Journal of the American Heart Association

ORIGINAL RESEARCH

Eligibility and Implementation of Rivaroxaban for Secondary Prevention of Atherothrombosis in Clinical Practice—Insights From the CANHEART Study

Maya S. Sheth, BMSc; Bing Yu, PhD; Anna Chu, MHSc; Joan Porter, MSc; Derrick Y Tam, MD, PhD; Laura E. Ferreira-Legere, MScN; Shaun G. Goodman, MD; Michael E. Farkouh, MD; Dennis T. Ko, MD; Husam Abdel-Qadir, MD, PhD; Jacob A. Udell, MD, MPH

BACKGROUND: The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial decreased major adverse cardiovascular events with very low-dose rivaroxaban and aspirin in patients with coronary artery disease and peripheral artery disease. We examined the eligibility and potential real-world impact of this strategy on the COMPASS-eligible population.

METHODS AND RESULTS: COMPASS eligibility criteria were applied to the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) registry, a population-based cohort of Ontario adults. We compared 5-year major adverse cardiovascular events and major bleeding rates stratified by COMPASS eligibility and by clinical risk factors. We applied COMPASS trial rivaroxaban/aspirin arm hazard ratios to estimate the potential impact on the COMPASS-eligible cohort. Among 362 797 patients with coronary artery disease or peripheral artery disease, 38% were deemed eligible, 47% ineligible, and 15% indeterminate. Among eligible patients, a greater number of risk factors was associated with higher rates of cardiovascular outcomes, whereas bleeding rates increased minimally. Over 5 years, applying COMPASS treatment effects to eligible patients resulted in a 2.4% absolute risk reduction of major adverse cardiovascular events and a number needed to treat of 42, and a 1.3% absolute risk increase of major bleeding and number needed to harm (NNH) of 77. Those with at least 2 risk factors had a 3.0% absolute risk reduction of major adverse cardiovascular events (number needed to treat =34) and a 1.6% absolute risk increase of major bleeding (number needed to harm =61).

CONCLUSIONS: Implementation of very-low-dose rivaroxaban therapy would potentially impact ≈2 in 5 patients with atherosclerotic disease in Ontario. Eligible individuals with ≥2 comorbidities represent a high-risk subgroup that may derive the greatest benefit-to-risk ratio. Selection of patients with high-risk predisposing factors appears appropriate in routine practice.

Key Words: coronary artery disease ■ peripheral artery disease ■ rivaroxaban

Despite advances in medical therapy, atherosclerotic cardiovascular disease, including coronary artery disease (CAD) and peripheral artery disease (PAD), remains the leading cause of death worldwide. Patients are at high risk for myocardial infarction, repeat revascularization, and stroke, which, if not fatal, have a tremendous negative impact on quality of life and place substantial economic burden on the health care system.[1–3] Consequently, the development and validation of secondary prevention strategies is necessary for individuals with cardiovascular disease.[4]

Recently, the COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial examined the effectiveness of the anticoagulant factor

Correspondence to: Jacob A. Udell, MD, Cardiovascular Division, Peter Munk Cardiac Centre, Toronto General Hospital and Women's College Hospital, University of Toronto, 76 Grenville Street, Toronto, ON M5S 1B1, Canada. Email: jay.udell@utoronto.ca

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.026553

For Sources of Funding and Disclosures, see page 9.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Through an analysis of the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) population-based registry in Ontario, Canada, we determined that implementation of very-low-dose rivaroxaban therapy would impact ≈40% of patients with atherosclerotic disease in Ontario.
- Eligible individuals with ≥2 comorbidities represent a high-risk subgroup that had a 3.0% absolute risk reduction of major adverse cardiovascular events, and a 1.6% absolute risk increase of major bleeding, over 5 years.
- When stratified by age, patients aged <65 years had a number needed to treat : number needed to harm ratio of ≈1:13, ages 65–74 had a ratio of ≈1:2, and patients aged ≥75 years had an approximate ratio of 2:1.

What Are the Clinical Implications?

- Selection of patients with high-risk predisposing factors appears appropriate in routine practice, as patients with at least 2 risk factors and patients aged <75 years have an enhanced benefit of using very-low-dose rivaroxaban therapy.
- Population-based registries and observational cohort studies of patients with atherosclerosis are increasingly resourceful for measuring the appropriateness and comparative effectiveness of new therapies in routine practice.

Nonstandard Abbreviations and Acronyms

ARI	absolute risk increase
CANHEART	Cardiovascular Health in Ambulatory Care Research Team
COMPASS	Cardiovascular Outcomes for People Using Anticoagulation Strategies
MACEs	Major adverse cardiovascular events

Xa inhibitor rivaroxaban with or without aspirin in the secondary prevention of major adverse cardiovascular events (MACEs) such as cardiovascular death, stroke, or myocardial infarction.[5] Treatment with a combination of aspirin and very-low-dose rivaroxaban reduced MACEs by 24% (hazard ratio, 0.76 [95% CI, 0.66–0.86]; $P<0.001$) but also increased major bleeding events by 70% (hazard ratio, 1.70 [95% CI, 1.40–2.05]; $P<0.001$).[5]

While the findings of the COMPASS trial serve as a novel treatment strategy for patients with stable CAD and PAD, the generalizability of the trial warrants further investigation. Strict eligibility criteria in the clinical trial setting may preclude many patients with comorbidities from receiving treatment and skew results in a highly selected population.[6] Furthermore, prior studies in different patient populations were inconsistent in estimating whether trial-eligible or -ineligible patients were at the highest risk for clinical events.[7,8] Finally, Mortensen and colleagues[9] also examined the proportion of individuals eligible for secondary prevention treatments studied in recent randomized clinical trials. However, all of these studies insufficiently considered benefit in the context of potential risk. As a result, there remains a need to further assess the potential population benefit and safety associated with adopting very-low-dose rivaroxaban for secondary prevention of atherosclerosis. Further, it remains unclear how the trial results will translate to the Canadian health care setting and the therapeutic potential if routinely implemented across clinical practice.

To address these gaps in knowledge, we examined the representativeness of the COMPASS trial population in the CANHEART (Cardiovascular Health in Ambulatory Care Research Team) cohort. Using administrative claim-based, laboratory, and hospitalization data, we examined ischemic and bleeding events of clinically relevant subgroups within the CANHEART cohort, to estimate which groups could potentially benefit from very-low-dose rivaroxaban therapy. Finally, we applied the risk reduction effects and safety signals seen within the COMPASS trial to the CANHEART study population to assess the projected impact in routine Canadian clinical practice.

METHODS

Although data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/das.

Study Population, Data Sources, and Cohort Design

Our study population was derived from the CANHEART initiative, which comprises a population-based cohort composed of 9.8 million adults aged ≥20 years living in Ontario, Canada, created using linkages between multiple individual-level data sets. These data sets were linked using unique encoded identifiers, analyzed, and held securely in coded form at ICES (Figure S1).[10] ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without individual patient consent, for health system evaluation and improvement. Use of

these databases for the purposes of this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. Full details on the methods used to create the CANHEART cohort have been previously described.[10]

We linked individuals identified within the Ontario Registered Persons Database, a repository of population demographics and death information, to health administrative databases. The Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System were used to identify nonfatal cardiac outcomes and past hospitalizations and emergency department presentations. The Ontario Health Insurance Plan and Ontario Laboratories Information System provided information on comorbidities and laboratory-derived inclusion criteria. Linkage to the CorHealth Ontario registry, a repository of cardiac, stroke, and vascular care, provided additional information on single/multivessel CAD, heart failure, baseline tobacco use, and body mass index. The Ontario Diabetes Database and the Ontario Hypertension Database provided information on baseline diabetes and hypertension, respectively.[11,12] The Ontario Drug Benefit database provided prescription drug information for individuals aged ≥65 years.

For this study, we included community-dwelling patients *aged* ≥40 years on January 1, 2011, eligible for Ontario Health Insurance Plan between 2006 and 2010, that met COMPASS-like inclusion criteria for either CAD or PAD. We excluded residents of long-term care facilities, as our focus was on community-dwelling adults.[10] The 5-year Ontario Health Insurance Plan eligibility criteria enabled a look-back period to assess for CAD or PAD. With lags in data availability, particularly for cause of death, we chose January 1, 2011, as the inception date to allow a complete 5-year follow up and complete ascertainment of death. In addition, a 2011 cohort avoided the potential for implementation of COMPASS regimens in a more contemporary study population, which could bias our results.

Detailed descriptions of the COMPASS eligibility criteria are reported in the original publications, some of which is described below and reported in Tables S1 through S3.[10] We mapped these criteria to the CANHEART cohort using *International Classification of Diseases*, *Ninth Revision* (*ICD-9*) and *Tenth Revision–Canada* (*ICD-10-CA*) diagnostic codes; Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; and Canadian Classification of Health Interventions codes and data from CorHealth (Tables S1 and S2).[10] Patients with CAD were defined as those with a history of hospitalization for myocardial infarction, angiographic evidence of at least a >50% obstruction in a major coronary artery, or history of percutaneous or surgical coronary revascularization between April 1, 1988 (earliest date of data availability) and December 31, 2010 (Table S1). Although the COMPASS trial applied further conditions based on additional clinical risk factors for patients aged <65 years, we elected to forego application of these factors for simplicity and because rivaroxaban's approved product monograph does not distinguish its use on the basis of age. Patients with PAD included those with a history of aortofemoral bypass surgery, limb bypass surgery, percutaneous transluminal angioplasty revascularization of iliac or infrainguinal arteries, carotid revascularization, limb or foot amputation for arterial vascular disease, or diabetic angiopathy, or were defined using a modified version of an established claims-based algorithm that required any combination of 2 diagnostic and/or revascularization procedure codes for various PAD conditions, with a similar evaluation time frame (Table S2).[13,14]

Next, we defined a group of patients meeting the COMPASS trial's exclusion criteria using administrative diagnostic codes and laboratory values (Table S3). This included any individuals with a known history of major bleeding (or risk), hemorrhagic stroke, New York Heart Association class III to IV heart failure, cancer within the past 5 years, hepatic disease, or advanced chronic kidney disease (patients with an estimated glomerular filtration rate <30 or chronic dialysis).[15] History or risk of major bleeding was defined as a HAS-BLED score ≥3 or a history of hemophilia or other hemorrhagic disorder, cardiac tamponade, hemothorax, or gastrointestinal bleed with transfusion.[16] The HAS-BLED score is a predictive tool of bleeding risk, assigning 1 point to the presence of various risk factors, with a cumulative score ≥3 indicating high risk.[16,17]

In addition, among those aged >65 years, for whom medication use was available, we excluded patients treated with antiplatelet or antithrombotic therapy, certain cytochrome P450 3A4 and P-glycoprotein inhibitors or inducers of cytochrome P450 3A4 (Table 3). Individuals that met the CAD/PAD criteria and did not meet any exclusion criteria were classified as "COMPASS eligible," meaning potentially eligible for rivaroxaban therapy for secondary prevention. Individuals with any exclusion criteria were classified as "COMPASS ineligible," and those who could not be categorized definitively into 1 of the 2 aforementioned groups because of insufficient information were classified as "COMPASS indeterminate."

