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Study Design

INTERBLEED: Design of an International Study of Risk Factors for Gastrointestinal Bleeding and Cardiovascular Events After Gastrointestinal Bleeding

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ABSTRACT

Background: Bleeding is the most common adverse event in those with cardiovascular (CV) disease receiving antithrombotic therapy, and it most commonly occurs in the gastrointestinal (GI) tract. Clinicians often

RÉSUMÉ

Contexte : L'hémorragie est l'effet indésirable le plus fréquent chez les patients atteints de maladies cardiovasculaires (CV) qui reçoivent un traitement antithrombotique, et elle survient le plus souvent dans le

Cardiovascular (CV) disease accounts for an estimated 17 million deaths worldwide each year.[1] Atherosclerosis is the most common cause of CV disease, and in patients with atherosclerosis, atherothrombosis is the most common mechanism leading to myocardial infarction, stroke, and related mortality.[2] Together with lifestyle changes (eg, optimal nutrition, regular exercise, smoking cessation), and modification of CV risk factors (eg, dyslipidemia, dysglycemia, and hypertension), antithrombotic therapy is one of the pillars of CV disease prevention. Although highly effective in reducing CV events, antithrombotic therapy is associated with bleeding in 5% to 10% of patients each year.[3-6] Despite the availability of numerous risk

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Ethics Statement: Participants were asked to provide written consent, which was approved by ethics boards at each site. When we are unable to obtain consent, and at sites where ethics boards gave approval, we retrospectively collected data from charts, and these participants are not followed prospectively.

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dismiss bleeding as an adverse event that is reversible with effective antithrombotic therapy, but bleeding is associated with substantial morbidity and mortality, most likely mediated through an increased risk of CV events. Reducing the burden of bleeding requires knowledge of the potentially modifiable risk factors for bleeding and the potentially modifiable risk factors for adverse outcomes after bleeding.

Methods: INTERBLEED is an international, multicentre, 2-component, observational study, with an incident case-control study examining the risk factors for GI bleeding, and a prospective cohort study of risk factors for CV events after GI bleeding. Cases either have CV disease and present to the hospital with GI bleeding or develop GI bleeding during hospitalization. Controls have CV disease, but no history of GI bleeding. We use a questionnaire to obtain detailed information on known and potential risk factors for GI bleeding and for CV events and outcomes after bleeding. We obtain CV and anthropometric measurements, perform functional and cognitive assessments, and follow participants at 3 months and 12 months.

Results: As of April 1, 2022, the study is ongoing in 10 countries at 31 centres and has recruited 2407 cases and 1478 controls.

Conclusions: Knowledge of risk factors for bleeding, and risk factors for CV events and functional decline after bleeding, will help develop strategies to prevent bleeding and subsequent complications.

tractus gastro-intestinal (GI). Les cliniciens considèrent souvent l'hémorragie comme une simple manifestation indésirable réversible par un traitement antithrombotique efficace, mais une morbidité et une mortalité considérables y sont associées, probablement en raison d'un risque accru d'événements CV. Une réduction du fardeau de l'hémorragie nécessite une connaissance des facteurs de risque potentiellement modifiables tant de l'hémorragie que des événements indésirables qui surviennent après l'hémorragie.

Méthodologie : INTERBLEED est une étude internationale, observationnelle et multicentrique à deux volets; le premier volet est une étude cas-témoins incidents visant à examiner les facteurs de risque d'hémorragie GI, alors que le second volet est une étude de cohorte prospective visant à examiner les facteurs de risque d'événements CV après une hémorragie GI. Les cas sont des patients atteints de maladies CV qui consultent les services hospitaliers pour une hémorragie GI ou qui présentent une hémorragie GI en cours d'hospitalisation. Les témoins sont des patients atteints de maladies CV, mais sans antécédents d'hémorragie GI. Un questionnaire est utilisé pour obtenir des renseignements détaillés au sujet de facteurs de risque connus et potentiels d'hémorragie GI et d'événements CV et d'autres résultats de santé après une hémorragie. Des mesures cardiovasculaires et anthropométriques ainsi que des évaluations fonctionnelles et cognitives sont réalisées, et les participants sont revus après trois mois et 12 mois.

Résultats : En date du 1er avril 2022, l'étude est en cours dans 10 pays et 31 établissements de santé; 2 407 cas et 1 478 témoins ont été recrutés.

