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

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

Lifestyle changes
- Smoking
- Poor nutrition
- Lack of exercise
- Overweight

Risk factors
- Dyslipidemia
- Hypertension
- Dysglycemia

Atherosclerosis
- Plaque fissuring or rupture
- Thromboembolism

Risk factor modification

Antithrombotic Therapy
- Myocardial infarction
- Ischemic stroke
- Acute limb ischemia
Bleeding and subsequent adverse outcomes

- **Antithrombotic drugs**
  - Risk factors for bleeding

- **Bleeding**
  - Mechanism linking bleeding with CV outcomes

- **Cardiovascular events and mortality**
  - Modifiable?
How common is bleeding compared with vascular events? Randomized trials in atrial fibrillation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stroke</th>
<th>Stroke CHADS$_2$ 3+</th>
<th>Maj. bleeding</th>
<th>Maj. bleed CHADS$_2$ 3+</th>
<th>Any Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARISTOTLE</td>
<td>1.3%</td>
<td>2.0%</td>
<td>2.1%</td>
<td>2.9%</td>
<td>18%</td>
</tr>
<tr>
<td>(5/2.5mg bid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ENGAGE</td>
<td>1.5%</td>
<td>-</td>
<td>2.8%</td>
<td>-</td>
<td>14%</td>
</tr>
<tr>
<td>(60/30 mg od)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RELY</td>
<td>1.1%</td>
<td>1.9%</td>
<td>3.3%</td>
<td>4.8%</td>
<td>16%</td>
</tr>
<tr>
<td>(150 mg bid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROCKET</td>
<td>1.7%</td>
<td>-</td>
<td>3.6%</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td>(20/15mg od)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>


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

### Weighing the importance of bleeding

<table>
<thead>
<tr>
<th>Event</th>
<th>Death HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>6.5 (5.9-7.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>5.8 (4.7-7.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>21.3 (17.6-25.7)</td>
<td>3.29</td>
</tr>
<tr>
<td>Subdural bleeding</td>
<td>5.1 (3.8-6.9)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Extracranial Bleeding</strong></td>
<td><strong>4.6 (4.2-5.1)</strong></td>
<td><strong>0.71</strong></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6.2 (5.4-7.1)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Proportion affected</th>
<th>People living with CV disease</th>
<th>Major or CRNM bleeding</th>
<th>MI, ischemic stroke, death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canada</td>
<td>1 in 25 of population</td>
<td>5-10% per year in those with CV disease</td>
<td>At least 1 in 10 within 12 months of bleed</td>
</tr>
<tr>
<td>Worldwide</td>
<td>1.5 million</td>
<td>100,000</td>
<td>10,000</td>
</tr>
<tr>
<td></td>
<td>300 million</td>
<td>20 million</td>
<td>2 million</td>
</tr>
</tbody>
</table>
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%

Mortality excess is explained by bleeding

<table>
<thead>
<tr>
<th></th>
<th>Enoxaparin</th>
<th>Fondaparinux</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bleeds</td>
<td>526</td>
<td>523</td>
<td>+3</td>
</tr>
<tr>
<td>Minor bleeds</td>
<td>33</td>
<td>13</td>
<td>+20</td>
</tr>
<tr>
<td>Major bleeds</td>
<td>79</td>
<td>38</td>
<td>+41</td>
</tr>
<tr>
<td>Total</td>
<td>638</td>
<td>574</td>
<td>+64</td>
</tr>
</tbody>
</table>
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)
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)
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
- HAEMORR²HAGES
- 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