Outcome Measures and Follow-Up

The primary outcome was a composite of cardiovascular death, myocardial infarction, and stroke. Our definition of cardiovascular death was consistent with that of COMPASS.[5] Secondary outcomes included the individual components of the primary outcome as well

as all-cause death, heart failure, and major bleeding (Table S4). Major bleeding as an outcome was defined by a validated list of diagnostic codes (Table S5).[14] For our findings to be comparable with other trials, we followed all patients to the earliest of death, an outcome event, loss of Ontario Health Insurance Plan eligibility, or end of study, defined as 5 years or December 31, 2015.

Statistical Analysis

Baseline demographic and clinical characteristics of the estimated COMPASS-eligible, -indeterminate, and -ineligible groups were described. Trend tests across COMPASS-eligible, -indeterminate, and -ineligible populations were performed using the Cochran–Armitage test for categorical variables and linear regression for continuous variables. Incidence rates for all primary and secondary outcomes were calculated as crude events per 100 patient-years of follow-up for each group. We further stratified outcome rates among the COMPASS-eligible population by the presence of an increasing number of ischemic risk factors (ie, 1 to ≥4 of age ≥65 years, polyvascular disease (CAD and PAD), diabetes, heart failure, chronic kidney disease (estimated glomerular filtration rate, 15–60), current smoker, or ischemic stroke). Trend tests across the number of baseline risk factors were performed using linear regression. We hypothesized that the presence of an increasing number of ischemic risk factors at baseline would disproportionally enhance the risk for major adverse cardiovascular events over bleeding events because these disparate outcomes do not share many similar risk factors. We also examined outcomes among a subgroup of patients of ≥2 risk factors. Further, we examined outcome rates for each year, over 5 years.

To estimate the impact of initiating very-low-dose rivaroxaban treatment among the COMPASS eligible population, survival probabilities using the Kaplan–Meier method were constructed for primary and secondary outcomes under control or no treatment and

Table 1. Baseline Characteristics of Patients Within the CANHEART Cohort by Estimated Eligibility for the COMPASS Trial

	COMPASS eligible (n=137 895)	COMPASS indeterminate (n=55 616)	COMPASS ineligible (n=169 286)	*P* value for trend
Demographics				
Follow-up time, y	4.7 ± 0.9	4.5 ± 1.1	4.1 ± 1.5	<0.001
Age, y	65.8 ± 11.0	66.5 ± 12.7	73.8 ± 10.2	<0.001
Age ≥65 y	68 686 (49.8)	27 740 (49.9)	142 404 (84.1)	<0.001
Female sex	35 798 (26.0)	15 186 (27.3)	56 555 (33.4)	<0.001
Medical history				
Hyperlipidemia	12 233 (8.9)	2988 (5.4)	9597 (5.7)	<0.001
Ever smoker*	18 222 (58.1)	4524 (61.9)	24 119 (55.2)	<0.001
Hypertension	104 576 (75.8)	38 602 (69.4)	152 871 (90.3)	<0.001
Diabetes	51 864 (37.6)	17 194 (30.9)	78 490 (46.4)	<0.001
Previous stroke	2502 (1.8)	1503 (2.7)	17 102 (10.1)	<0.001
Previous MI	73 238 (53.1)	35 281 (63.4)	92 808 (54.8)	<0.001
HF hospitalization	1456 (1.1)	13 641 (24.5)	39 378 (23.3)	<0.001
CAD	111 600 (80.9)	43 526 (78.3)	122 447 (72.3)	<0.001
PAD	15 576 (11.3)	6539 (11.8)	24 174 (14.3)	<0.001
CAD and PAD	10 719 (7.8)	5551 (10.0)	22 665 (13.4)	<0.001
Moderate CKD (eGFR 30–60)	19 974 (14.5)	3213 (5.8)	59 554 (35.2)	<0.001
Prescriptions in the 100 d before January 1, 2011†				
ACE inhibitor	32 999 (48.0)	10 715 (38.6)	70 379 (49.4)	<0.001
ARB	14 265 (20.8)	4199 (15.1)	34 305 (24.1)	<0.001
Calcium channel blocker	18 276 (26.6)	5731 (20.7)	50 078 (35.2)	<0.001
Diuretic	14 717 (21.4)	6436 (23.2)	55 874 (39.2)	<0.001
Beta blocker	34 443 (50.1)	11 785 (58.4)	86 232 (60.6)	<0.001
Lipid-lowering agent	53 542 (78.0)	16 188 (58.4)	116 519 (81.8)	<0.001

Values are n (%) or mean±SD unless otherwise specified. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CAD, coronary artery disease; CANHEART, Cardiovascular Health in Ambulatory Care Research Team; CKD, chronic kidney disease; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; and PAD, peripheral artery disease.

*77.3% of total cohort has missing smoking history.

†Available for individuals aged ≥65 years on September 23, 2010.

Table 2. Outcomes Among COMPASS-Eligible, -Indeterminate, and -Ineligible Patients in CANHEART Versus Referent COMPASS Trial Aspirin-Arm Participants

	COMPASS-eligible event rate in 100 patient-years	COMPASS-indeterminate event rate in 100 patient-years	COMPASS-ineligible event rate in 100 patient-years	*P* value for indeterminate vs eligible	COMPASS participants treated with aspirin alone, event rate in 100 patient-years[7]
Primary outcome					
Cardiovascular death, MI or stroke	2.19	3.02	5.13	<0.001	2.9
Secondary outcomes					
All-cause death	2.37	3.40	7.84	<0.001	2.2
Cardiovascular	0.84	1.40	3.02	<0.001	1.2
Noncardiovascular	1.54	2.00	4.82	<0.001	1.0
MI hospitalization	1.12	1.43	1.82	<0.001	1.2
Stroke hospitalization	0.45	0.54	0.96	<0.001	0.8
Ischemic	0.40	0.49	0.84	<0.001	—
Hemorrhagic	0.05	0.05	0.11	<0.001	—
Heart failure hospitalization	0.58	1.11	2.58	<0.001	—
Major bleeding	0.38	0.40	1.21	<0.001	—

Event rates among CANHEART patients are over 5 years, and among the referent COMPASS trial aspirin arm participants are over 23 months. CANHEART indicates Cardiovascular Health in Ambulatory Care Research Team; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; and MI, myocardial infarction.

compared with the estimated survival function if the effect sizes for outcomes in COMPASS (rivaroxaban plus aspirin versus aspirin alone) were applied to the survival probability. We performed this analysis applying the trial's outcome-specific hazard ratios for the primary outcome and each secondary outcome using a cause-specific hazard model accounting for competing risks.[18] The absolute risk reduction (ARR) in cardiovascular events and absolute risk increase (ARI) in bleeding events were then estimated as the difference in survival at 5 years as a conventional reference duration. CIs (95%) were estimated from the 2.5 and 97.5 percentiles of the ARR estimated from 1000 bootstrap samples of the study population. The number needed to treat (NNT) or harm (NNH) was calculated as the inverse of the ARR (or ARI). The estimated number of events prevented (or increased) was calculated as the product of the eligible population size and ARR (or ARI). To account for potential differing rates of background aspirin use and assuming a synergy of rivaroxaban and new use of aspirin, we conducted a sensitivity analysis to calculate effect estimates considering various fractional rates of background antiplatelet use in the population (ranging from 20% to 100%).[19] All analyses were conducted at ICES in Toronto, Canada, using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

From 9.4 million individuals in the CANHEART cohort on January 1, 2011, 362 797 patients had a history of atherosclerotic cardiovascular disease to include in the present analysis (Figure S1). Among these patients, 169 286 (46.7%) individuals had at least 1 exclusion criterion deeming them "COMPASS ineligible." The highest prevalence of reasons for exclusion were a HAS-BLED score ≥3 (33.1%), prescription for dual antiplatelet therapy (22.9%), hemophilia (7.2%), cancer diagnosis (5.9%), and hepatic disease associated with coagulopathy (3.6%).

There were 55 616 (15.3%) individuals with insufficient data to determine COMPASS eligibility primarily because of missing data on renal function and thus were deemed COMPASS indeterminate. The remaining 137 895 (38.0% with CAD or PAD, or 1.5% of community dwelling adults in Ontario) were classified as estimated COMPASS eligible (Figure S1).

Baseline characteristics of COMPASS-eligible, -indeterminate, and -ineligible populations are reported in Table 1. COMPASS-eligible patients had a lower proportion of cardiovascular events and risk factors compared with the COMPASS-ineligible population, while the COMPASS-indeterminate group had intermediate baseline risk. COMPASS-indeterminate patients aged >65 years had overall fewer prescriptions for cardiovascular medications compared with COMPASS-eligible patients (Table 1). Compared with the ineligible group, the eligible group was younger and more frequently male.

