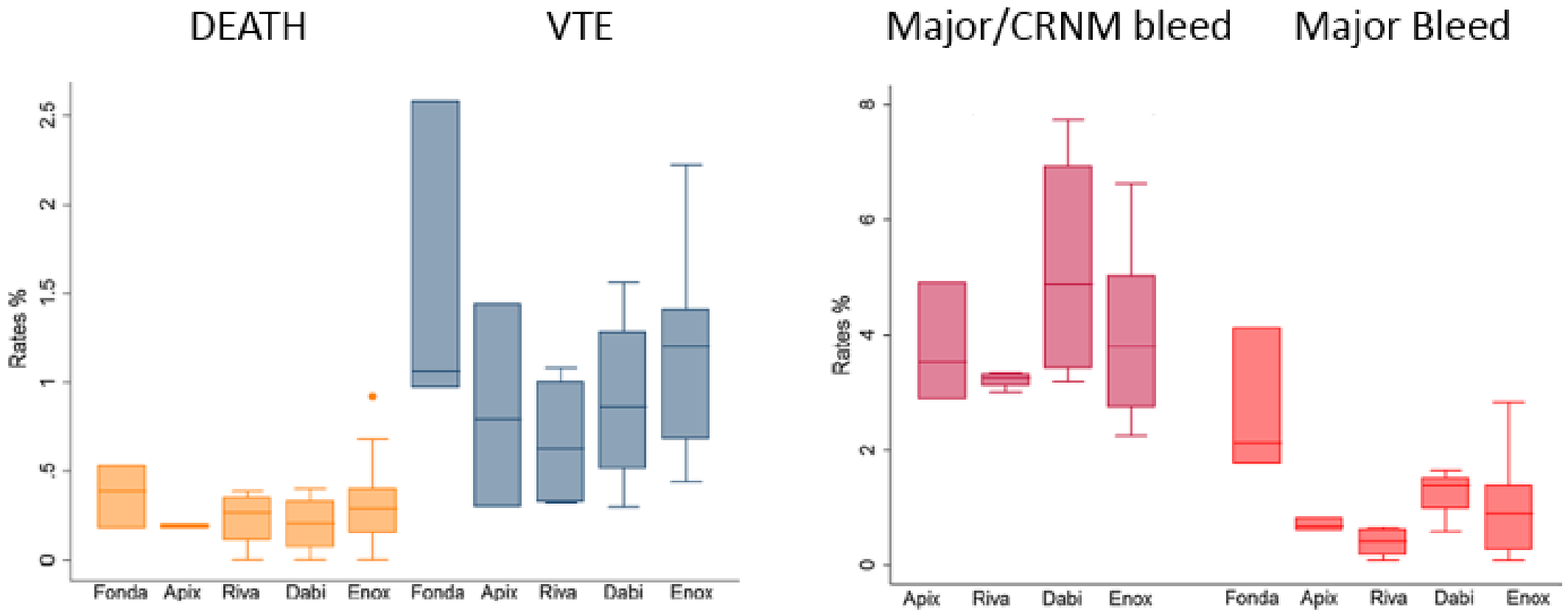
Mechanism linking bleeding with CV outcomes

How common is bleeding compared with vascular events? Randomized trials in atrial fibrillation

Trial	Stroke	Stroke $CHADS_2$ 3+	Maj. bleeding	Maj. bleed $CHADS_2$ 3+	Any Bleeding
ARISTOTLE (5/2.5mg bid)	**1.3%**	2.0%	**2.1%**	2.9%	**18%**
ENGAGE (60/30 mg od)	**1.5%**	-	**2.8%**	-	**14%**
RELY (150 mg bid)	**1.1%**	1.9%	**3.3%**	4.8%	**16%**
ROCKET (20/15mg od)	**1.7%**	-	**3.6%**	-	**15%**

Granger CB, et al. N Engl J Med 2011; 365: 981-92. Giugliano RP, et al. N Engl J Med 2013; 369: 2093-104.
Connolly SJ, et al. N Engl J Med 2010;363:1875-6. Patel M, et al. N Engl J Med 2011;365:883-91.

How common is bleeding compared with vascular events? Randomized trials in venous thromboembolism



Chan NC, et al. *J Thromb Thrombolysis* 2015;40:231-39.

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Weighing the importance of bleeding

