Circulation

ORIGINAL RESEARCH ARTICLE

Bleeding and New Cancer Diagnosis in Patients With Atherosclerosis

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BACKGROUND: Patients treated with antithrombotic drugs are at risk of bleeding. Bleeding may be the first manifestation of underlying cancer.

METHODS: We examined new cancers diagnosed in relation to gastrointestinal or genitourinary bleeding among patients enrolled in the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) and determined the hazard of new cancer diagnosis after bleeding at these sites.

RESULTS: Of 27 395 patients enrolled (mean age, 68 years; women, 21%), 2678 (9.8%) experienced any (major or minor) bleeding, 713 (2.6%) experienced major bleeding, and 1084 (4.0%) were diagnosed with cancer during a mean follow-up of 23 months. Among 2678 who experienced bleeding, 257 (9.9%) were subsequently diagnosed with cancer. Gastrointestinal bleeding was associated with a 20-fold higher hazard of new gastrointestinal cancer diagnosis (7.4% versus 0.5%; hazard ratio [HR], 20.6 [95% CI, 15.2–27.8]) and 1.7-fold higher hazard of new nongastrointestinal cancer diagnosis (3.8% versus 3.1%; HR, 1.70 [95% CI, 1.20–2.40]). Genitourinary bleeding was associated with a 32-fold higher hazard of new genitourinary cancer diagnosis (15.8% versus 0.8%; HR, 32.5 [95% CI, 24.7–42.9]), and urinary bleeding was associated with a 98-fold higher hazard of new urinary cancer diagnosis (14.2% versus 0.2%; HR, 98.5; 95% CI, 68.0–142.7). Nongastrointestinal, nongenitourinary bleeding was associated with a 3-fold higher hazard of nongastrointestinal, nongenitourinary cancers (4.4% versus 1.9%; HR, 3.02 [95% CI, 2.32–3.91]).

CONCLUSIONS: In patients with atherosclerosis treated with antithrombotic drugs, any gastrointestinal or genitourinary bleeding was associated with higher rates of new cancer diagnosis. Any gastrointestinal or genitourinary bleeding should prompt investigation for cancers at these sites.

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Clinical Perspective

What Is New?

- Cancer was diagnosed in 1084 of 27 395 patients (4%) with coronary or peripheral artery disease during a mean of 23 months of follow-up in the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies).
- Among patients who experienced bleeding during the trial, 1 in 11 was subsequently diagnosed with cancer, and 23.8% of all new cancer diagnoses were in patients with prior bleeding.
- Sites of bleeding most commonly associated with new cancer diagnosis were gastrointestinal, associated with a 20-fold higher hazard for gastrointestinal cancer diagnosis, and genitourinary, associated with a 32-fold higher hazard for genitourinary cancer diagnosis.

What Are the Clinical Implications?

- Gastrointestinal or genitourinary bleeding in patients with atherosclerosis treated with antithrombotic therapy should prompt careful investigation for possible underlying cancer in the respective organ systems, even if the bleeding is minor.

Patients treated with antithrombotic drugs are at higher risk of bleeding. Bleeding may be the first manifestation of underlying cancer in the general community[1,2] and in patients with cardiovascular disease treated with antithrombotic drugs.[3–7] The gastrointestinal and genitourinary tracts are common sites of bleeding in patients treated with antithrombotic drugs, but the association between bleeding at these sites and new cancer diagnosis is uncertain.

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) demonstrated that in patients with chronic coronary artery disease or peripheral artery disease, the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily compared with aspirin 100 mg once daily reduced major adverse cardiovascular events and mortality, whereas rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily did not produce a benefit.[8–10] Both rivaroxaban regimens were associated with higher risks of gastrointestinal and genitourinary bleeding compared with aspirin.

Here, we explore the association between bleeding and new diagnosis of cancer in the COMPASS trial. We examine the number and proportion of new cancers diagnosed in patients with bleeding and determine the hazard of new cancer diagnosis in patients who experience bleeding.