Cardiovascular and major bleeding outcomes among the 3 patient groups over the 5-year study period are reported in Table 2 and Figure S2. Compared with indeterminate patients, eligible patients had

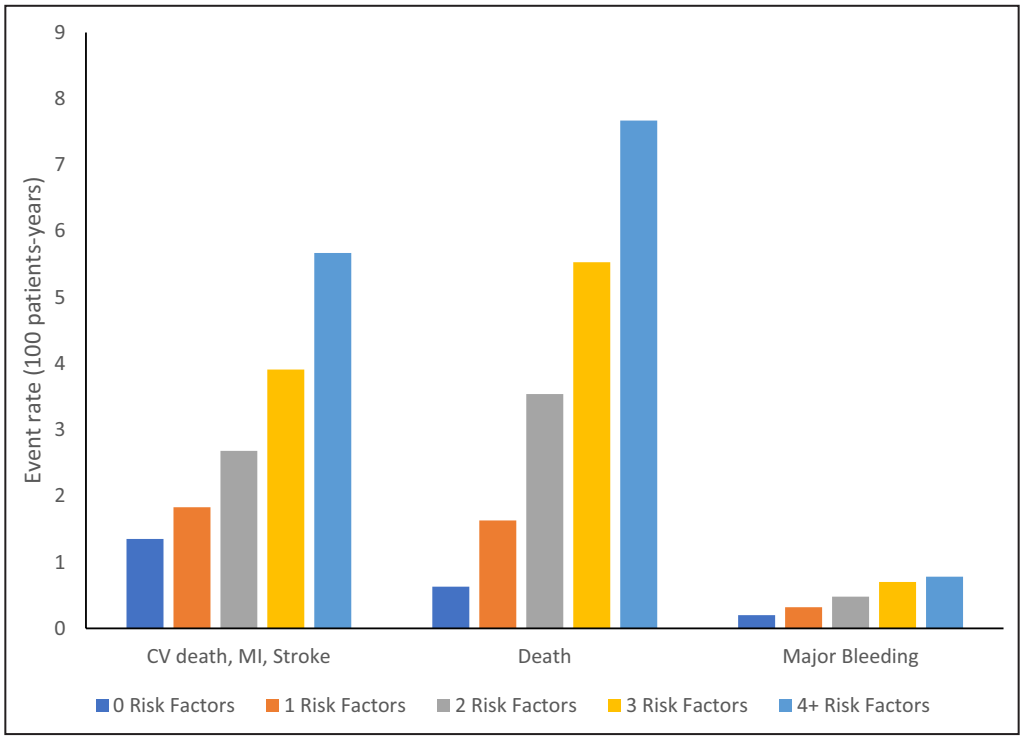


Figure. Outcomes among COMPASS eligible patients in the CANHEART registry by presence of risk factor.
Risk factors include age ≥65 years, polyvascular disease (coronary artery disease or peripheral artery disease), diabetes, heart failure, chronic kidney disease (estimated glomerular filtration rate <60), current smoker, or ischemic stroke. Patients were categorized by presence of 0, 1, 2, 3 or 4+ risk factors. All *P* value for trend <0.0001. CANHEART indicates Cardiovascular Health in Ambulatory Care Research Team; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CV, cardiovascular; and MI, myocardial infarction.

a lower rate of MACEs (2.19 versus 3.02 events per 100 patient-years) and experienced lower rates of all secondary outcomes, including major bleeding (0.38 versus 0.40 events per 100 patient-years). COMPASS-ineligible patients had the highest event rate across all groups. Notably, compared with COMPASS trial participants treated with aspirin alone, our COMPASS-eligible patients had substantially lower event rates for most outcomes, including the primary outcome. By age group, primary outcome and major bleeding rates were also lower among eligible patients compared with indeterminate patients and increased with older age groups (Table S6).

Prevalence of number of clinical risk factors at baseline in the COMPASS-eligible, -indeterminate, and -ineligible populations are presented in Figure S3. Most eligible patients possessed at least 1 risk factor (89.4%), while 54.6% had at least 2. Outcome rates according to the number of clinical risk factors are shown in the Figure 1 and Table 3. A higher number of comorbidities was associated with a progressively increased rate of MACEs. In contrast, the presence of more risk factors was associated with a modest increase in major bleeding events (Figure 1).

Results from applying the COMPASS trial treatment regimen of very-low-dose rivaroxaban plus aspirin in the CANHEART population of potentially COMPASS-eligible patients are shown in Table 4 (overall over 5 years) and Table S7 (each year over 5 years). With 13 880 (10.1%) MACE events observed over 5 years among 137 895 COMPASS eligible patients, initiation of very-low-dose rivaroxaban would result in 3306 (95% CI, 3259–3355) fewer events and an ARR of 2.4% (NNT_5=42). With 2454 (1.8%) major bleeding events observed during this same period, initiation of very-low-dose rivaroxaban would result in an increase of 1788 (95% CI, 1720–1860) events, an ARI of 1.3% (NNH_5=77). These estimates translate at 2 years to an approximate NNT_2=107 for the primary outcome and NNH_2=223 for major bleeding (Table S7). The original COMPASS trial yielded an ARR of the primary outcome of 1.3% (NNT_2=77) and an ARI of major bleeding of 1.3% (NNH_2=75) at 2 years. The results of this comparison are presented in Table S8.

When stratified by number of risk factors, presence of a greater number of risk factors was associated with a greater ARR for MACEs and a greater ARI for major bleeding (Table S9). If this therapy were initiated among patients with at least 2 risk factors, 9375 MACE events would be prevented, at the cost of 1671 major bleeding events after 5 years. When stratified by age, patients aged <65 years had an NNT:NNH ratio of ≈1:13, patients aged 65 to 74 had a ratio of ≈1:2, and patients aged ≥75 years had an ratio of ≈2:1 (Table S10).

Results from the sensitivity analysis, comparing effect estimates with different rates of background antiplatelet use are shown in Table S11. Assuming 0% background aspirin use, the NNT:NNH ratio was ≈1:1. If 100% of the population was assumed to be taking aspirin already, the COMPASS regimen was expected to result in an NNT:NNH of 1:2. Decreasing the assumed proportion of background aspirin use at baseline resulted in a higher ARR for MACEs and ARI for major bleeding.

DISCUSSION

Our study examined the estimated impact of very-low-dose rivaroxaban plus aspirin therapy on MACEs and bleeding outcomes in patients with stable CAD or PAD in Ontario. COMPASS-eligible patients represented ≈38% of individuals with CAD or PAD in the CANHEART cohort; and at the population level, ≈1.5% of Ontario community-dwelling adults. The COMPASS-eligible group had the lowest outcome rates, and the COMPASS-indeterminate group had intermediate risk across all 3 groups. The COMPASS-ineligible group had the highest incidence of outcomes, likely attributable to significant comorbidities, particularly high bleeding risk.

If very-low-dose rivaroxaban is initiated in Ontario among appropriate patients, after 5 years ≈3306 atherothrombotic events may be prevented, at the cost of about half the number of major bleeding events. Our findings suggest that patients with at least 1 risk factor, which represents almost 90% of eligible patients in Ontario, and patients with at least 2 risk factors, which represents almost half of the population, have an enhanced benefit of using very-low-dose rivaroxaban therapy. Appropriate patient selection for those with high-risk predisposing factors is crucial. If patients are newly started on very-low-dose rivaroxaban and aspirin, one can expect a higher ARR for MACE but at the expense of a higher ARI for major bleeding.

Despite an apparent reduction in MACEs regardless of age, patients aged <75 years may derive the greatest benefit, whereas those aged ≥75 years experience greater risks for harm, regardless of the number of risk factors they have. This potentially could be a pragmatic

Table 3. Outcomes of COMPASS-Eligible Patients Stratified by Number of Risk Factors

Variable	0 Risk factors n=14 616 (10.6%)		1 Risk factor n=47 949 (34.8%)		2 Risk factors n=46 316 (33.6%)		3 Risk factors n=22 139 (16.1%)		4 Risk factors n=6875 (5.0%)		*P* value for trend
	Events, n	Rate per 100 patient-years	Events, n	Rate per 100 patient-years	Events, n	Rate per 100 patient-years	Events, n	Rate per 100 patient-years	Events, n	Rate per 100 patient- years	
Cardiovascular death, MI, or stroke	833	1.19	3672	1.63	4923	2.33	3107	3.20	1345	4.69	<0.001
All-cause death	365	0.51	3228	1.39	5785	2.65	4249	4.21	1868	6.22	<0.001
Cardiovascular death	143	0.20	1122	0.48	2018	0.93	1484	1.47	707	2.36	<0.001
Noncardiovascular death	222	0.31	2106	0.91	3767	1.73	2765	2.74	1161	3.87	<0.001
MI	605	0.86	2127	0.94	2454	1.15	1369	1.39	559	1.92	<0.001
Stroke	126	0.18	711	0.31	1031	0.48	720	0.72	294	0.99	<0.001
Ischemic	98	0.14	617	0.27	912	0.42	661	0.66	274	0.93	<0.001
Hemorrhagic	28	0.04	94	0.04	119	0.05	59	0.06	20	0.07	0.003
Heart failure hospitalization	72	0.10	621	0.27	1361	0.63	1111	1.12	560	1.92	<0.001
Major bleeding	129	0.18	654	0.28	900	0.42	539	0.54	232	0.78	<0.001

COMPASS indicates Cardiovascular Outcomes for People Using Anticoagulation Strategies; and MI, myocardial infarction.
Risk factors include age ≥65 years, polyvascular disease, diabetes, heart failure, chronic kidney disease (estimated glomerular filtration rate <60), current smoker, or ischemic stroke.