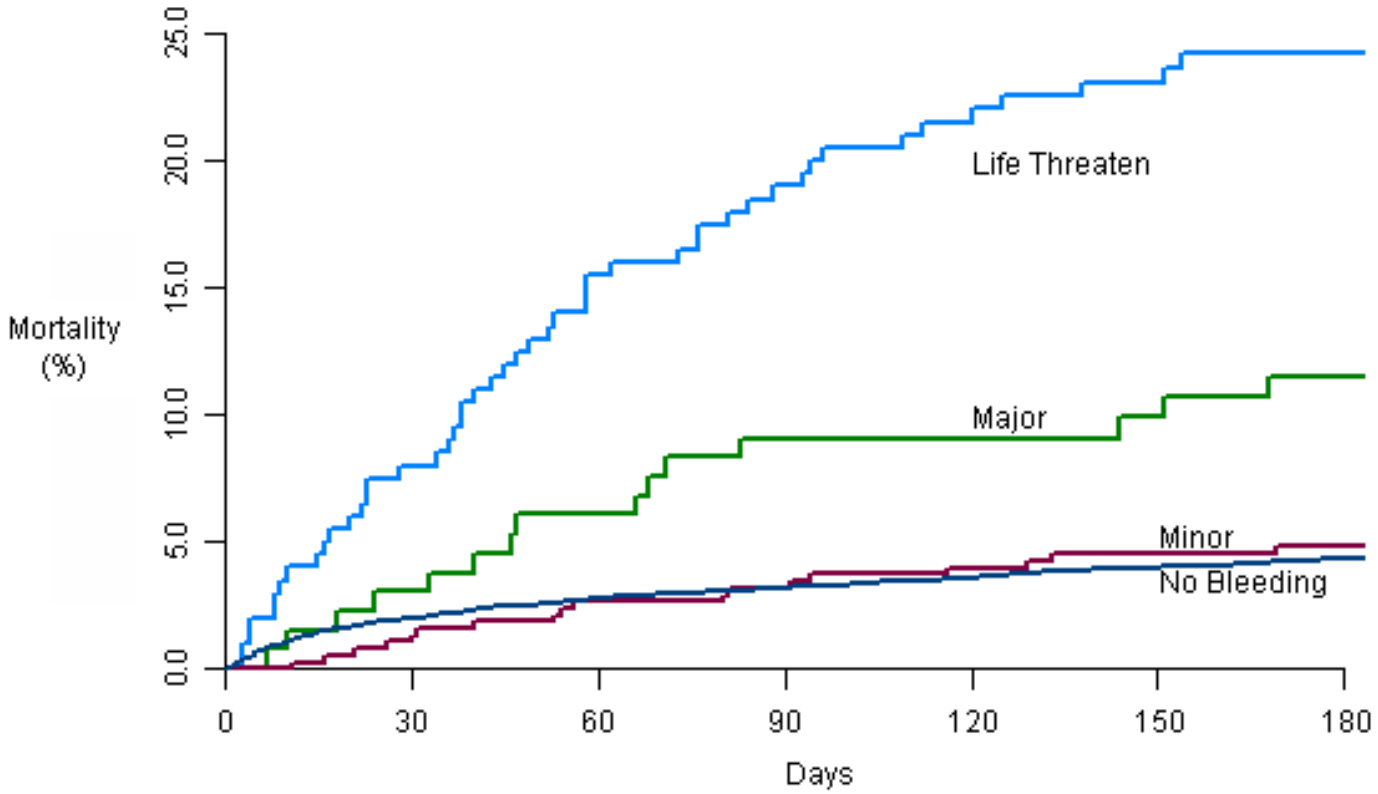
Event	Death HR (95% CI)	Weight
Ischemic stroke	**6.5 (5.9-7.1)**	**1.00**
Systemic embolism	5.8 (4.7-7.3)	0.90
Hemorrhagic stroke	21.3 (17.6-25.7)	3.29
Subdural bleeding	5.1 (3.8-6.9)	0.79
Extracranial Bleeding	**4.6 (4.2-5.1)**	**0.71**
Myocardial infarction	6.2 (5.4-7.1)	0.96

Eikelboom JW, et al. *J Am Coll Cardiol* 2013; 62: 900-8.

How common are post-bleeding complications in patients with cardiovascular disease?

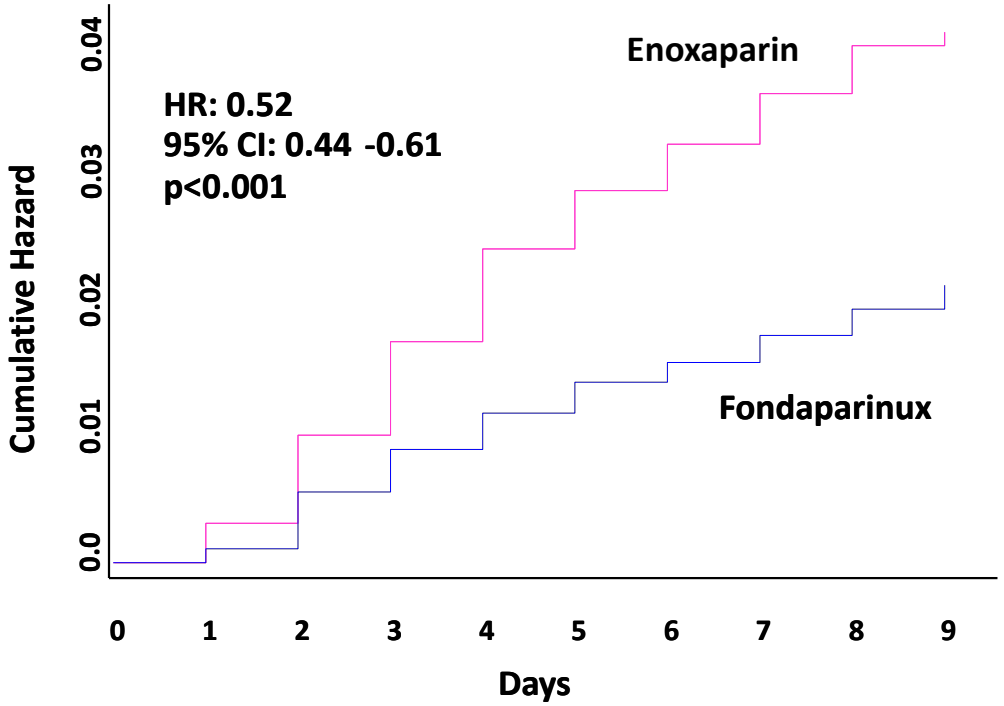
	People living with CV disease	→	Major or CRNM bleeding	→	MI, ischemic stroke, death
Proportion affected	*1 in 25 of population*		*5-10% per year in those with CV disease*		*At least 1 in 10 within 12 months of bleed*
Canada	1.5 million		100,000		10,000
Worldwide	300 million		20 million		2 million