Conclusions : La connaissance des facteurs de risque d'hémorragie, ainsi que des facteurs de risque d'événements CV et de déclin fonctionnel à la suite d'une hémorragie, aidera à mettre en place des stratégies pour prévenir les hémorragies et les complications qui peuvent en découler.

prediction models for bleeding,[7] little is known about how to prevent bleeding, and few approaches have been proven effective. Guidelines recommend controlling blood pressure, reducing alcohol consumption, and avoiding the use of nonsteroidal antiinflammatory drugs (NSAIDs), [8] and many clinicians use proton pump inhibitors to prevent upper gastrointestinal (GI) bleeding despite only limited evidence that this is effective.[9] When faced with a patient deemed to be at high risk of bleeding who requires antithrombotic therapy, clinicians frequently reduce the dose or avoid antithrombotic drugs, which may contribute to the increased risk of major adverse cardiovascular events (MACE) for these patients.

Observational studies and randomized trials suggest that about 10% of patients experience MACE within 1 year of bleeding from any site (an estimated 2 million people worldwide each year).[10-12] Bleeding also may be associated with impaired functional and cognitive outcomes, particularly when it is intracranial,[13,14] but such issues are less well studied in patients with bleeding in the GI tract, which is the most common site of extracranial bleeding. Uncertainty remains as to whether the association between GI bleeding and subsequent CV events, and functional or cognitive outcomes is directly causal (ie, a direct consequence of bleeding), or indirectly causal (eg, related to stopping of antithrombotic therapy), or whether the occurrence of GI bleeding simply identifies patients at increased risk. If the association between GI bleeding and subsequent MACE, as well as any effect on functional or cognitive decline, is causal, then successfully targeting modifiable risk factors for bleeding[15] and modifiable risk factors for MACE after GI bleeding has the potential to reduce subsequent CV morbidity and mortality and may improve functional outcomes. Testing of this hypothesis is constrained by knowledge gaps—we have only a very limited ability to identify patients who will develop GI bleeding, we do not fully understand the effects of GI bleeding on functional and cognitive outcomes, and we know little about how to prevent GI bleeding, subsequent MACE, and functional and cognitive decline, if it occurs.

INTERBLEED addresses 3 knowledge gaps in patients with GI bleeding. The first knowledge gap concerns risk factors for GI bleeding, and especially modifiable risk factors. Known risk factors for bleeding, both modifiable and nonmodifiable (eg, age, impaired renal function, comorbidities, and antithrombotic drugs), are reported to account for only about one-half of the population attributable risk,[16] but this issue has been incompletely studied. Without knowing the additional risk factors for bleeding, and whether they are modifiable, we are limited in our ability to evaluate interventions to prevent bleeding.

The second knowledge gap concerns risk factors for MACE after bleeding. Without knowing whether risk factors exist, beyond the risk factors known for MACE, and whether they are potentially modifiable, we are limited in our ability to evaluate interventions to prevent these events. The third

Table 1. INTERBLEED methodological approaches

Method component	Objective 1: Risk factors for GI bleeding	Objective 2: Risk factors for MACE after GI bleeding	Objective 3: Effect of GI bleeding on function and cognition
Design	Prospective case-control	Prospective cohort	Prospective cohort
Participants	Patients with CV disease - Cases (GI bleeding) - Controls (no GI bleeding)	Patients with CV disease (includes cases and controls)	Patients with CV disease (includes cases and controls)
Timing of data collection	At the onset of bleed (cases) or baseline (controls)	As for objective 1, plus at 3 and 12 mo of follow-up	As for objective 1, plus at 3 and 12 mo of follow-up
Data collection (see Table 3 for details)	Demographics, CV risk factors,* medical history, socioeconomic factors, stress, anxiety-depression,† medical therapies,‡ function and cognition	The bleeding site, severity, treatments for bleeding, changes in drug therapies, CV events, non-CV events, hospitalization, mortality	Function: measured with the Standard Assessment of Global Everyday Activities scale, which captures basic, instrumental, and executive functional activities Cognition: measured with the telephone Montreal Cognitive Assessment
The dependent variable for the primary outcome	GI bleeding (yes = case, no = control)	Time to major adverse cardiovascular events (survival variable)	Change in functional and cognitive status (continuous variable)
Independent variables	Potential and known risk factors for GI bleeding	Case/control (includes the severity of bleeding), potential and known risk factors for MACE, interventions, antithrombotic therapies and changes, other post-enrollment variables and their timing	Case/control (includes the severity of bleeding), potential and known risk factors for MACE, interventions, antithrombotic therapies and changes, other post-enrollment variables and their timing

CV, cardiovascular; GI, gastrointestinal; MACE, major adverse cardiovascular events (includes myocardial infarction, stroke, and cardiovascular death).
* Includes blood pressure, heart rate, weight, and height.
† Depression, locus of control, perceived stress, life events.
‡ Includes transfusions, and pharmaceutical, percutaneous, and surgical interventions.

knowledge gap concerns the impact of bleeding, from a patient perspective. Most studies have measured the clinical consequences of bleeding on hospitalization and transfusion and largely have ignored the potential functional and cognitive impact, which are important for patients. This focus might also explain why bleeding is relatively underappreciated as a patient-important outcome. INTERBLEED focuses on GI bleeding because this is the most common reason for hospitalization for bleeding and it is probably the most preventable type of bleeding.