Table 4. Observed Event Rates and Projected Absolute Risk Reduction (or Increase for Hemorrhagic Stroke and Major Bleeding) in COMPASS-Eligible Patients at 5 Years in the CANHEART Registry

Outcome	COMPASS-eligible event rate, n (%)	COMPASS trial hazard ratio (95% CI)*	Estimated absolute risk reduction (or increase) (95% CI)	Number of events prevented (or increased) (95% CI)	Number needed to treat (or harm) (95% CI)
Cardiovascular death, MI, or stroke	13 880 (10.1%)	0.76 (0.66–0.86)	2.40% (2.36–2.43)	3306 (3259–3355)	42 (41–42)
All-cause death	15 495 (11.2%)	0.82 (0.71–0.96)	1.93% (1.90–1.96)	2662 (2626–2696)	52 (51–53)
Cardiovascular death	5474 (3.7%)	0.78 (0.64–0.96)	0.89% (0.87–0.92)	1232 (1203–1262)	112 (109–115)
Noncardiovascular death	10 021 (7.27%)	0.87 (0.70–1.08)	0.94% (0.92–0.95)	1291 (1267–1313)	107 (105–109)
MI	7114 (5.2%)	0.86 (0.70–1.05)	0.74% (0.73–0.76)	1023 (1002–1045)	135 (132–138)
Stroke	2882 (2.1%)	0.58 (0.44 0.76)	0.92% (0.89–0.96)	1270 (1228–1317)	109 (105–112)
Ischemic	2562 (1.9%)	0.51 (0.38–0.68)	0.96% (0.92–0.99)	1320 (1274–1370)	104 (101–108)
Hemorrhagic	320 (0.2%)	1.49 (0.67–3.31)	0.12% (0.11–0.13)	166 (148–183)	830 (753–931)
Major bleeding	2454 (1.8%)	1.70 (1.40–2.05)	1.30% (1.25–1.35)	1788 (1720–1860)	77 (74–80)

CANHEART indicates Cardiovascular Health in Ambulatory Care Research Team; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; and MI, myocardial infarction.
*Hazard ratios to estimate treatment effect were obtained from the COMPASS regimen of rivaroxaban 2.5 mg twice daily plus aspirin vs aspirin alone comparison.

method of identifying appropriate patients to treat with this strategy.

Our findings on eligibility add further insights to previous studies that assessed the representativeness of the COMPASS trial in other large population registries.[7–9] Potential estimates may vary on the basis of eligibility and underlying patient populations. Our hospitalization and laboratory data allowed us to capture information about major bleeding events, unlike the prior studies, which did not assess bleeding risk in the creation of an eligible cohort. We aimed to provide a balanced perspective on the relationship between increasing number of ischemic risk factors and MACEs and bleeding events, by assessing bleeding with an approach consistent with the modified International Society on Thrombosis and Hemostasis definition used in the COMPASS trial. Our results highlighting which subgroups would derive the most favorable benefit–risk ratio for very-low-dose rivaroxaban therapy were consistent with prior research.[20,21]

For better appreciation of the anticipated impact in Ontario with that presented in the original trial, we estimated the NNT and NNH within CANHEART each year through 5 years of follow-up. This allowed us to compare results to the original COMPASS trial, which was stopped early after 23 months of follow-up. After 2 years, the anticipated treatment effects in the real-world COMPASS-eligible population were smaller than that of the original trial. It is possible that differences exist for several reasons, including the selection of patients, distribution of risk factors, and varying background aspirin use. It is also possible that when a trial is stopped early, as was seen in the COMPASS trial, treatment results may be exaggerated.[22]

The COMPASS trial eligibility criteria excluded a significant number of secondary prevention patients because of comorbidities including risk of major bleeding. An unmet need exists to investigate beyond antithrombotic medications to target this high-risk patient population. Additionally, trials may consider expanding their inclusion criteria to include some patients with a higher risk, yet higher reward.

Limitations

Our findings should be interpreted in the context of some limitations. First, health administrative claims data have limits to the extent of information available for the diagnosis of CAD and PAD (eg, details of ankle-branchial index results). Nevertheless, our choice of coding relied on multiple prior chart abstraction validation studies and diagnostic algorithms to optimize specificity and sensitivity, and diagnoses were enhanced with clinical information derived from cardiac registries. Additionally, we did not differentiate between single- and multivessel CAD, percutaneous

coronary intervention, and coronary artery bypass grafting. While the original COMPASS trial required additional clinical risk factors for patients aged <65 years, [23] the current analysis included these patients, and our results for patients aged <65 years demonstrate that any misclassification of patients would bias our results toward the null. In addition, eligibility was assessed at 1 time point, leaving the possibility for individuals to become eligible/ineligible over the course of follow-up. Further, Health Canada has approved the COMPASS treatment regimen in patients with CAD or PAD without any specific qualifications [24]; thus, our study emphasized a reasonable definition of eligibility. Differences in the distribution of baseline characteristics between cohorts may potentially influence treatment estimates and outcomes. Thus, future studies should consider reweighting trial results according to the distribution of a cohort's baseline characteristics to provide a weighted treatment estimate among real-world studies.[25]

Our analysis of medication use was limited to individuals aged ≥65 years, which represent 66% of our total cohort. We had limited information on the use of aspirin, as this drug is typically purchased without a prescription. As such, we conducted a sensitivity analysis calculating effect estimates under various background rates of aspirin use.[19] The results of this analysis provide estimates of risk for relevant subsets of the population.

CONCLUSIONS

Approximately 2 of 5 patients in the CANHEART cohort with CAD/PAD appear to be eligible for very-low-dose rivaroxaban therapy. Among eligible patients, implementation of very-low-dose rivaroxaban therapy in routine clinical practice for atherothrombotic risk reduction in Ontario, Canada, could prevent a substantial number of atherothrombotic events though the risk of major bleeds would also increase. Over half of eligible individuals have multiple comorbidities and demonstrate an elevated risk of MACE yet only modest predisposition for bleeding and thus are expected to derive the highest benefit from very-low-dose rivaroxaban therapy. In contrast, patients aged ≥75 years may have a lower benefit-to-risk ratio in clinical practice.

ARTICLE INFORMATION

Received June 16, 2022; accepted October 25, 2022.

Affiliations

Women's College Research Institute, Toronto, Canada (M.S.S., H.A., J.A.U.); Dalla Lana School of Public Health (M.S.S.), Institute of Health Policy, Management, and Evaluation (D.Y.T., D.T.K., H.A., J.A.U.), and Department of Medicine, Faculty of Medicine (S.G.G., M.E.F., H.A., J.A.U.), University of Toronto, Toronto, Canada; ICES, Toronto, Canada (B.Y., A.C., J.P., D.Y.T., L.E.F., D.T.K., H.A., J.A.U.); Schulich Heart Centre, Sunnybrook Health Sciences Centre, Toronto, Canada (D.Y.T., D.T.K.); Applied Health Research Centre, Li Ka Shing Knowledge Institute, St Michael's Hospital, Toronto, Canada (S.G.G., M.E.F., J.A.U.); Peter Munk Cardiac Centre, University Health Network, Toronto, Canada (M.E.F., H.A., J.A.U.); and Cardiovascular Division, Department of Medicine, Women's College Hospital, Toronto, Canada (H.A., J.A.U.)..

Acknowledgments

The authors thank IQVIA Solutions Canada Inc. for use of their Drug Information File. Part of this material is based on data and information provided by Ontario Health (OH). The opinions, results, view, and conclusions reported in this paper are those of the author and do not necessarily reflect those of OH. No endorsement by OH is intended or should be inferred.

Sources of Funding

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-Term Care. The CANHEART initiative was funded by an operating grant from the Institute of Circulatory and Respiratory Health–Canadian Institutes of Health Research Chronic Diseases Team (grant no. TCA 118349), and is currently funded by a Canadian Institutes of Health Research foundation grant (FDN-143313) and Canadian Institutes of Health Research Strategy for Patient-Oriented Research Innovative Clinical Trial Multi-Year grant (MYG-151211). Parts of this material are based on data and information compiled and provided by the Ministry of Health, Canadian Institute for Health Information, Cancer Care Ontario, CorHealth Ontario, and Service Ontario. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. The authors acknowledge that the clinical registry data used in this publication is from participating hospitals through CorHealth Ontario, which serves as an advisory body to the Ministry of Health, is funded by the Ministry of Health, and is dedicated to improving the quality, efficiency, access, and equity in the delivery of the continuum of adult cardiac, vascular, and stroke services in Ontario, Canada.

Disclosures

M.S. Sheth has no disclosures to report. Dr Farkouh receives research grant support from Amgem, Novartis, and Novo Nordisk. Dr Goodman receives research grant support and speaker/consulting honoraria from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CSL Behring, Daiichi-Sankyo/American Regent, Eli Lilly, Esperion, Ferring Pharmaceuticals, GlaxoSmithKline, HLS Therapeutics, Janssen/Johnson & Johnson, Merck, Novartis, Novo Nordisk A/C, Pendopharm, Pfizer, Regeneron, Sanofi, and Servier; and salary support/honoraria from the Heart and Stroke Foundation of Ontario/University of Toronto (Polo) Chair, Canadian Heart Research Centre and MD Primer, Canadian VIGOR Centre, Duke Clinical Research Institute, New York University Clinical Coordinating Centre, and PERFUSE Research Institute. Dr Ko is supported by the Jack Tu Chair in Cardiovascular Outcomes Research, Sunnybrook Health Sciences Centre, and University of Toronto. Dr Udell is supported by a University of Toronto Department of Medicine Clinician Scientist Merit Award and an Ontario Ministry of Research Innovation and Science Early Researcher Award; received personal fees for consulting for or honoraria from Amgen, AstraZeneca, Boehringer-Ingelheim, Janssen, Merck, Novartis, and Sanofi; and reports grant support to his institutions from AstraZeneca, Novartis, and Sanofi. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S11
Figures S1–S3