OASIS studies: strong, consistent association ("dose effect") between bleeding and mortality

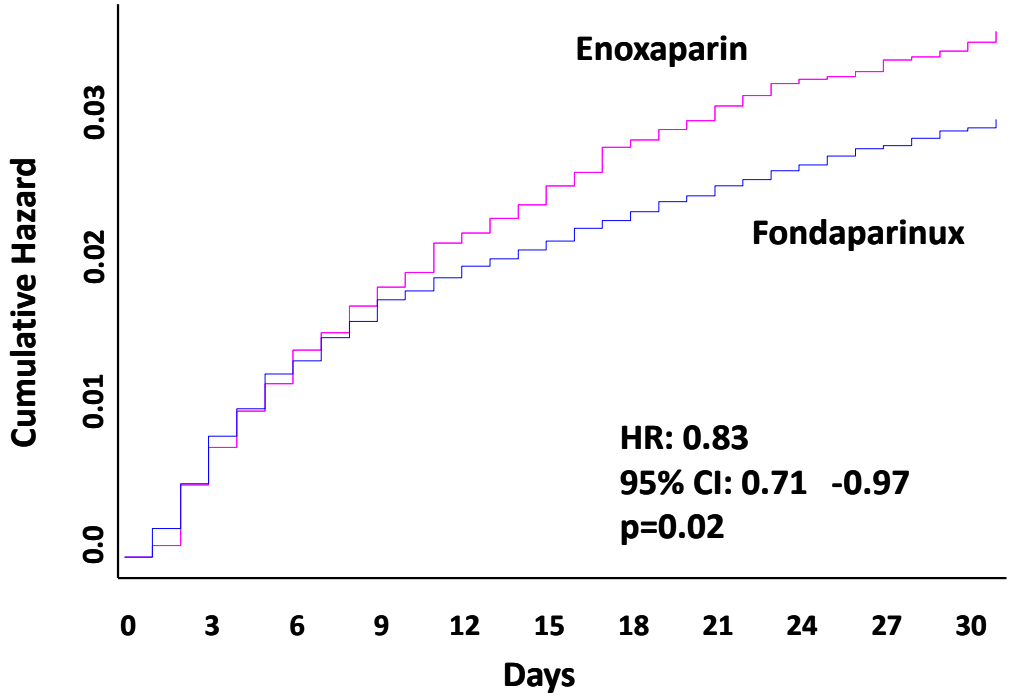


Less bleeding is associated with lower mortality

Bleeding reduced by 38%



Deaths reduced by 17%



OASIS-5 Investigators. *N Engl J Med* 2006;354:1567-77.

Mortality excess is explained by bleeding

	Enoxaparin	Fondaparinux	Difference
No Bleeds	526	523	+3
Minor bleeds	33	13	+20
Major bleeds	79	38	+41
Total	638	574	+64

OASIS-5 Investigators. *N Engl J Med* 2006;354:1567-77.

Hypothesis

Improved prevention and optimal management of bleeding in patients with cardiovascular disease will reduce the risk of subsequent major adverse cardiovascular events, including myocardial infarction, stroke and cardiovascular death.

Potential approaches to prevent bleeding

- Avoidance of use of antithrombotics in high risk patients
- Use of lower doses of drugs (but does this compromise efficacy?)
- Safer drugs that are associated lower risk of bleeding (e.g., factor XI inhibitors)
- Modification of risk factors for bleeding (so far limited to avoidance of aspirin, NSAIDs, BP control, use of proton pump inhibitors)

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Prevention of bleeding: knowledge gaps

- Risk factors incompletely explored
- Known bleeding risk factors are poorly predictive

Why the knowledge gap regarding risk factors?

- Lack of dedicated studies
- Limitations of available data
  - ✓ Exploratory
  - ✓ Modest numbers of patients
  - ✓ Combine different sites of bleeding despite evidence that mechanisms of bleeding may differ according to site (e.g., peptic ulcer vs angiodysplasia vs diverticulosis)

Historical thinking on bleeding is reflected in our approach to the way we try to predict bleeding

Risk prediction models

- HAS-BLED
- HAEMORR$_2$HAGES
- ATRIA,
- ORBIT
- ABC bleeding score

} Only modestly predictive of bleeding

Prediction models do not take into account site of bleeding

Known risk factors are poorly predictive of bleeding

	Myocardial Infarction PAR	Stroke PAR	Major Bleeding PAR
Current smoking	35.7%	12.4%	0.83%
Diabetes	9.9%	3.9%	?
Hypertension	17.9%	47.9%	?
Abdominal obesity	20.1%	18.6%	?
Psychosocial factors	32.5%	17.4%	?
Fruit/vegetable consumption	13.7%	-	?
Exercise	12.2%	16.3%	?
Alcohol	6.7%	5.8%	2.9%
AopB/ApoA-1 ratio	49.2%	26.8%	?
Cardiac causes	-	9.1%	-
Non-gastrointestinal comorbidities	-	-	19.8%
Non-steroidal anti-inflammatories	-	-	3.1%
Aspirin	-	-	3.0%
Clopidogrel	-	-	0.3%
Anticoagulants			1.2%
Composite PAR	90.4%	90.7%	?

