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Vulnerable blood in high risk vascular patients: Study design and methods ☆

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ABSTRACT

Background: Basic research suggests that rapid increases in circulating inflammatory and hemostatic blood markers may trigger or indicate impending plaque rupture and coronary thrombosis, resulting in acute ischemic heart disease (IHD) events. However, these associations are not established in humans.

Methods and results: The Biomarker Risk Assessment in Vulnerable Outpatients (BRAVO) Study will determine whether levels of inflammatory and hemostatic biomarkers rapidly increase during the weeks prior to an acute IHD event in people with lower extremity peripheral artery disease (PAD). The BRAVO Study will determine whether biomarker levels measured immediately prior to an IHD event are higher than levels not preceding an IHD event; whether participants who experience an IHD event (cases) have higher biomarker levels immediately prior to the event and higher biomarker levels at each time point leading up to the IHD event than participants without an IHD event (controls); and whether case participants have greater increases in biomarkers during the months leading up to the event than controls. BRAVO enrolled 595 patients with PAD, a population at high risk for acute IHD events. After a baseline visit, participants returned every two months for blood collection, underwent an electrocardiogram to identify new silent myocardial infarctions, and were queried about new hospitalizations since their prior study visit. Mortality data were also collected. Participants were followed prospectively for up to three years.

Conclusions: BRAVO results will provide important information about the pathophysiology of IHD events and may lead to improved therapies for preventing IHD events in high-risk patients.

1. Introduction

Approximately 8 million men and women in the United States have lower extremity peripheral artery disease (PAD) and the prevalence of PAD is increasing worldwide [1,2].

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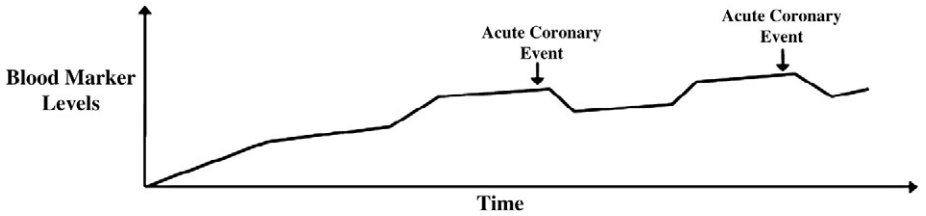

Fig. 1. Theoretical model for the association of short-term increases in inflammatory biomarkers and D-dimer with short-term risk for acute ischemic heart disease events. Marker levels increase shortly before and decline soon after an event.

People with PAD have a 2 to 4-fold increased rate of cardiovascular events compared to those without PAD, even after taking into account cardiovascular disease risk factors [3]. Despite major treatment advances, current diagnostic methods and therapies are insufficient to prevent atherosclerotic disease progression. Many patients suffer cardiovascular events despite optimal medical therapy [4,5]. Thus, preventing cardiovascular morbidity and mortality in the large and growing number of people with PAD is an important public health goal.

Evidence from intra-vascular ultrasound, angiography, and pathology examinations indicates that ischemic heart disease (IHD) events often result from plaque rupture on areas of non-obstructive coronary atherosclerosis [6–11]. Approximately 70% of IHD events are thought to result from plaque rupture and subsequent luminal thrombosis at arterial sites with minimally occlusive atherosclerosis [5]. However, hemostatic and inflammatory protein triggers of acute plaque rupture and subsequent IHD events are not clearly identified.

Animal studies and in-vitro models suggest that increases in circulating inflammatory and hemostatic biomarkers may trigger plaque rupture and coronary thrombosis, resulting in IHD events [12–14]. Inflammatory and hemostatic blood markers are significantly elevated in people with PAD compared to those without PAD [15,16]. Because people with PAD have higher rates of cardiovascular events than those without PAD and because of their increased levels of circulating inflammatory and hemostatic biomarkers, they are an optimal study population in which to assess associations of circulating biomarkers with cardiovascular events. (See Fig. 1.)

Establishing whether blood biomarkers increase shortly before an IHD event will help elucidate the pathophysiology of acute vascular events and determine whether acute increases in circulating biomarkers identify persons at high risk for near-term (i.e. less than 60 days) IHD events. This information may lead to improved therapies for preventing and treating acute cardiovascular events in vulnerable populations, such as those with PAD.

The purpose of the Biomarker Risk Assessment in Vulnerable Outpatients (BRAVO) Study is to assemble a cohort of patients at high-risk for IHD events and follow them prospectively with frequent follow-up visits in order to determine whether circulating levels of inflammatory and hemostatic factors increase acutely during the weeks and months leading up to an IHD event. The primary aim of the BRAVO Study is to determine whether among PAD participants who experience an IHD event, biomarker levels measured immediately prior to an IHD event are higher than levels not preceding an event. The second primary aim of the BRAVO Study is to determine whether participants who experience an IHD event (cases) have higher biomarker levels immediately prior to the event than participants who do not experience an event (controls). The second primary aim of the BRAVO Study will also determine whether case participants have greater increases in biomarkers during the months leading up to the IHD event, compared to controls (see Table 1). The biomarkers studied are D-dimer, C-reactive protein (CRP) and serum amyloid A (SAA).

2. Methods

2.1. Overview

The Institutional Review Board at Northwestern University and all participating sites approved the protocol. All participants provided written, informed consent. Enrollment took place between September 2009 and September 2012. Follow-up visits took place through January 2013.

Table 1
Specific aims of the BRAVO Study.

	Specific aim	Analysis plan/design
Primary Aim #1	Among participants who experience an acute ischemic heart disease event, we will determine whether biomar ker levels measured immediately prior to the event are higher than levels not preceding the event.	Case–crossover design. Analyses will be performed within the subset of BRAVO participants who experience an event during follow-up.
Primary Aim #2a	We will determine whether participants who experience an acute ischemic heart disease event (cases) have higher biomarker levels immediately prior to the event than participants who do not experience an event (controls).	Case–control study design. Two controls will be randomly selected among those matched by age, sex, and length of time in the study.
Primary Aim #2b	We will determine whether case p articipants have greater increases in biomarkers during the months leading up to the event, compared to controls.	Case–control study design. Two controls will be randomly selected among those matched by age, sex, and length of time in the study.