METHODS

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

The primary objective of COMPASS was to determine whether rivaroxaban 2.5 mg twice daily in combination with aspirin 100 mg once daily or rivaroxaban 5 mg twice daily compared with aspirin 100 mg once daily reduced the risk of the primary outcome, a composite of cardiovascular death, stroke, or myocardial infarction among patients with chronic coronary artery disease or peripheral artery disease.[11] We randomized 27 395 patients from 602 sites in 33 countries. On the recommendation of the Data Safety Monitoring Board, the Steering Committee and sponsor stopped the rivaroxaban versus aspirin arms of the trial after a mean of 23 months of follow-up because of clear evidence of superiority of the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily compared with aspirin 100 mg once daily.

We defined major bleeding using a modification of the International Society on Thrombosis and Haemostasis definition,[12] which included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization (including presentation to an acute care facility without an overnight stay). Any bleeding that did not meet the definition for major bleeding was classified as minor.

For the purpose of these analyses, we defined gastrointestinal bleeding as hematemesis, melena, or hematochezia and genitourinary bleeding as hematuria or vaginal bleeding. We defined gastrointestinal cancer as cancer involving the esophagus, stomach, duodenum, jejunum, ileum, colon, or rectum; and we defined genitourinary cancers as cancer involving the prostate, spermatic cord, uterus, cervix, vagina, kidney, ureter, bladder, or urethra. We defined cancers of the kidney, ureter, bladder, or urethra as urinary cancers. All cancers that did not meet these definitions were defined as nongastrointestinal, nongenitourinary cancers.

Patients with preexisting cancer were eligible for inclusion in COMPASS unless they were deemed to have a poor prognosis. In those with a history of cancer, we recorded the year of diagnosis and site of cancer. At each follow-up, we recorded new cancer diagnosis, including date of diagnosis and site, and whether the cancer was diagnosed for the first time or whether it was a new recurrence (previously diagnosed cancer thought to be eradicated but with a local, regional, or metastatic recurrence). Cancer outcomes were not adjudicated.

We examined the frequency of new cancer diagnosis (ie, first or new recurrence) in patients with bleeding, new gastrointestinal cancer diagnosis in patients with gastrointestinal bleeding, and new genitourinary cancer diagnosis in patients with genitourinary bleeding and compared these with the frequencies of the same cancers diagnosed in patients without bleeding. Among patients with genitourinary bleeding, we further examined new urinary cancer diagnosis in patients with urinary bleeding.

Statistical Analyses

We examined the number and proportion of new cancers diagnosed with and without prior bleeding and with or

without prior gastrointestinal or genitourinary bleeding. We examined the association between bleeding and new cancer diagnosis using stratified Cox proportional hazards models with the bleeding event modeled as a time-dependent covariate. We did not include any covariates in the Cox models, and we checked the proportional hazards assumption using plots of the log of the negative log of the survival function against the log of time. We explored potential interaction between antithrombotic treatment and the time-dependent covariate index bleeding event. Cumulative hazards were estimated as minus log of the Kaplan-Meier survival function and plotted against time since the index event. We considered a 2-sided value of $P<0.05$ to be statistically significant and did not adjust for multiple testing. Analyses were performed with SAS software for Linux, version 9.4 (SAS Institute Inc, Cary, NC).

The COMPASS trial was approved by all relevant institutional review committees, and all patients provided written informed consent.

RESULTS

There was no significant effect of randomized treatment on the frequency of new cancer diagnosis (rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily versus aspirin 100 mg once daily: 366 of 9152 [4.0%] versus 352 of 9126 [3.9%]; hazard ratio [HR] 1.03 [95% CI, 0.89–1.20]; $P=0.66$; rivaroxaban 5 mg twice daily versus aspirin 100 mg once daily: 366 of 9117 [4.0%] versus 352 of 9126 [3.9%]; HR, 1.04 [95% CI, 0.90–1.21]; $P=0.57$) or on cancer-related mortality (rivaroxaban 2.5 mg twice daily plus aspirin 100 mg twice daily versus aspirin 100 mg once daily: 70 of 9152 [0.8%] versus 85 of 9126 [0.9%]; HR, 0.82 [95% CI, 0.60–1.12]; $P=0.21$; rivaroxaban 5mg twice-daily versus aspirin 100 mg once daily: 87 of 9152 [1.0%] versus 85 of 9126 [0.9%]; HR, 1.03 [95% CI, 0.76–1.38]; $P=0.87$).