Potential approaches to prevent adverse outcomes after bleeding

- Avoidance of hemostatic treatments
- Avoidance of transfusion
- Restart of antithrombotic therapies after bleeding

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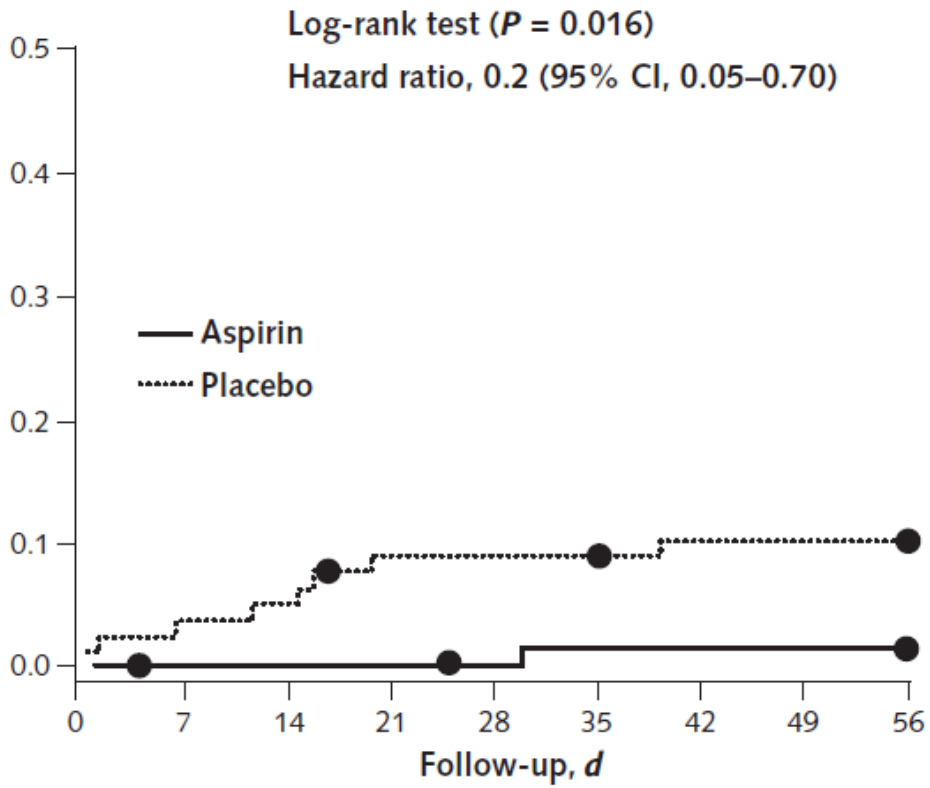
Risk of cardiovascular events during interruption of antithrombotic therapy

Trial	Risk of Stroke within 30 days of transition		
	NOAC to VKA	VKA to VKA	HR (95% CI)
ROCKET	6.42%	1.73%	3.72 (1.51-9.16)
ARISTOTLE	4.02%	0.99%	4.06 (1.53-10.77)
ENGAGE LD	1.57% (30mg)	1.94%	0.81 (0.22-3.02)
ENGAGE HD	2.80% (60mg)	1.94%	1.03 (0.36-2.94)

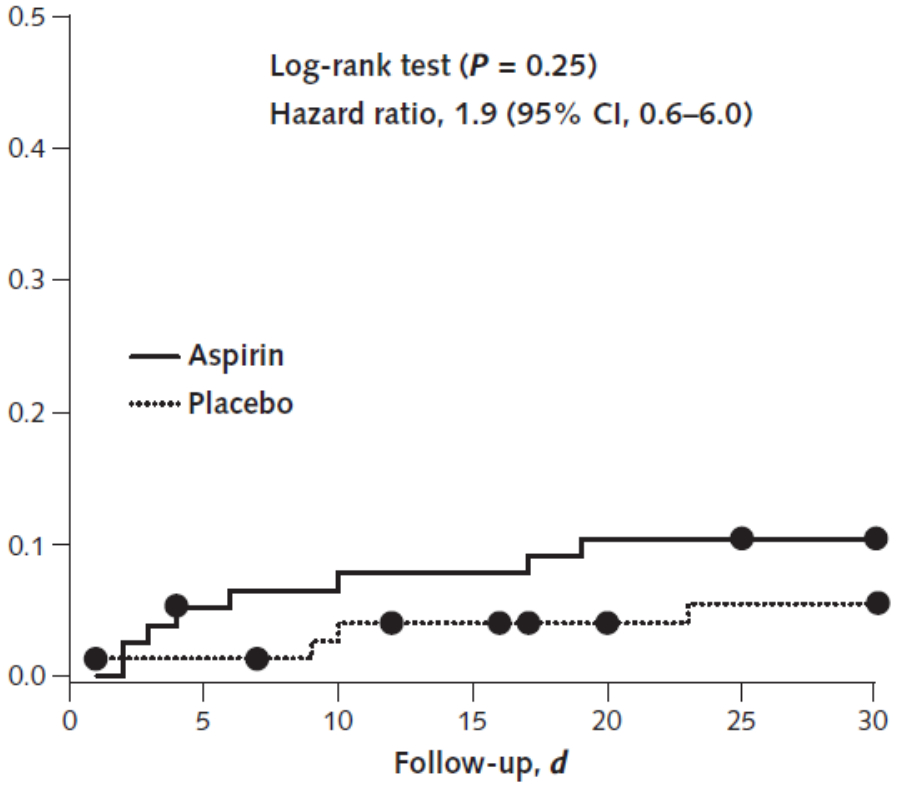
Eikelboom JW, et al. *J Am Coll Cardiol* 2014;64:585-7.