Methods

INTERBLEED is an international multicentre observational study of patients with CV disease with a unique, hybrid, 2-component design, as follows: (i) an incident case-control component, in which we evaluate novel risk factors for GI bleeding; and: (ii) a prospective cohort component, in which we follow cases and controls for 12 months to identify risk factors for MACE after GI bleeding. We also measure the effect of GI bleeding on functional and cognitive outcomes. Table 1 summarizes our methodological approach.

Specific objectives

Specific objectives are to determine the following in patients with CV disease:

1. Are there novel, modifiable risk factors for GI bleeding?
2. Is the risk of MACE higher in the first year after GI bleeding, and if so, what are the risk factors?
3. What are the functional and cognitive outcomes 1 year after GI bleeding? How do they compare to functional and cognitive outcomes in those with CV disease and no GI bleeding?

Population

Case definition and sampling frame. We define cases as adult patients (age $\geq$ 18 years) with CV disease (regardless of severity) who present to the hospital with GI bleeding, or who

Table 2. Case and control eligibility

Definitions
Cardiovascular disease:
Includes any one or more of the following: myocardial infarction, stable angina, unstable, angina, coronary revascularization, lower-limb peripheral artery disease, upper-limb peripheral artery disease, carotid stenosis, aortic aneurysm, peripheral revascularization, ischemic stroke or transient ischemic attack, heart failure, atrial fibrillation or flutter, venous thromboembolism
Gastrointestinal bleeding:
Any overt blood loss from the pharynx to the rectum (melena, hematochezia, and/or hematemesis). Clinical judgement should be used to determine if significant. An example of a nonsignificant gastrointestinal bleed is < 2 tablespoons (30 mL) per month.
Cases:
Adult patients (age $\geq$ 18 y) with cardiovascular disease, presenting to the hospital with a gastrointestinal bleed
Controls:
Adult patients (age $\geq$ 18 y) with cardiovascular disease but no history of gastrointestinal bleeding

experience GI bleeding while in the hospital (full criteria are provided in Table 2). We define GI bleeding as overt blood loss from the GI tract, which includes hematemesis, melena, and hematochezia. We include patients with CV disease and GI bleeding irrespective of treatment with antithrombotic drugs so that we can explore the contribution of antithrombotic therapy to the risk of bleeding and the risk of MACE after bleeding. We attempt to enroll all patients who are in participating centres and fulfill the case definition for GI bleeding, to participate in the study.

Controls and sampling frame. We define controls as adults (age $\geq$ 18 years) with CV disease from the same broad geographic region as cases but without a significant history of GI bleeding (Table 2). We include either community-based or hospital-based controls. We do not prespecify approaches to identifying community-based controls, as a standardized approach may not be applicable in all settings. Controls from hospital-based settings may include patients admitted to the hospital, patients visiting the hospital for conditions or procedures not related to GI bleeding, and their friends and relatives.

Data collection

Table 3 details the data collection for cases and controls and their potential role as predictors of GI bleeding and subsequent outcomes. We are collecting data on demographics, CV risk factors, history of CV and non-CV disease, history of GI bleeding (cases) and non-GI bleeding (cases and controls), medication use, psychosocial factors, socioeconomic factors, and for cases, pre-bleeding functional status, details of the bleeding (site, pathology, severity, and acuity of the bleed), and treatments for bleeding. We also collect outcomes after bleeding in cases (which generally coincides with enrollment) and after enrollment in controls, including CV events, (recurrent) bleeding, hospitalization, and mortality. We collect the use of antithrombotic therapies in relation to the initial bleeding event in cases and in relation to events that occur after bleeding (cases) or enrollment (controls). We define outcomes using the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials (Box 1),[17] and bleeding outcomes according to the International Society on Thrombosis and Haemostasis criteria (Box 1).[18,19] We assess function using the Standardized Assessment of Global Everyday Activities (SAGEA tool) and the European Quality of Life, 5 Dimensions, 3-Level Version (EQ-5D-3L). The SAGEA tool measures cognitive, instrumental, and basic activities of daily living and functional abilities that are important to older adults and has been used widely to evaluate function in multiethnic populations in North America, Europe, and China.[20,21] We assess cognition using the Montreal Cognitive Assessment (MoCA)[22] and quality of life using the EQ-5D-3L.[23] All assessments can be conducted by telephone.