REFERENCES

1. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, Hirsch AT. The impact of peripheral arterial disease on health-related quality of life in the peripheral arterial disease awareness, risk, and treatment: new resources for survival (PARTNERS) program. *Vasc Med.* 2008;13:15–24. doi: 10.1177/1358863X07084911
2. Aronow H, Hiatt WR. The burden of peripheral artery disease and the role of antiplatelet therapy. *Postgrad Med.* 2009;121:123–135. doi: 10.3810/pgm.2009.07.2038
3. Khoury H, Lavoie L, Welner S, Folkerts K. The burden of major adverse cardiac events and antiplatelet prevention in patients with coronary

or peripheral arterial disease. *Cardiovasc Ther.* 2016;34:115–124. doi: 10.1111/1755-5922.12169
4. Fitchett DH, Goodman SG, Leiter LA, Lin P, Welsh R, Stone J, Grégoire J, Mcfarlane P, Langer A. Secondary prevention beyond hospital discharge for acute coronary syndrome: evidence-based recommendations. *Can J Cardiol.* 2016;32:S15–S34. doi: 10.1016/j.cjca.2016.03.002
5. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P, Aboyans V, Alings M, Kakkar AK, Keltai K, et al. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet.* 2018;391:219–229. doi: 10.1016/S0140-6736(17)32409-1
6. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377:1319–1330. doi: 10.1056/NEJMoa1709118
7. Darmon A, Bhatt DL, Elbez Y, Aboyans V, Anand S, Bosch J, Branch KR, Connolly SJ, Dyal L, Eikelboom JW, et al. External applicability of the COMPASS trial: an analysis of the reduction of atherothrombosis for continued health (REACH) registry. *Eur Heart J.* 2018;39:750–757a. doi: 10.1093/eurheartj/ehx658
8. Würtz M, Olesen KKW, Thim T, Kristensen SD, Eikelboom JW, Maeng M. External applicability of the COMPASS trial: the Western Denmark heart registry. *Eur Heart J Cardiovasc Pharmacother.* 2019;5:192–199. doi: 10.1093/ehjcvp/pvz013
9. Mortensen MB, Blaha MJ, Nordestgaard BG. Eligibility and preventive potential for new evidence-based cardiovascular drugs in secondary prevention. *JAMA Cardiol.* 2020;5:209–215. doi: 10.1001/jamacardio.2019.4759
10. Tu JV, Chu A, Donovan LR, Ko DT, Booth GL, Tu K, Maclagan LC, Guo H, Austin PC, Hogg W, et al. The cardiovascular health in ambulatory care research team (CANHEART): using big data to measure and improve cardiovascular health and healthcare services. *Circ Cardiovasc Qual Outcomes.* 2015;8:204–212. doi: 10.1161/CIRCOUTCOMES.114.001416
11. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care.* 2002;25:512–516. doi: 10.2337/diacare.25.3.512
12. Tu K, Chen Z, Lipscombe LL, Taskforce CHEPOR. Prevalence and incidence of hypertension from 1995 to 2005: a population-based study. *CMAJ.* 2008;178:1429–1435. doi: 10.1503/cmaj.071283
13. Fan J, Arruda-Olson AM, Leibson CL, Smith C, Liu G, Bailey KR, Kullo IJ. Billing code algorithms to identify cases of peripheral artery disease from administrative data. *J Am Med Inform Assoc.* 2013;20:e349–e354. doi: 10.1136/amiajnl-2013-001827
14. Xu Y, Schulman S, Dowlatshahi D, Holbrook AM, Simpson CS, Shepherd LE, Wells PS, Giulivi A, Gomes T, Mamdani M, et al. Direct Oral anticoagulant- or warfarin-related major bleeding: characteristics, reversal strategies, and outcomes from a multicenter observational study. *Chest.* 2017;152:81–91. doi: 10.1016/j.chest.2017.02.009
15. Quinn RR, Laupacis A, Austin PC, Hux JE, Garg AX, Hemmelgarn BR, Oliver MJ. Using administrative datasets to study outcomes in dialysis patients: a validation study. *Med Care.* 2010;48:745–750. doi: 10.1097/MLR.0b013e3181e419fd
16. Atzema CL, Jackevicius CA, Chong A, Dorian P, Ivers NM, Parkash R, Austin PC. Prescribing of oral anticoagulants in the emergency department and subsequent long-term use by older adults with atrial fibrillation. *CMAJ.* 2019;191:E1345–E1354. doi: 10.1503/cmaj.190747
17. Lane DA, Lip GY. Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. *Circulation.* 2012;126:860–865. doi: 10.1161/CIRCULATIONAHA.111.060061
18. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation.* 2016;133:601–609. doi: 10.1161/CIRCULATIONAHA.115.017719
19. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71–86. doi: 10.1136/bmj.324.7329.71
20. Darmon A, Sorbets E, Ducrocq G, Elbez Y, Abtan J, Popovic B, Ohman EM, Röther J, Wilson PF, Montalescot G, et al. Association of multiple enrichment criteria with ischemic and bleeding risks among COMPASS-eligible patients. *J Am Coll Cardiol.* 2019;73:3281–3291. doi: 10.1016/j.jacc.2019.04.046
21. Anand SS, Eikelboom JW, Dyal L, Bosch J, Neumann C, Widimsky P, Avezum AA, Probstfield J, Cook Bruns N, Fox KAA, et al. Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial. *J Am Coll Cardiol.* 2019;73:3271–3280. doi: 10.1016/j.jacc.2019.02.079
22. Darmon A, Ducrocq G. Early stopping of a randomised trial for efficacy: a medical, ethical and regulatory challenge. *Heart.* 2021;107:1109–1110. doi: 10.1136/heartjnl-2021-318941
23. Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA. The COMPASS trial: net clinical benefit of low-dose rivaroxaban plus aspirin as compared with aspirin in patients with chronic vascular disease. *Circulation.* 2020;142:40–48. doi: 10.1161/CIRCULATIONAHA.120.046048
24. CADTH Canadian Drug Expert Committee Recommendation: Rivaroxaban (Xarelto — Bayer Inc.): indication: coronary artery disease with or without peripheral artery disease. In, 2018 [cited 2020 Sept 3]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK541456/
25. Dahabreh IJ, Robertson SE, Tchetgen EJ, Stuart EA, Hernán MA. Generalizing causal inferences from individuals in randomized trials to all trial-eligible individuals. *Biometrics.* 2019;75:685–694. doi: 10.1111/biom.13009

Supplemental Material

Table S1. **Coronary Artery Disease Inclusion Criteria Applied to CANHEART Registry.**

Criterion – any of the below:	Codes
1. Myocardial infarction (MI)	**ICD-9:** 410 **ICD-10**: I21, I22
2. Single or multi-vessel coronary artery disease (stenosis of ≥50% in 1 or more coronary artery, confirmed by invasive coronary angiography)	As recorded in the CorHealth database
3. Single/multi-vessel percutaneous coronary intervention (PCI)	**CCP:** 4802, 4803 **CCI:** 1IJ50, 1IJ57GQ, 1IJ54.
4. Single/multi-vessel coronary artery bypass graft (CABG)	**CCP** code 481 **CCI** code 1IJ76.

Data source for ICD-9, ICD-10, CCP and CCI codes are from the Canadian Institute for Health Information Discharge Abstract Database. ICD-9, International Classification of Diseases 9th Revision; ICD-10, International Classification of Diseases 10th Revision, CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP); CCI, Canadian Classification of Health Interventions.

Table S2. PAD Inclusion Criteria Applied to CANHEART Registry.

Criterion and codes – 1, 2, or 3 listed below	
1. **Related procedure** – **any of a, b, c, d, or e**	
a) Aorto-femoral bypass surgery	**CCI:** 1KE76MZXXK, 1JM76MIXXN, 1KE76MZXXN, 1KE76MZXXA, 1JM76MIXXA, 1KE80LAXXN, 1KE76MUXXA, 1KE76MZXXQ, 1KE80LA, 1KE76MUXXN, 1KE80LAXXA, 1KE50LABD, 1KE50LABP, 1KG76MIXXA, 1KG76MIXXN, 1KG76MIXXQ, 1KG76MZXXA, 1KG76MZXXN, 1KG80LAXXN, 1KG87LAXXN, 1KG80LAXXA, 1KG87LA, 1KG80LA, 1KG87LAXXA, 1KG87LAXXL, 1KY80LAXXN, 1KV80LAXXA **CCP:** 5125, 5126, 5128, 5129 **OHIP fee codes:** R802, R875, E627, R817, R877
b) Limb bypass surgery	See Aorto-femoral bypass surgery
c) Percutaneous transluminal angioplasty revascularization of iliac or infrainguinal arteries	**CCI:** 1KG50GQBD, 1KY50GPBD, 1KG50LAOA, 1KG80GQNRN, 1KG50GQOA, 1KG50GQBF, 1KG50GQBP, 1KE50GQOA, 1KT50GQBD, 1KE50GQBD, 1KT50GQOA, 1KE80GQNRN, 1KT50GQBP, 1KA50, 1KE50, 1KG50, 1KQ50, 1KR50, 1KT50, 1KT76, 1KG80, 1KG87 **CCP:** 5149, 5156, 5157, 5158, 5159 **OHIP fee codes:** J025, J058, R878, R879
d) Carotid revascularization (endarterectomy or stenting)	**CCI:** 1JE57L, 1JE50 **CCP:** 5012 **OHIP fee codes:** N220, R792
e) Limb/foot amputation for arterial vascular disease	Arterial vascular disease codes: **ICD-9:** 440.2, 440.8,440.9, 443.9,444.0 **ICD-10: I**70.2, I70.8, I70.9, I73.8, I73.9, I73.0, I74.3, I713, I714, I715, I716, I718, I719
	Amputation codes: **CCI:** 1TK93LA, 1VC93LA, 1VG93LA, 1VQ93LA, 1WA93LA, 1WE93LA, 1WI93LA, 1WJ93LA, 1WK93LA,1WL93LA, 1WM93LA, 1WN93LA **CCP:** 9606,9611, 9612, 9613, 9614, 9615
2. **Diabetic angiopathy**	
ICD-10: E1150, E1151	
3. **Atherosclerosis -** any combination of 2 codes (1 dx AND 1 procedural, OR 2 dx, OR 2 procedural)[1]	

ICD-9: 440.2, 443.9, 440.9
ICD-10:: I70.2, I73.9, I70.9, I71.2
CCP: 5088, 0276, 0287, 96.11
CCI: 1WK93 with the following **ICD10 diagnosis codes on the same record excluded**: C40, D16, D48.0, D48.1, D48.2, Q65-Q79, S70-S99, T20, T32, 3KG10, 3KG40, 3KG20, 3KG30

Data source for ICD-9, ICD-10, CCP and CCI codes are from the Canadian Institute for Health Information Discharge Abstract Database. CANHEART, Cardiovascular Health in Ambulatory Care Research Team; DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD-9, International Classification of Diseases 9th Revision; ICD-10, International Classification of Diseases 10th Revision, CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CCI, Canadian Classification of Health Interventions; OHIP, Ontario Health Insurance Plan.

Table S3. Exclusion Criteria Applied to CANHEART Registry.