Continuing vs stopping aspirin after gastrointestinal bleeding appears to be protective

Death



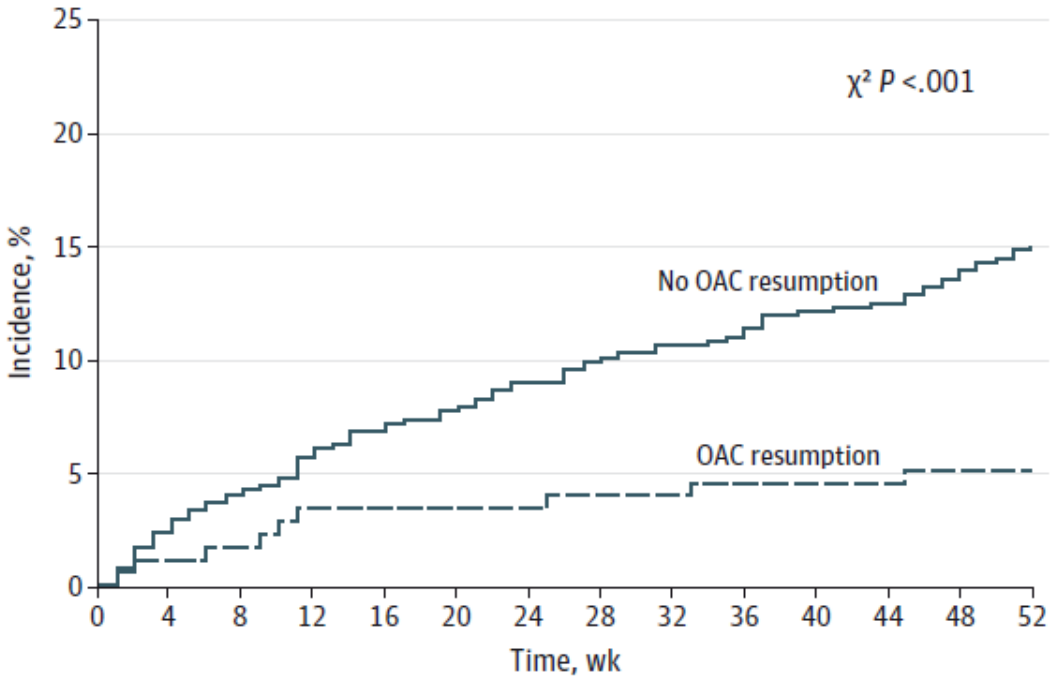
Recurrent GI Bleeding



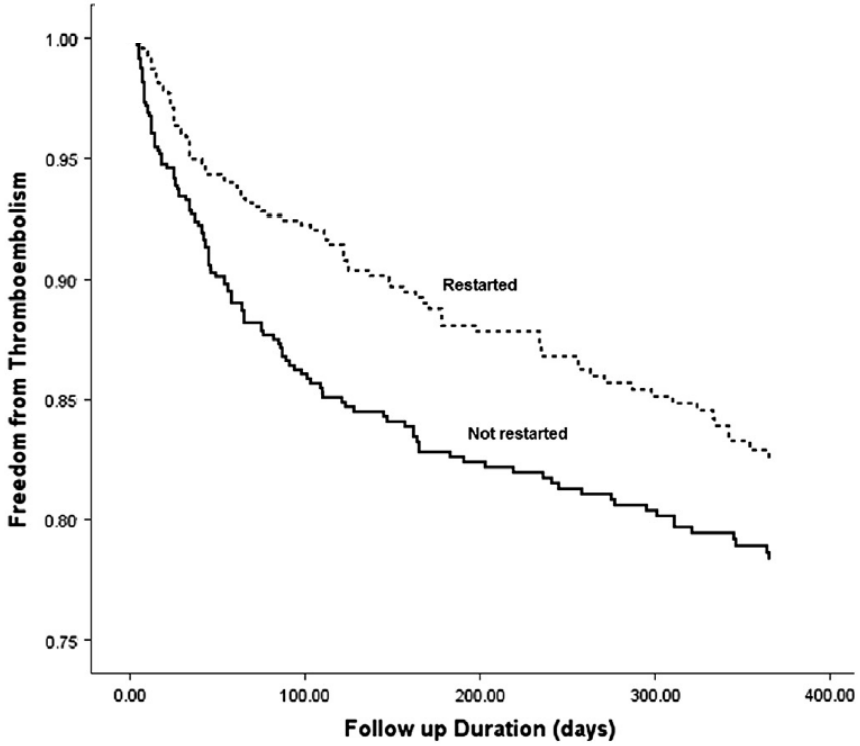
Sung JJY et al. *Ann Intern Med* 2010

Restarting of antithrombotic therapy after intracranial or gastrointestinal bleeding appears to be protective

After intracranial bleeding



After gastrointestinal bleeding



Karamatsu JB, et al. *JAMA* 2015; 313: 824-36. Qureshi W, et al. *Am J Cardiol* 2014; 113: 662-8.

Why the knowledge gaps regarding prevention of adverse outcomes after bleeding

- Lack of dedicated studies
- Limitations of available data
  - ✓ Mostly observational
  - ✓ Modest numbers of patients
  - ✓ Did not record hemostatic treatments for bleeding and management of antithrombotic therapy around the time of bleeding

Why the knowledge gap regarding risk factors?