Statistical considerations

Table 4 provides a summary of observable outcomes for each objective and the approaches to statistical analyses.

Sample size. We aim to recruit 2500 cases and 2500 controls; patients will be recruited from Canada, South America, Western Europe, Turkey, Australia, China, and India. This number of participants will provide 80% power to detect odds ratios in the range of 1.24-1.59 to explore risk factors in the overall study population of 2500 cases and 2500 controls and in smaller subgroups of 500 cases and 500 controls. Assuming a sample size of 1500 in each arm, and an expected MACE rate in controls of 3%-5%, we will be able to detect hazard ratios for MACE in the range of 1.48-1.64 for bleeding compared to no bleeding. We will also have adequate power to detect the minimum difference in changes in function or cognition (change of 0.1-0.55, assuming a standard deviation between 1.0 and 5.0).

Approach to statistical analysis. We will use logistic regression to examine the relationship between risk factors and GI bleeding in the overall population and by world region. We will adjust for a priori identified confounding variables and will assess other variables empirically. A variable that is not identified a priori will be considered a confounder if it results in a minimum 10% change in the regression coefficient of the risk factor of interest when included in the model.

We will use Kaplan-Meier curves to plot MACE event rates in those with baseline GI bleeding (cases) that have follow-up data (any data collected past baseline), and controls. Survival curves will be compared using the log-rank test. We will use a Cox proportional hazards regression model to assess the relationship between GI bleeding and other known and potential risk factors for MACE, considering variables that change over time (eg, antithrombotic use post bleed as tune-varying covariates). This approach will allow us to quantify the impact of GI bleeding on the risk of MACE, as well as determine the relative impact of other risk factors for MACE in the presence and absence of prior exposure to bleeding. We will also consider competing risk models for MACE, mortality, and bleeding. In our primary analysis, we will not consider bleeding that occurs after baseline, but we will separately perform a secondary analysis that considers these bleeds. For the analysis examining the impact of GI bleeding on function and cognition, we will first use 2-sample Z-tests comparing the change in score between the bleeding and the nonbleeding group. We will also use multiple linear regression models, considering change between pre-baseline and follow-up SAGEA or cognitive scores, respectively, and adjusting for baseline variables.

Additional design considerations, challenges, and solutions

Case-control and cohort design—an efficient and novel design. Although cohort and randomized trials have substantial methodological advantages over case-control studies for the study of risk factors, they are usually prohibitively expensive because they require very large sample sizes and a long follow-up duration to obtain a sufficient number of subjects with the outcome of interest. A standardized incidence case-control study is much more efficient for the study of risk factors because it can provide quick and reliable information on the importance of a range of risk factors for bleeding, providing that considerable thought is given to minimizing potential biases and confounders in the design, analysis, and interpretation phases of the study. The INTERHEART[24] and INTERSTROKE[25] case-control