Criterion and codes – any of 1-10 listed below	
1. Risk of Major Bleeding: Any of a, b or c	
a. HAS-BLED score ≥3	Equal to sum of the 8 conditions below (each=1 point) in the 5 years prior to January 1, 2011 unless otherwise specified.
	1. Hypertension: prior to Jan 1, 2011
	2. Hospitalization, emergency department or physician visit for renal disease[2] **ICD-10**: E102, E112, E132, E142, I12, I13, N08, N18, N19 **OHIP diagnostic code:** 403, 585
	3. Hospitalization, emergency department or physician visit for liver disease[2] **ICD-10:** B15, B16, B17, B18, B19, I982, K70, K71, K72, K73, K74, K75, K76, K77, Z944 **OHIP diagnostic code:** 571, 070, 964, 573
	4. Hospitalization for stroke **ICD-10:** I60, I61, I63, I64, H341 (excluding I63.6)
	5. Age >65 on Jan 1, 2011
	6. Major bleeding: See Supplemental Table S4
	7. Hospitalization or emergency department visit for alcohol use[2] **ICD-10:** F10, K70, E52, T51, K860, E244, G312, I426, O354, Z714, Z721, G621, G721, K292
	8. Prescription for medication predisposing to bleeding in the 100 days prior to Jan 1, 2011 – includes anti-platelets, anti-coagulants (for individuals with atrial fibrillation) and non-steroidal anti-inflammatory medication
b. Any history of hemophilia or other hemorrhagic disorder	**ICD-9:** 2860, 2861, 2862, 2863, 2864, 2865, 2866, 2867, 2869, 2870, 2871, 2872, 2873, 2874, 2875, 2878, 2879 **ICD-10:** D680, D681, D682, D683, D684, D685, D686, D688, D6880, D6881, D6888, D689, D690, D691, D692, D6930, D6938, D694, D695, D696, D698, D699 **OHIP diagnostic code:** 286, 287
c. Cardiac tamponade	In the prior 5 years: **ICD-10:** I230, I233, I312
2. Hemothorax	
In the prior 5 years: **ICD-10:** J942	
3. GI bleed with transfusion	
In the prior 5 years: **ICD-10:** See upper/lower GI bleed codes in Supplemental Table S4 **CCI:** 1LZ19 except 1LZ19HHU2A, 1LZ19HHU6A, 1LZ19HHU7A, 1LZ19HHU8A, 1LZ19HHU9A	
4. Hemorrhagic stroke	
Any history:	

ICD-9: 430, 431 **ICD-10**: I60, I61
5. Severe heart failure (NYHA class 3 or 4)
History of hospitalization for heart failure and NYHA class 3 or 4 symptoms If no NYHA class available, then classified as indeterminate
6. **Advanced chronic kidney disease**[3]
Most recent eGFR before Jan 1, 2011 <30 OR on chronic dialysis If no eGFR measurement available, then classified as indeterminate
7. Use of dual antiplatelet therapy, anticoagulation, or other antithrombotic medications
Prescription in the prior 100 days
8. Cancer diagnosis (proxy for known non-cardiovascular disease that is associated with poor prognosis)
In the prior 5 years
9. Systemic treatment with strong inhibitors of CYP 3A4 and p-glycoprotein or inducers of CYP 3A4
Prescription in the prior 100 days
10. Any known hepatic disease associated with coagulopathy
Any history: **ICD-10:** B15, B16, B17, B18, B19, I982, K70, K71, K72, K73, K74, K75, K76, K77, Z944 **OHIP diagnostic code:** 571, 070, 964, 573.

Data source for ICD-9, ICD-10, CCP and CCI codes are from the Canadian Institute for Health Information Discharge Abstract Database. Data source for OHIP codes are the OHIP Physicians Claims database. CANHEART, Cardiovascular Health in Ambulatory Care Research Team; ICD-9, International Classification of Diseases 9th Revision; ICD-10, International Classification of Diseases 10th Revision, CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP); CCI, Canadian Classification of Health Interventions; NYHA OHIP, Ontario Health Insurance Plan.

Table S4. Primary and Secondary Outcome Codes Applied to the CANHEART Registry.

Criterion	Source	Codes
Primary Outcome		
CV death, MI or stroke		Time to first occurrence. See definitions below
Secondary Outcomes		
MI hospitalization	CIHI DAD	**ICD-10**: I21, I22
All cause death	RPDB and ORGD	Death flag (RPDB) or death record (ORGD)
CV death	ORGD	**ICD-10**: I00-I99
Non-CV death	ORGD	**ICD-10:** not I00-I99 (includes missing)
Ischemic stroke hospitalization	CIHI DAD	**ICD-10:** I63, I64, H34.1 (excluding I63.6)
Hemorrhagic stroke hospitalization	CIHI DAD	**ICD-10**: I60, I61
Heart failure hospitalization	CIHI DAD	**ICD-10**: I50
Major bleeding	CIHI DAD	See Supplemental Table S5

Abbreviations: CANHEART, Cardiovascular Health in Ambulatory Care Research Team; CIHI DAD, Canadian Institute for Health Information Discharge Abstract Database; CV, cardiovascular; ICD-10, International Classification of Diseases 10th Revision; MI, myocardial infarction; ORGD, Office of the Registrar General of Ontario Database; RPDB, Registered Persons Database.

Table S5. Major Bleeding Outcome Codes.

Area of Bleed	ICD-10-CA Code	Description
Intracranial	I60	Subarachnoid haemorrhage
	I61	Intracerebral haemorrhage
	I620	Subdural haemorrhage (acute) (nontraumatic)
	I621	Nontraumatic extradural haemorrhage
	I629	Intracranial haemorrhage (nontraumatic), unspecified
	S064	Epidural haemorrhage
	S065	Traumatic subdural haemorrhage
	S066	Traumatic subarachnoid haemorrhage
Upper GI	K920	Haematemesis
	K921	Melaena
	I850	Oesophageal varices with bleeding
	I9820	Oesophageal varices in diseases classified elsewhere with bleeding
	I983	Oesophageal varices with bleeding in diseases classified elsewhere
	K2210	Ulcer of oesophagus, acute with haemorrhage
	K2212	Ulcer of oesophagus, acute with haemorrhage and perforation
	K2214	Ulcer of oesophagus, chronic or unspecified with haemorrhage
	K2216	Ulcer of oesophagus, chronic or unspecified with both haemorrhage or perforation
	K250	Gastric ulcer, acute with haemorrhage
	K252	Gastric ulcer, acute with both haemorrhage and perforation
	K256	Gastric ulcer, chronic or unspecified with both haemorrhage and perforation
	K260	Duodenal ulcer, acute with haemorrhage
	K262	Duodenal ulcer, acute with both haemorrhage and perforation
	K270	Peptic ulcer, acute with haemorrhage
	K272	Peptic ulcer, acute with both haemorrhage and perforation
	K276	Peptic ulcer, chronic or unspecified with both haemorrhage and perforation
	K280	Gastro-jejunal ulcer, acute with haemorrhage
	K282	Gastro-jejunal ulcer, acute with both haemorrhage and perforation
	K284	Gastro-jejunal ulcer, chronic or unspecified with haemorrhage

	K290	Acute haemorrhagic gastritis
	K6380	Angiodysplasia of small intestine, except duodenum with bleeding
	K3180	Angiodysplasia of stomach and duodenum with bleeding
Lower GI	K5520	Angiodysplasia of colon with bleeding
	K625	Haemorrhage of anus and rectum
	K922	Gastrointestinal haemorrhage, unspecified
Other	N020	Recurrent and persistent haematuria, minor glomerular abnormality
	N021	Recurrent and persistent haematuria, focal and segmental glomerular lesions
	N022	Recurrent and persistent haematuria, diffuse membranous glomerulonephritis
	N023	Recurrent and persistent haematuria, diffuse mesangial proliferative glomerulonephritis
	N024	Recurrent and persistent haematuria, diffuse endocapillary proliferative glomerulonephritis
	N025	Recurrent and persistent haematuria, diffuse mesangiocapillary glomerulonephritis
	N026	Recurrent and persistent haematuria, dense deposit disease
	N027	Recurrent and persistent haematuria, diffuse crescentic glomerulonephritis
	N028	Recurrent and persistent haematuria, other
	N029	Recurrent and persistent haematuria, unspecified
	K661	Hemoperitoneum
	N938	Other specified abnormal uterine and vaginal bleeding
	N939	Abnormal uterine and vaginal bleeding, unspecified
	N950	Postmenopausal bleeding
	R041	Haemorrhage from throat
	R042	Hemoptysis
	R048	Haemorrhage from other sites in respiratory passages
	R049	Haemorrhage from respiratory passages, unspecified
	R58	Haemorrhage, not elsewhere classified
	H356	Retinal haemorrhage
	H431	Vitreous haemorrhage

	H450	Vitreous haemorrhage in diseases classified elsewhere
	M250	Hemarthrosis
Anticoagulant-specific	D683	Haemorrhagic disorder due to circulating anticoagulants
	D684	Acquired coagulation factor deficiency
	D688	Other specified coagulation defects
	D689	Coagulation defect, unspecified
	T455	Poisoning by anticoagulants
	T44	Poisoning by anticholinesterase agents, drugs affecting the autonomic nervous system
	Y442	Anticoagulants causing adverse effect in therapeutic use
	Y443	Anticoagulant antagonists, vitamin K and other coagulants causing adverse effect in therapeutic use

ICD-10, International Classification of Diseases 10th Revision.

Table S6. Outcomes of COMPASS Eligible, Indeterminate and Ineligible Patients in CANHEART, by Age.

	COMPASS Eligible Event Rate in 100 patient-years	COMPASS Indeterminate Event Rate in 100 patient-years	COMPASS Ineligible Event Rate in 100 patient-years
Age <65			
CV death, MI or stroke	1.67	2.27	3.31
Major bleeding	0.23	0.25	0.77
Age 65-74			
CV death, MI or stroke	1.82	2.70	3.63
Major bleeding	0.34	0.39	0.92
Age ≥75			
CV death, MI or stroke	3.89	4.94	6.95
Major bleeding	0.76	0.74	1.59

CV, cardiovascular; MI, myocardial infarction.