- Lack of dedicated studies
- Limitations of available data
  - ✓ Exploratory
  - ✓ Modest numbers of patients
  - ✓ Combine different sites of bleeding despite evidence that mechanisms of bleeding may differ according to site (e.g., peptic ulcer vs angiodysplasia vs diverticulosis)

Outline

- Importance of bleeding in patients with CV disease
- **INTERBLEED design**

Specific objectives

In patients with cardiovascular disease, to determine:

1. risk factors for gastrointestinal bleeding;
2. mechanisms linking gastrointestinal bleeding with risk of subsequent major adverse cardiovascular events; and
3. impact of GI bleeding on functional outcomes.

Design

Case-control
Risk factors

Prospective cohort
Mechanisms linking bleeding with adverse outcome

Case ⇢ 12 months

Final follow-up at 12 months

Control ⇢ 12 months

Baseline
data collection

Treatments,
Cardiovascular events

Definition of cases and controls

A case is defined as:

1. 18 or over
2. History of CV disease
3. First-ever or recurrent significant GI bleeding
4. No history of significant, non-GI bleeding in past 10 years

A control is defined as:

1. 18 or over
2. History of CV disease
3. No history of significant GI bleeding
4. No history of significant, non-GI bleeding in past 10 years

CV disease eligibility

Coronary artery disease

- ✓ MI
- ✓ Stable/unstable angina
- ✓ Any coronary revasc.

Peripheral artery disease

- ✓ Lower/upper limb PAD
- ✓ Carotid stenosis
- ✓ Aortic aneurysm
- ✓ Any peripheral revasc.

Cerebrovascular disease

- ✓ Ischemic stroke / TIA

Other

- ✓ Heart failure
- ✓ Atrial fibrillation or flutter
- ✓ Venous thromboembolism

Gastrointestinal bleeding

GI Bleeding

- ✓ Melena: black, tarry, malodorous, loose stools
- ✓ Hematochezia: bright red blood per rectum (BRBPR)
- ✓ Hematemesis: vomiting blood

Not significant = minor/trivial bleeding (≤ 2 tablespoons once per month)

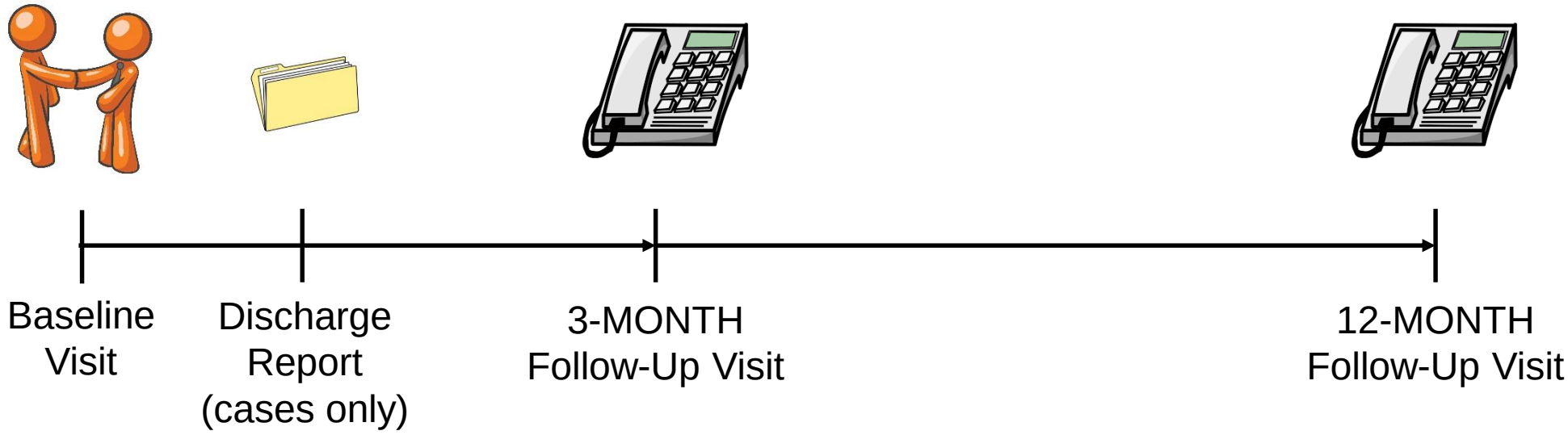
Study visits

Baseline Visit

- Baseline done in person
- Discharge info. from chart

Follow-Up Visits

- 3-MONTH and 12-MONTH via telephone



Scheduling of study follow up

For Cases - Schedule the 3 Month Follow-Up Call for 3 months (+/- 2 weeks) after **Date of Bleed**.

For Controls - Schedule the 3 Month Follow-Up Call for 3 months (+/- 2 weeks) after **Baseline Visit.**

Data collection

Baseline Visit (30 minutes)