Table 3. Data collected in the INTERBLEED study

Data	Risk factor for:		Potentially modifiable	Used in the analysis for objective:		
	GI bleeding	MACE		1. Risk factors for GI bleeding	2. Risk factors for MACE after GI bleeding	3. Function
Collected at onset of bleed (cases) or baseline (controls)						
Demographics						
Age	Y	Y	N	Y	Y	Y
Sex (self-report)	U	Y	N	Y	Y	Y
Ethnicity	U	Y	N	Y	Y	Y
CV risk factors						
Hypertension	U	Y	Y	Y	Y	Y
Increased heart rate	U	Y	Y	Y	Y	Y
Diabetes	U	Y	Y	Y	Y	Y
Dyslipidemia	U	Y	Y	Y	Y	Y
Smoking	U	Y	Y	Y	Y	Y
Exposure to secondhand smoke	U	Y	Y	Y	Y	Y
Elevated body mass index	U	Y	Y	Y	Y	Y
Lack of physical activity	U	Y	Y	Y	Y	Y
Increased alcohol intake	Y	Y	Y	Y	Y	Y
Too little/too much sleep	U	Y	Y	Y	Y	Y
History of CV disease (coronary, cerebral, peripheral, other)	Y	Y	N	Y	Y	Y
History of non-CV disease						
Liver disease	Y	Y	N	Y	Y	Y
Renal dysfunction	Y	Y	N	Y	Y	Y
Creatinine clearance	Y	Y	N	Y	Y	Y
GI disease	Y	U	N	Y	Y	Y
Anemia	Y	Y	Y	Y	Y	Y
Cancer	Y	Y	N	Y	Y	Y
History of non-GI bleeding						
Significant non-GI bleed	Y	Y	N	Y	Y	Y
Non-significant GI bleed	Y	Y	N	Y	Y	Y
Medication use						
NSAIDs	Y	Y	Y	Y	Y	Y
Aspirin	Y	N	Y	Y	Y	Y
Other antiplatelets	Y	N	Y	Y	Y	Y
Anticoagulants	Y	N	Y	Y	Y	Y
Other	DS	DS	Y	Y	Y	Y
Anthropometrics*	U	Y	Y	Y	Y	Y
Psychosocial factors†	N	Y	Y	Y	Y	Y
Socioeconomic factors						
Education	U	Y	Y	Y	Y	Y
Income	U	Y	Y	Y	Y	Y
Patient expenditure on healthcare	U	Y	Y	Y	Y	Y
Functional status	U	U	Y	Y	Y	Y
Collected post bleed (cases) or baseline (controls)						
Anti-thrombotic medications	N/A	Y	Y	N	Y	Y
Other medication	DS	DS	Y	N	Y	Y
Quality of life	N/A	U	Y	N	Y	Y
Functional status	N/A	U	Y	N	Y	Y
Cognition	N/a	U	Y	N	Y	Y
CV events	N/A	Y	Y	N	Y	Y
Non-CV events	N/A	U	Y	N	Y	Y
Bleeding	N/A	Y	Y	N	Y	Y
Cases only						
Bleeding presentation	N/A	U	Y	N	Y	Y
Site of GI bleed	N/A	U	Y	N	Y	Y
Pathology of GI bleed	N/A	U	Y	N	Y	Y
Severity of bleeding	N/A	U	Y	N	Y	Y
Acuity (Forrest Classification)	N/A	U	Y	N	Y	Y
Treatment for bleeding‡	N/A	U	Y	N	Y	Y
Length of hospitalization post bleed	N/A	U	Y	N	Y	Y

CV, cardiovascular; DS, drug specific; GI, gastrointestinal; MACE, major adverse cardiovascular events (includes myocardial infarction, stroke, and cardiovascular death); N, no; N/A, not applicable; NSAID, nonsteroidal antiinflammatory drug; U, unknown; Y, yes.

* Includes blood pressure, heart rate, weight, and height.

† Depression, locus of control, perceived stress, life events.

‡ Includes transfusions, and pharmaceutical, percutaneous, and surgical interventions.

Box 1. Cardiovascular and bleeding event definitions

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.
Noncardiovascular death is defined as any death with a specific cause that is not thought to be CV in nature.
Undetermined cause of death refers to death not attributable to either one of the above categories of CV death or a non-CV cause.
The diagnosis of **myocardial infarction** requires the combination of evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathologic findings); andsupporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.
Stroke is defined as an acute episode of focal or global neurologic dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.
Transient ischemic attack is defined as a transient episode of focal neurologic dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction.
Major bleeding is defined as fatal bleeding, symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, or bleeding causing a fall in hemoglobin level of $\geq$ 2 g/dL, or leading to transfusion of $\geq$ 2 units of whole blood or red cells.

studies provide successful templates for this approach, both methodologically and practically. By including thousands of cases and controls, these studies had the power to explore risk factors in key subgroups defined by patient characteristics, geographic region, and ethnicity. INTERBLEED builds on the successes of these studies using a similar design to determine the risk factors for GI bleeding. The INTERBLEED study also uses a prospective cohort design to determine the importance of GI bleeding and other risk factors for MACE after GI bleeding, and the impact of GI bleeding on function.

Selection of cases and controls. Unbiased evaluation of risk factors for GI bleeding and outcomes after bleeding requires a systematic approach to the inclusion of cases. Patients with minor GI bleeding are frequently managed in the community, and these cases are extremely challenging to identify. By restricting inclusion to patients who are hospitalized, we ensure that more severe cases can be systematically identified, recognizing that some patients with severe GI bleeding will not present to hospital or will die before consent can be obtained, and those with less severe GI bleeding may be hospitalized for a short period before consent can be obtained. When we are unable to obtain consent, and at sites where ethics boards gave approval, we retrospectively collected data from charts, and these participants are not followed prospectively.