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Myocardial Infarction PAR</th>
<th>Stroke PAR</th>
<th>Major Bleeding PAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoking</td>
<td>35.7%</td>
<td>12.4%</td>
<td>0.83%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9.9%</td>
<td>3.9%</td>
<td>?</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17.9%</td>
<td>47.9%</td>
<td>?</td>
</tr>
<tr>
<td>Abdominal obesity</td>
<td>20.1%</td>
<td>18.6%</td>
<td>?</td>
</tr>
<tr>
<td>Psychosocial factors</td>
<td>32.5%</td>
<td>17.4%</td>
<td>?</td>
</tr>
<tr>
<td>Fruit/vegetable consumption</td>
<td>13.7%</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td>Exercise</td>
<td>12.2%</td>
<td>16.3%</td>
<td>?</td>
</tr>
<tr>
<td>Alcohol</td>
<td>6.7%</td>
<td>5.8%</td>
<td>2.9%</td>
</tr>
<tr>
<td>AopB/ApoA-1 ratio</td>
<td>49.2%</td>
<td>26.8%</td>
<td>?</td>
</tr>
<tr>
<td>Cardiac causes</td>
<td>-</td>
<td>9.1%</td>
<td>-</td>
</tr>
<tr>
<td>Non-gastrointestinal comorbidities</td>
<td>-</td>
<td>-</td>
<td>19.8%</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatories</td>
<td>-</td>
<td>-</td>
<td>3.1%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>-</td>
<td>-</td>
<td>3.0%</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>-</td>
<td>-</td>
<td>0.3%</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>-</td>
<td>-</td>
<td>1.2%</td>
</tr>
<tr>
<td>Composite PAR</td>
<td>90.4%</td>
<td>90.7%</td>
<td>?</td>
</tr>
</tbody>
</table>
Potential approaches to prevent adverse outcomes after bleeding

- Avoidance of hemostatic treatments
- Avoidance of transfusion
- Restart of antithrombotic therapies after bleeding
## Risk of cardiovascular events during interruption of antithrombotic therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Risk of Stroke within 30 days of transition</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NOAC to VKA</td>
<td>VKA to VKA</td>
</tr>
<tr>
<td>ROCKET</td>
<td>6.42%</td>
<td>1.73%</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>4.02%</td>
<td>0.99%</td>
</tr>
<tr>
<td>ENGAGE LD</td>
<td>1.57%</td>
<td>1.94%</td>
</tr>
<tr>
<td>ENGAGE HD</td>
<td>2.80%</td>
<td>1.94%</td>
</tr>
</tbody>
</table>

Continuing vs stopping aspirin after gastrointestinal bleeding appears to be protective.

**Death**

Log-rank test ($P = 0.016$)

Hazard ratio, 0.2 (95% CI, 0.05–0.70)

**Recurrent GI Bleeding**

Log-rank test ($P = 0.25$)

Hazard ratio, 1.9 (95% CI, 0.6–6.0)

Sung JJY et al. *Ann Intern Med* 2010
Restarting of antithrombotic therapy after intracranial or gastrointestinal bleeding appears to be protective

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.

Date of Bleed

3 months (+/- 2 weeks)

3 Month Follow-up Visit/Call

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

Baseline Visit

3 months (+/- 2 weeks)

3 Month Follow-up Visit/Call
## Data collection

<table>
<thead>
<tr>
<th>Baseline Visit (30 minutes)</th>
<th>Follow-up (15 minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Informed consent</td>
<td>1. Outcome events</td>
</tr>
<tr>
<td>2. Physical measurements</td>
<td>2. Medications</td>
</tr>
<tr>
<td>3. Medical history</td>
<td>3. Telephone</td>
</tr>
<tr>
<td>4. Medications</td>
<td>questionnaires</td>
</tr>
<tr>
<td>5. Bleeding details (cases)</td>
<td></td>
</tr>
<tr>
<td>6. Questionnaires</td>
<td></td>
</tr>
</tbody>
</table>
Antithrombotic drug log
One row for each of four antithrombotic drug classes

<table>
<thead>
<tr>
<th>6m to 0d</th>
<th>-4d</th>
<th>-3d</th>
<th>-2d</th>
<th>-1d</th>
<th>0d</th>
<th>+1d</th>
<th>+2d</th>
<th>+3d</th>
<th>+4d</th>
<th>+5d</th>
<th>+6d</th>
<th>+7d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Yes</strong></td>
<td></td>
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</tr>
</tbody>
</table>

CASES ONLY

- Complete at baseline visit
- Complete at hospital discharge
- Complete at 3-month follow-up
- Complete at 12-month follow-up

‘0d’ for CONTROLS - Baseline visit date
‘0d’ for CASES - Date of bleed
Outcomes and medication use

1. Myocardial infarction

   Was the participant ON antithrombotic medication at any time in the 6 months preceding the event?

   a. Yes
   No

   6m to -4d -3d -2d -1d 0d

   6m to -4d -3d -2d -1d 0d

   6m to -4d -3d -2d -1d 0d
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)

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

**GI Bleed**

6 months

lab tests

**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.

Baseline date

6 months

lab tests

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

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