Table S7. Observed Event Rates and Projected Absolute Risk Reduction (or Increase) in COMPASS Eligible Patients over 5 years in the CANHEART Registry.

Outcome/Year	Event Rate per 100 patient-years	Absolute Risk Reduction (or Increase) (95% CI)	Number Needed to Treat (or Harm) (95% CI)
CV death, MI, stroke			
Year 1	1.93	0.46% (0.44-0.48)	217 (210-225)
Year 2	3.96	0.94% (0.92-0.96)	107 (104-109)
Year 3	6.02	1.41% (1.38-1.44)	71 (69-72)
Year 4	8.20	1.91% (1.88-1.94)	52 (52-53)
Year 5	10.42	2.4% (2.36-2.43)	42 (41-42)
All cause death			
Year 1	1.55	0.28% (0.27-0.29)	362 (347-377)
Year 2	3.57	0.63% (0.62-0.65)	158 (154-162)
Year 3	5.85	1.03% (1.01-1.05)	97 (95-99)
Year 4	8.51	1.48% (1.45-1.50)	68 (67-69)
Year 5	11.27	1.93% (1.90-1.96)	52 (51-53)
CV death			
Year 1	0.62	0.14% (0.13-0.14)	740 (691-794)
Year 2	1.36	0.30% (0.29-0.31)	335 (321-350)
Year 3	2.16	0.47% (0.45-0.49)	213 (206-220)
Year 4	3.14	0.68% (0.66-0.70)	147 (142-151)
Year 5	4.13	0.89% (0.87-0.92)	112 (109-115)
Non-CV death			
Year 1	0.94	0.12% (0.11-0.13)	825 (783-871)
Year 2	2.24	0.29% (0.28-0.30)	347 (334-359)
Year 3	3.78	0.48% (0.47-0.50)	207 (202-213)
Year 4	5.54	0.70% (0.69-0.72)	142 (139-145)
Year 5	7.45	0.94% (0.92-0.95)	107 (105-109)
MI			
Year 1	1.06	0.15% (0.14-0.16)	678 (645-713)
Year 2	2.13	0.30% (0.29-0.31)	338 (326-350)
Year 3	3.24	0.45% (0.44-0.46)	223 (217-230)
Year 4	4.33	0.60% (0.58-0.61)	168 (164-172)
Year 5	5.43	0.74% (0.73-0.76)	135 (132-138)
Stroke			
Year 1	0.40	0.17% (0.15-0.18)	602 (558-659)
Year 2	0.81	0.34% (0.32-0.36_	293 (277-311)
Year 3	1.23	0.52% (0.49-0.54)	193 (185-203)
Year 4	1.70	0.71% (0.68-0.74)	141 (135-146)
Year 5	2.21	0.92% (0.89-0.96)	109 (105-112)
Ischemic stroke			
Year 1	0.36	0.18% (0.16-0.19)	561 (517-615)

Year 2	0.74	0.36% (0.34-0.38)	278 (261-296)
Year 3	1.10	0.54% (0.51-0.57)	186 (177-195)
Year 4	1.51	0.74% (0.71-0.77)	136 (130-142)
Year 5	1.96	0.96% (0.92-0.99)	104 (101-108)
Hemorrhagic stroke			
Year 1	0.03	0.02% (0.01-0.02)	6349 (4985-8892)
Year 2	0.08	0.04% (0.03-0.05)	2604 (2207-3193)
Year 3	0.13	0.07% (0.06-0.08)	1523 (1330-1780)
Year 4	0.19	0.10% (0.08-0.11)	1051 (941-1206)
Year 5	0.25	0.12% (0.11-0.13)	830 (753-931)
Major bleeding			
Year 1	0.30	0.21% (0.19-0.23)	473 (428-521)
Year 2	0.64	0.45% (0.42-0.48)	223 (209-238)
Year 3	1.04	0.72% (0.69-0.76)	138 (131-146)
Year 4	1.45	1.00% (0.96-1.05)	100 (95-104)
Year 5	1.88	1.30% (1.25-1.35)	77 (74-80)

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

Table S8. Observed Event Rates and Projected Absolute Risk Reduction (or Increase for Major Bleeding) in COMPASS Eligible Patients Stratified by Number of Risk Factors at 5 years in the CANHEART Registry.

Outcome	Number of Risk Factors	Event Rate, n (%)	Absolute Risk Reduction (or Increase) (95% CI)	Number of Events Prevented (or Increased) (95% CI)	Number Needed to Treat (or Harm) (95% CI)
CV Death, MI, or Stroke	0	833 (5.7%)	1.35% (1.27-1.44)	197 (185-210)	74 (69-79)
	1	3672 (7.6%)	1.82% (1.77-1.88)	873 (846-901)	55 (53-57)
	2	4923 (10.6%)	2.535 (2.47-2.60)	1174 (1148-1206)	39 (38-40)
	3	3107 (14.0%)	3.36% (3.26-3.46)	744 (723-767)	30 (29-31)
	4+	1345 (19.6%)	4.64% (4.44-4.84)	319 (304-332)	22 (21-23)
	Combined 2+	9375 (12.5%)	2.97 (2.92-3.02)	2237 (2199-2275)	34 (33-34)
Major Bleeding	0	129 (0.9%)	0.62% (0.52-0.74)	91 (78-108)	161 (136-193)
	1	654 (1.4%)	0.98% (0.91-1.05)	469 (436-503)	102 (95-110)
	2	900 (1.9%)	1.42% (1.33-1.52)	658 (619-700)	70 (66-75)
	3	539 (2.4%)	1.83% (1.69-1.99)	406 (373-440)	55 (50-59)
	4+	232 (3.4%)	2.61% (2.30-2.94)	180 (159-202)	38 (34-43)
	Combined 2+	1671 (2.2%)	1.64% (1.57-1.72)	1238 (1185-1297)	61 (58-64)

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.
*Risk factors include age ≥65 years, polyvascular disease, diabetes mellitus, heart failure, chronic kidney disease (estimated glomerular filtration rate <60), current smoker, or ischemic stroke.

Table S9. Projected Absolute Risk Reduction (or Increase and Major Bleeding) in COMPASS Eligible Patients, by Age.

Outcome	COMPASS Trial Age-Specific Hazard Ratio (95% CI)	Estimated Absolute Risk Reduction (or Increase) (95% CI)	Number of Events Prevented (or Increased) (95% CI)	Number Needed to Treat (or Harm) (95% CI)
Age <65				
CV death, MI, stroke	0.63 (0.48-0.84)	2.89% (2.82-2.96)	2000 (1952-2050)	35 (34-35)
Major bleeding	1.18 (0.70-1.97)	0.21% (0.20-0.23)	145 (135-156)	478 (444-511)
Age 65-74				
CV death, MI, stroke	0.74 (0.61-0.90)	2.20% (2.12-2.27)	794 (768-822)	46 (44-47)
Major bleeding	1.63 (1.26-2.10)	1.06% (0.98-1.15)	383 (355-415)	94 (87-102)
Age ≥75				
CV death, MI, stroke	0.89 (0.69-1.14)	1.80% (1.76-1.84)	585 (527-598)	56 (54-57)
Major bleeding	2.12 (1.50-3.00)	4.08% (3.86-4.30)	1328 (1254-1400)	24 (23-26)

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

Table S10. Projected Effect Estimates in the COMPASS Trial Aspirin Only Arm Compared with COMPASS Eligible Patients at 2 years.

	COMPASS Participants Treated with Aspirin Alone				COMPASS Eligible Cohort
Outcome	**Event Rate, n (%)**	**COMPASS Trial Hazard Ratio (95% CI)***	**Estimated Absolute Risk Reduction (or Increase)**	**Number Needed to Treat (or Harm)**	**Number Needed to Treat (or Harm)**
CV death, MI or stroke	496 (5.4%)	0.76 (0.66-0.86)	1.30%	**77**	**107**
All cause death	378 (4.1%)	0.82 (0.71-0.96)	0.74%	**136**	**158**
CV death	203 (2.2%)	0.78 (0.64-0.96)	0.48%	**207**	**335**
Non-CV death	175 (1.9%)	0.87 (0.70-1.08)	0.25%	**405**	**347**
MI	205 (2.2%)	0.86 (0.70-1.05)	0.31%	**325**	**338**
Stroke	142 (1.6%)	0.58 (0.44 0.76)	0.67%	**149**	**293**
Ischemic	132 (1.4%)	0.51 (0.38-0.68)	0.69%	**146**	**278**
Hemorrhagic	10 (0.1%)	1.49 (0.67-3.31)	0.05%	**2041**	**2604**
Major bleeding	170 (1.9%)	1.70 (1.40-2.05)	1.33%	**75**	**223**