Biases in case selection may also result from the exclusion of patients admitted with life-threatening or fatal GI bleeding, the exclusion of patients with cognitive impairment, and the failure to include consecutive eligible patients (for example, patients admitted by subspecialists or in specialist institutions not participating in the study). We minimize the impact of these biases by including, wherever practicable, all patients admitted to participating hospitals with GI bleeding, as well as those experiencing GI bleeding during hospitalization (we include data on those who do not consent or who die, if approved by local ethics committees), and by inviting representative centres within a defined region to participate.

Controls should reflect the population base (without the disease, in this case GI bleeding), particularly if one wishes to estimate the population-attributable risk of individual risk factors. In general, community-based controls are preferred to hospital-based controls because they are least likely to be biased, as the reason for presentation to hospital can vary due to issues such as access to services. However, the possibility of including controls identified from either the community or the hospital (inpatients or outpatients) provides sites with the flexibility to use strategies that are most efficient for recruitment in their own environment.

Case-control studies often match cases and controls to remove matching factors as potential confounders. The limitation of this approach is that it is not possible to determine the contribution of the matching factors (for example, age and sex) to risk. These factors are of particular relevance for GI bleeding because the impact of bleeding risk factors is likely to vary by age and sex. Thus, instead of matching, we will adjust for these factors and explore potential interactions (as indicated by biological considerations) to quantify their relative impact on GI bleeding. This approach is preferable to explicit matching, particularly in large case-control studies when potential matching factors are known to be key risk factors.

Our approach to recruiting cases and controls is like the approaches successfully used in the INTERHEART and INTERSTROKE studies.[24,25]

Data collection

At baseline, medical history, including detailed bleeding and CV information, demographic data, (socioeconomic status, tobacco use, alcohol use, sleep, physical activity, and psychosocial factors), anthropometric measures (blood pressure, heart rate, height, and weight), medication use, and validated assessments of cognition (Montreal Cognitive Assessment [MoCA]), function (SAGEA), and quality of life (EQ-5D-3L) are collected for both cases and controls. For cases, detailed information is collected about the bleed (hemoglobin, creatinine, diagnostics, treatments for the bleed, site of the bleed, and pathology of the bleed) and the hospitalization.

As previously noted, selection bias is a concern, particularly for cases of patients who are relatively well and are discharged early and for those who die soon after admission. To minimize this potential bias, if we were unable to contact the participant to request consent, when possible, we obtained permission from ethics boards to retrospectively collect data available from charts.

Potential additional biases

Recall bias. Such bias may result when the presence or absence of a medical condition may influence patients' or caregivers' ability to recall events. We recruit cases after admission to hospital with GI bleeding or shortly after the occurrence of GI bleeding, in those who experience bleeding while already hospitalized, thereby minimizing the risk of recall bias. We also use multiple overlapping sources of information (admission lists, medical records, discharge summaries, correspondence, family physicians, and relatives) to validate medical

Table 4. Summary of sample size, approximate power, detectable differences, and statistical analyses

	Objective 1: Risk factors for GI bleeding	Objective 2: Risk of MACE after GI bleeding; risk factors for MACE	Objective 3: Effect of GI bleeding on function
Design	Case-control	Prospective cohort (case and control follow-up)	Prospective cohort (case and control follow-up)
Dependent variable	GI bleeding	Time to MACE	Change in functional status
Target sample size	2500 cases and 2500 controls	1500 (compared to the risk of MACE in 1500 controls)	1500 cases and 1500 controls (function measured at 1 year)
Approximate power, %	80	80	80
Detectable effect estimates	ORs: 1.24-1.59 in different subsets of varying sizes of regions and subgroups of patients • OR ~1.24 if N = 2500/group • OR ~1.59 if N = 500/group	The expected MACE event rate in the nonbleeding group is 3%−5%. Minimum detectable hazard ratios of MACE range between 1.48 and 1.64 for bleeding participants, compared to nonbleeding participants	The minimum detectable difference in SAGEA score change for bleeding vs nonbleeding groups ranges between 0.1 and 0.55 (assuming an equal SD ~ 1.0−5.0) with 80% power and 5% level of significance using a 2-sided 2-sample equal-variance *Z*-test.
Statistical analysis plan	Logistic regression model to assess the relationship between risk factors and being a case (GI bleeding) vs a control (no GI bleeding)	Kaplan-Meier curves, log-rank test comparing survival curve for bleeding vs nonbleeding group. We will also use Cox proportional hazards regression model to assess the relationship between GI bleeding and MACE, considering variables that change over time (eg, antithrombotic use post bleed as a time-varying covariate).	Two-sample *Z*-tests comparing the change in score for bleeding vs nonbleeding group. We will also use multiple linear regression models considering change as an outcome and adjust for baseline values and other potential confounders.
Additional analyses	Risk factor importance will be assessed by multivariable estimation of the population attributable risk (PAR) for each risk factor and their combinations	Competing risk models for MACE, mortality, and bleeding	