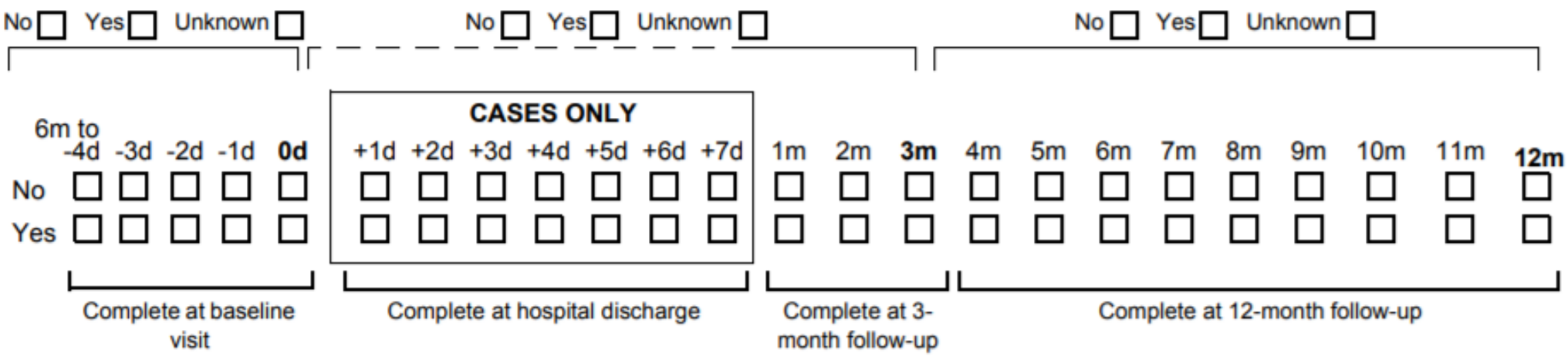
1. Informed consent
2. Physical measurements
3. Medical history
4. Medications
5. Bleeding details (cases)
6. Questionnaires

Follow-up (15 minutes)

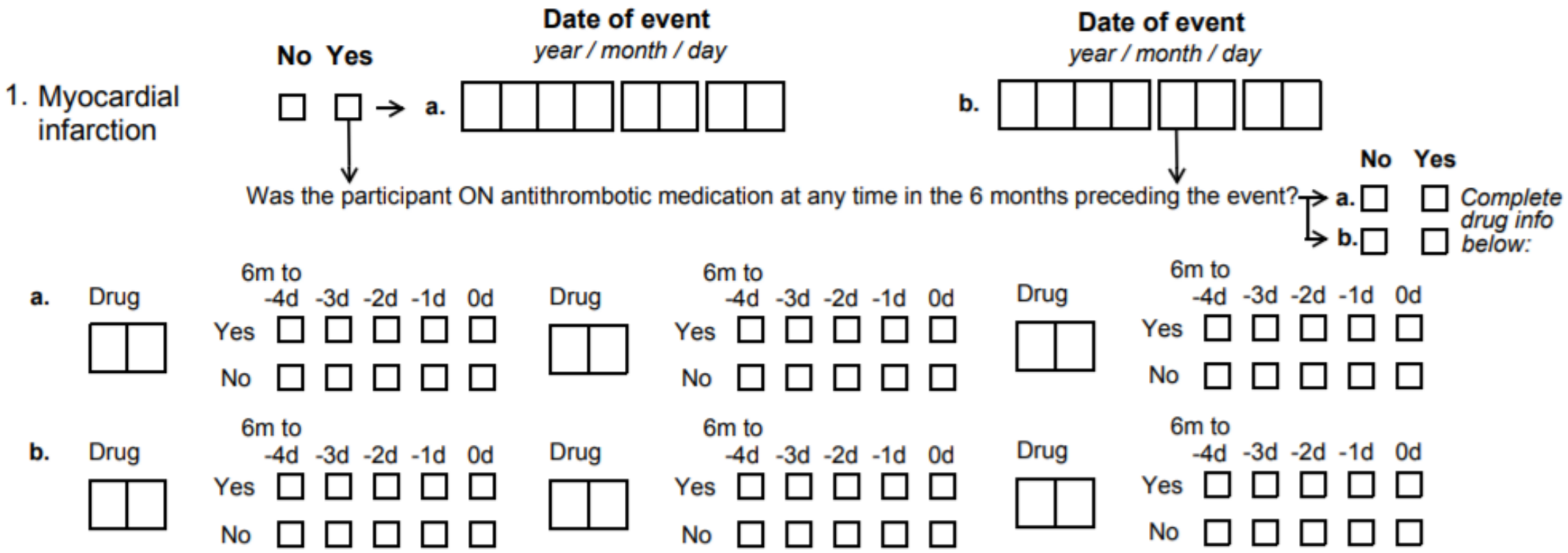
1. Outcome events
2. Medications
3. Telephone questionnaires

Antithrombotic drug log
One row for each of four antithrombotic drug classes

'0d" for CONTROLS - Baseline visit date
'0d' for CASES - Date of bleed



Outcomes and medication use



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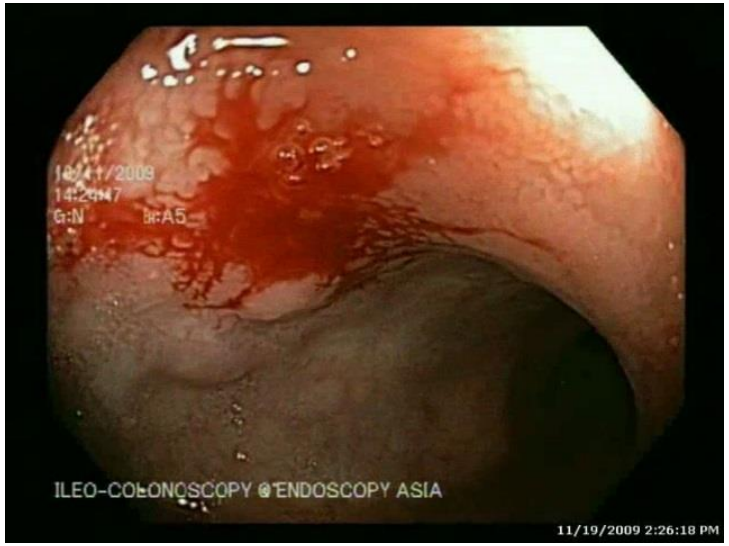
Key questions

- Why study gastrointestinal bleeding?
- Why is inclusion of consecutive patients important?
- Why restrict to in-hospital cases?
- Why allow both in-hospital and out-of-hospital controls?
- Why no specific drug names for antithrombotics?
- Why collect data on lifestyle / social / economic factors?
- Why examine functional outcomes?
- Why no blood collection?