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

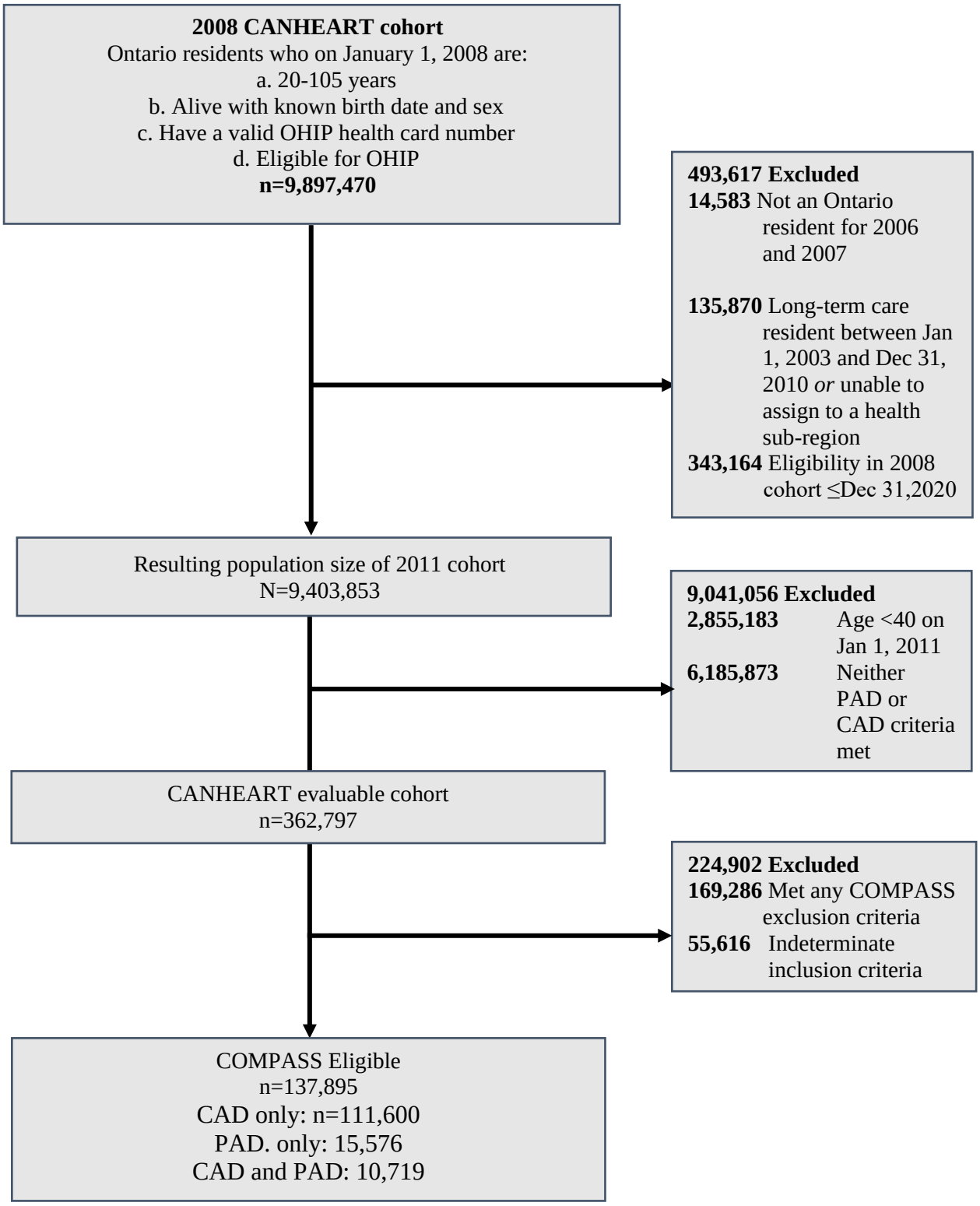
Table S11. Projected Effect Estimates in COMPASS Eligible Patients Accounting for Various Rates of Background Aspirin Use in the CANHEART Registry.

Outcome	COMPASS Eligible Event Rate, n (%)	Assumed Proportion of Aspirin Use	COMPASS Trial Hazard Ratio (95% CI) *	COMPASS Eligible Event Rate if Treated with Rivaroxaban *plus New Use of Aspirin* in 1-x% of the Population	Estimated Absolute Risk Reduction (or Increase)	Number Needed to Treat (or Harm)
CV death, MI or stroke	13,800 (10.1%)	1.00	0.76 (0.66-0.86)	7.68	2.42	41
		0.80	0.75 (0.65-0.85)	7.52	2.58	39
		0.60	0.73 (0.63-0.83)	7.36	2.74	37
		0.40	0.71 (0.61-0.81)	7.21	2.89	35
		0.20	0.70 (0.60-0.80)	7.05	3.05	33
		0.00	0.68 (0.58-0.78)	6.90	3.20	31
Major bleeding	2454 (1.8%)	1.00	1.70 (1.40-2.05)	3.06	1.26	79
		0.80	1.88 (1.58-2.23	3.38	1.58	63
		0.60	2.06 (1.76-2.41)	3.70	1.90	53
		0.40	2.23 (1.93-2.58)	4.02	2.22	45
		0.20	2.41 (2.11-2.76)	4.34	2.54	39
		0.00	2.59 (2.29-2.94)	4.66	2.86	35

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction

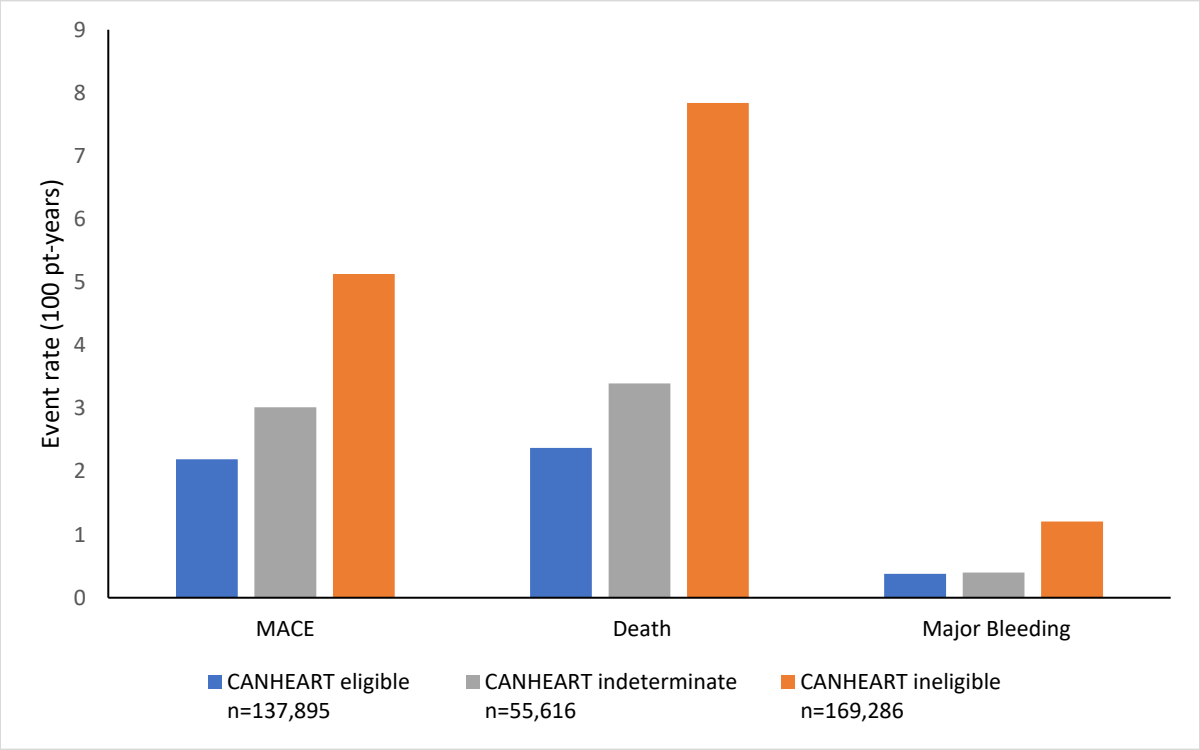
*Antiplatelet therapy effects on CV death, MI, or stroke: OR= 0.78, effects on major bleeding: OR=1.60[5]

Figure S1. CANHEART cohort creation and applying COMPASS inclusion/exclusion criteria.



Starting with the 2011 CANHEART cohort, the COMPASS trial inclusion/exclusion criteria were applied to those over 40 years old. A COMPASS eligible group was defined as patients potentially eligible for low-dose rivaroxaban therapy. CAD, coronary artery disease, OHIP, Ontario Health Insurance Plan, PAD, peripheral artery disease.

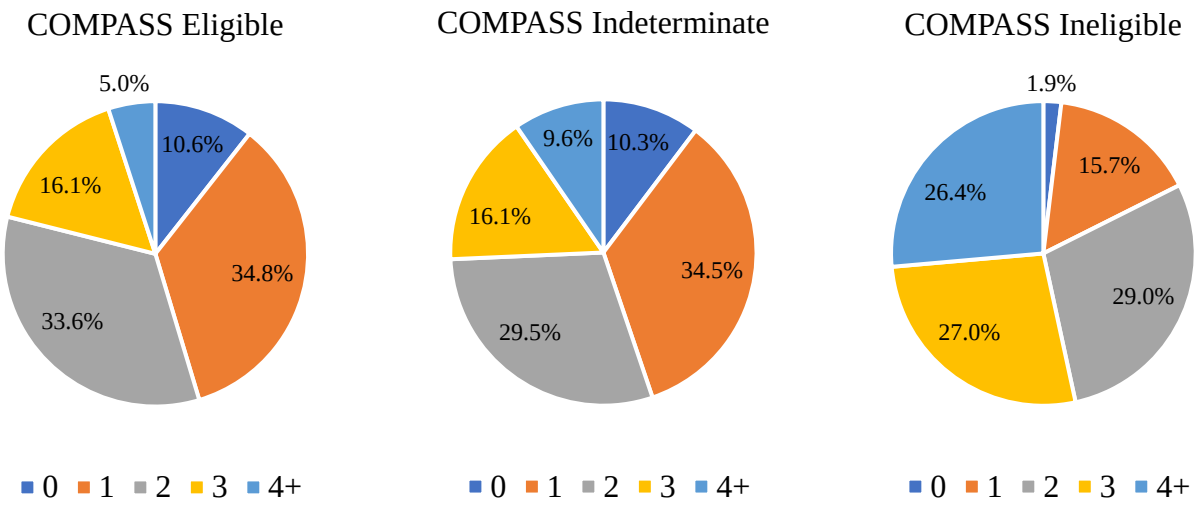
Figure S2. Event rates in 100 person-years for COMPASS eligible, indeterminate, and ineligible patients within the CANHEART registry.



All P-trends <0.001.

COMPASS eligible patients met the CAD/PAD inclusion criteria and did not meet any exclusion criteria. COMPASS indeterminate patients had insufficient data to make a determination of COMPASS eligibility. COMPASS ineligible patients met at least 1 exclusion criterion. MACE includes MI, stroke, CV death. MACE, major adverse cardiovascular events.

Figure S3. COMPASS eligible, indeterminate, and ineligible populations stratified by number of risk factors in the CANHEART registry.



Risk factors include age ≥65 years, poly-vascular disease, diabetes mellitus, heart failure, chronic kidney disease (estimated glomerular filtration rate <60), current smoker, or ischemic stroke. Poly-vascular disease defined as CAD and PAD. Patients were categorized by presence of 0, 1, 2, 3 or 4+ risk factors.