GI, gastrointestinal; MACE, major adverse cardiovascular events; OR, odds ratio; SAGEA, Standardized Assessment of Global Everyday Activities scale; SD, standard deviation.

information and outcomes reported by patients during follow-up. We require investigators to review the available supporting evidence for all outcomes before submitting. Although these requirements are not a guarantee of accuracy, they increase the likelihood that all outcomes are reported accurately.

Interviewer bias. Such bias may result from the knowledge of status (case or control), which may in turn influence the manner in which the questions are asked, or indirectly influence the interviewee's response. To overcome this potential bias, we train all interviewers to obtain information in a standardized fashion and we provide detailed guidance on the facing page of the data collection forms.

Trial coordination

The INTERBLEED study is being coordinated at the Population Health Research Institute, Hamilton Health Sciences, and McMaster University, all in Hamilton, Ontario, Canada. The Population Health Research Institute coordinated the global INTERHEART and INTERSTROKE studies. The INTERBLEED study is led by a steering committee that includes investigators at the Population Health Research Institute, as well as national leaders from participating countries.

Study progress

The first participant was enrolled in September 2015. As of April 1, 2022, the study is ongoing in 10 countries (Argentina, Australia, Belgium, Brazil, Canada, China, India, Ireland, Netherlands, and Turkey) at 31 centres (Appendix 1) and has recruited 2407 cases and 1478 controls (Table 5). Case recruitment has been most successful at centres where investigators and coordinators have identified efficient ways to identify those with GI bleeding, usually enlisting the help of staff in the GI service to flag potential cases for the study team. The use of endoscopy lists also has been effective, although this approach may not capture those with very short admissions.

Recruitment into the INTERBLEED study was severely impacted by the COVID-19 pandemic. Having reached a peak of 149 patients per month during 2019, recruitment fell to as low as 18 per month during 2020 and 2021, as a result of pandemic restrictions, and eventually, approximately one-third of sites in 3 countries (Brazil, China, and India) closed early. The majority of these sites were low-level recruiters and were closed only after follow-up and data collection were complete. Because these sites were low-level recruiters, early closure did not affect recruitment and is not expected to affect the generalizability of results.

For those recruited to date, cases tend to be older than controls (aged 75 vs 66 years), have less postsecondary education (14% vs 41%), and have more renal dysfunction (30% vs 11%), cancer (25% vs 17%), gastric ulcers (15% vs 5%), and diverticular disease (16% vs 7%; Table 6). More cases had hypertension (75% vs 65%), diabetes (36% vs 28%), and anemia (27% vs 13%), but less had dyslipidemia (50% vs 59%).

Table 5. Recruitment (as of April 29, 2022)

Country	Start date	Finish date	Sites, n	Cases, n	Prospective,*n	Retrospective, n	Controls, n
Argentina	June 2018	N/A	3	155	136	19	119
Australia	January 2022	N/A	1	21	21	0	54
Belgium	November 2017	N/A	1	129	129	0	129
Brazil	January 2019	N/A	9	80	80	0	114
Canada	September 2015	N/A	6	1785	802	983	918
China	July 2018	N/A	5	169	165	4	127
India	February 2020	N/A	1	10	10	0	0
Ireland	December 2017	October 2019	1	12	12	0	42
Netherlands	July 2019	N/A	1	24	24	0	11
Turkey	June 2021	N/A	3	44	44	0	30
Total			30	2429	1423	1006	1544

N/A, not applicable.

*Prospective cases will be followed for 12 months; all controls will be followed for 12 months

Discussion

The INTERBLEED study is the largest that is specifically designed to systematically evaluate risk factors for GI bleeding and outcomes after bleeding in diverse ethnic groups and geographic areas.

Although the Bradford-Hill criteria inform the potential for causation from an observational study, definitive evidence requires demonstration that modification of risk factors alters a clinical outcome. The goal of the INTERBLEED study is not to prove causation but to identify risk factors and associations, some of which may be modifiable. The information gained will inform future trials of interventions to modify risk factors.