Why study gastrointestinal bleeding?

- Well circumscribed condition
- Accounts for one-half of all clinically significant bleeding
- Studying all types of bleeding would require the collaboration of many specialties of physicians (logistically challenging)



Eikelboom JW, et al. *Circulation* 2011;123:2363-72.

Why is inclusion of consecutive patients important?

- Patients with less severe gastrointestinal bleeding are discharged prior to being included
- Patients with more severe gastrointestinal bleeding are less inclined to provide consent (they are sicker) or to die before they can be approached for consent

Selection biases!

Study sample not representative of patients hospitalized with gastrointestinal bleeding

Why restrict to in-hospital cases?

- Readily defined population
- Complete case ascertainment feasible
- Results readily generalizable

Why allow both in-hospital and out-of-hospital controls?

- Maximize feasibility
- Evidence from INTERHEART study indicates similar results irrespective of whether we use in-hospital controls (theoretically the ideal control) or out-of-hospital controls

Why collect data on lifestyle / social / economic factors?

- Reported to be important risk factors for myocardial infarction and stroke in the INTERHEART and INTERSTROKE studies
- Are also potentially modifiable

Socio-economic factors: CRF 2

C. SOCIO-ECONOMIC FACTORS

1. Education

a. How many years of formal education has the participant completed? *Check highest level only*

☐ None ☐ 1-8 ☐ 9-12 ☐ Trade school ☐ College/university ☐ Not available

2. Household income

a. Do you think your income negatively affects your health? ☐ No ☐ Yes ☐ Not available

3. Health care costs *Check all that apply*

a. Who covers the costs of your medical care (e.g. doctor's visits, tests, hospitalizations, medications)?

☐ Self/family ☐ Private insurance ☐ Public/government ☐ Not available

Lifestyle factors: CRF 4

D. LIFESTYLE FACTORS (continued) Was any of the following information collected? ☐ No → *Skip to Section E.*

☐ Yes → *Complete below*

4. Physical activity

a. How physically active are you?

- ☐ Seldom active
- ☐ Moderately active
- ☐ Vigorously active

b. Are you more or less active than your peers?

- ☐ More active
- ☐ Similarly active
- ☐ Less active

Psychosocial factors: CRF 4

E. PSYCHOSOCIAL FACTORS Was any of the follow information collected? ☐ No → *Skip to Section F.*

☐ Yes → *Complete below*

	Never Experienced Stress	Some Period of Stress	Several Periods of Stress	Permanent Stress
1. How often have you felt stress at home in the last year?	☐	☐	☐	☐

2. During the past year, was there ever a time when you felt sad, blue, or depressed for two weeks or more in a row? ☐ No ☐ Yes

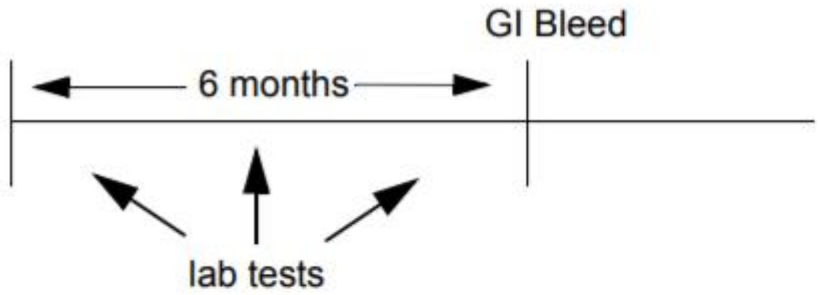
Why examine functional outcomes?

- Patients fear cardiovascular events more than bleeding
- Clinicians fear bleeding more than patients
- Impact of bleeding on patients is poorly understood

Why no blood collection?

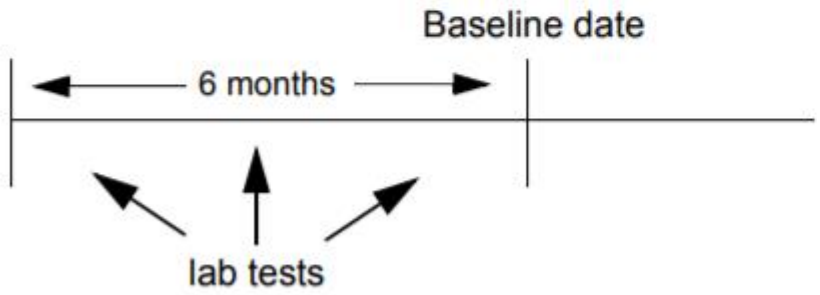
- While biomarkers and genetics can predict bleeding and outcomes after bleeding we do not currently have the funding for blood collection
- We collect laboratory information from blood samples collected as part of routine patient care

Collection of blood test results



Note: If no results are available in the 6 months before the bleed, please mark as “Results not available”.

For controls: Provide the most recent results from the last 6 months before or on the same day as the baseline visit.



Note: If no results are available in the last 6 months please mark as “Results not available”.