Despite facing important challenges, the INTERBLEED study is expected to achieve the target of at least 2500 cases with GI bleeding and 2000 controls by the end of 2022. The results of this study will expand our understanding of risk factors for GI bleeding and inform initiatives aimed at

Table 6. Baseline characteristics

Characteristic	GI bleeding cases n = 2371	GI bleeding cases with follow up n = 1459	Controls n = 1428
Age, y, M (SD)	75 (13)	74 (13)	66 (14)
Female	945 (40)	567 (39)	537 (38)
History of noncardiovascular morbidity			
Renal dysfunction	697 (30)	436 (30)	158 (11)
Liver disease	238 (10)	152 (10)	49 (3)
Cancer	588 (25)	377 (26)	240 (17)
Gastric ulcers	348 (15)	258 (18)	75 (5)
Diverticular disease	372 (16)	222 (15)	103 (7)
Inflammatory bowel disease	72 (3)	38 (3)	20 (1)
Varices	80 (3)	52 (4)	3 (0)
Anemia	630 (27)	441 (30)	178 (13)
History of cardiovascular morbidity			
Myocardial infarction	781 (33)	507 (35)	518 (36)
Revascularization			
PTCA/PCI	505 (21)	360 (25)	428 (30)
CABG	403 (17)	251 (17)	200 (14)
Heart failure	745 (31)	469 (32)	406 (28)
Stroke	423 (18)	268 (18)	161 (11)
History of CV risk factors			
Hypertension	1788 (75)	1104 (76)	932 (65)
Diabetes mellitus	860 (36)	523 (36)	401 (28)
Dyslipidemia	1194 (50)	794 (54)	842 (59)
Anthropometric measurements			
Arm blood pressure, mm Hg, M (SD)			
Systolic	124 (22)	124 (21)	128 (19)
Diastolic	68 (13)	69 (12)	74 (12)
Heart rate, bpm, M (SD)	81 (17)	80 (16)	72 (15)
Weight, kg, M (SD)	77.6 (19.7)	77.8 (20)	83.4 (21)
Height, cm, M (SD)	168 (10)	168 (10)	167 (10)
Creatinine clearance, umol/l, M (SD)	206.33 (709)	199.97 (730)	129.27 (614)

At the time of writing, baseline data are not yet available for all patients enrolled in the trials. Values are n (%), unless otherwise indicated.

bpm, beats per minute; CABG, coronary artery bypass graft; CV, cardiovascular; GI, gastrointestinal; M, mean; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SD, standard deviation.

preventing GI bleeding and subsequent MACE, as well as functional and cognitive outcomes.

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J.B. has received funding from Bayer AG for event adjudication activities. A.A. has been on scientific advisory boards and received honoraria from Boehringer Ingelheim and Bayer. A.B. reports receiving grants and consulting fees from and advisory board membership at Pendopharm and At-Gen, and advisory membership at Olympus and Cook. N.F. reports consultant and speaker fees, and receiving research funding from, Pentax Medical, consultant and speaker fees from Boston Scientific, and consultant fees from AstraZeneca and Pendopharm. Y.L. has received honoraria for lectures from Bayer, Boehringer, Sanofi, Roche, and Abbott. J.C.N. has research grants from Amgen, AstraZeneca, Bayer, CSL Behring, Daiichi Sankyo, Dalcor, Esperion, Janssen, Novartis, Novo Nordisk, Sanofi, and Vifor. G.O. has received honoraria from Janssen for consultancy and written scientific materials, and honoraria from Novartis as a speaker. T.V. has received honoraria for providing lectures and being on advisory boards from Bayer, Boehringer, Pfizer, BMS, Daiichi-Sankyo, Leo Pharma, and AstraZeneca. P.V. has received honoraria for providing lectures and being on advisory boards from Bayer, Boehringer, Pfizer, BMS, Daiichi-Sankyo, Anthos pharmaceuticals, and Portola (AstraZeneca). M.W. has study funding from CIHR, NHMRC (Australia), HRC (New Zealand), British Heart Foundation, and Vifor; has been on steering committees for Bayer; and has provided event adjudication for Novo NorDisk. C.W. has received honoraria for advisory board service and speaking engagements from Leo Pharma, Pfizer, Servier, and BMS-Pfizer. J.W.E. has received honoraria, research or in-kind support fromAstra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Glaxo-Smith-Kline, Pfizer, Janssen, Sanofi-Aventis and honoraria from Astra-Zeneca, Bayer, Boehringer-Ingelheim, Bristol-Myer-Squibb, Daiichi-Sankyo, Eli-Lilly, Glaxo-Smith-Kline, Merck, Pfizer, Janssen, Sanofi-Aventis, Servie. All the other authors have no conflicts of interest to disclose.

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Site number provided in brackets.