Table I in the online-only Data Supplement presents baseline characteristics of patients who experienced bleeding compared with those who did not experience bleeding. Compared with those who did not experience bleeding, patients with bleeding were older, had a lower body mass index, were more likely to be former or current smokers, were less likely to have heart failure, were more likely to have a history of cancer, and were more likely to be Asian. Of the 1084 new (first-ever or recurrent) cancers diagnosed during the trial, 910 occurred in 25673 patients without a prior history of cancer (3.5%), and 174 occurred in 1722 patients with a history of cancer (10.1%).

Table 1 presents the numbers of patients with bleeding and with a new cancer diagnosis and the proportion of new cancer diagnoses in patients with bleeding from any site, gastrointestinal bleeding, genitourinary bleeding, and urinary bleeding and in those with bleeding from sites other than the gastrointestinal and genitourinary tracts. Among patients with a new diagnosis of cancer, 257 of 1084 (23.7%) were diagnosed in patients with prior bleeding and 79 of 1084 (7.3%) in patients with prior major bleeding. A total of 503 patients were diagnosed with gastrointestinal or genitourinary cancer (6 patients had both). Among patients with a new diagnosis of gastrointestinal cancer, 67 of 212 (31.5%) were diagnosed in those with prior gastrointestinal bleeding, and 28 of 212 (13.2%) were diagnosed in those with prior major gastrointestinal bleeding. Among patients with a new diagnosis of genitourinary cancer, 72 of 297 (24.2%) were diagnosed in those with prior genitourinary bleeding, and 17 of 297 (5.7%) were diagnosed in those with prior major genitourinary bleeding.

Table 2 presents data on the association between bleeding and a new diagnosis of cancer. Among patients with any bleeding who did not have preexisting active cancer, 257 of 2609 (9.9%) were subsequently diagnosed with new cancer compared with 827 of 27395 (3.0%) diagnosed with cancer without prior bleeding (HR, 4.39 [95% CI, 3.80–5.07]; $P<0.0001$). Among patients with major bleeding who did not have preexisting active cancer, 79 of 672 (11.8%) were subsequently diagnosed with new cancer compared with 1005 of 27395 (3.7%) diagnosed with new cancer without prior major bleeding (HR, 5.65 [95% CI, 4.48–7.14]; $P<0.0001$).

Table 3 presents data on new cancer diagnosis in relation to gastrointestinal bleeding. Gastrointestinal bleeding was associated with a 20-fold higher hazard of new gastrointestinal cancer diagnosis (67 of 905 [7.4%] after prior gastrointestinal bleeding versus 145 of 27395 [0.5%] without prior gastrointestinal bleeding; HR, 20.6 [95% CI, 15.2–27.8]) compared with a 1.7-fold higher hazard of new nongastrointestinal cancer diagnosis (34 of 888 [3.8%] versus 844 of 27395 [3.1%]; HR, 1.70 [95% CI, 1.20–2.40]). Although fewer gastrointestinal cancers were diagnosed after major compared with any gastrointestinal bleeding (28 versus 67), the association between major gastrointestinal bleeding and gastrointestinal cancer was even stronger than for any bleeding (28 of 292 [9.6%] versus 184 of 27395 [0.7%]; HR, 26.8 [95% CI,17.7–40.4]).

Table 4 presents data on new cancer diagnosis in relation to genitourinary bleeding. Genitourinary bleeding was associated with a 30-fold higher hazard of new genitourinary cancer diagnosis (72 of 457 [15.8%] versus 225 of 27395 [0.8%]; HR, 32.5 [95% CI, 24.7–42.9]) and no significant difference in hazard of new nongenitourinary cancer diagnosis (15 of 462 [3.2%] versus 789 of 27395 [2.9%]; HR, 1.50 [95% CI, 1.90–2.51]). Nongenitourinary bleeding was not associated with a higher hazard of new genitourinary cancer diagnosis but was associated with a higher hazard of new nongenitourinary cancer diagnosis. Fewer genitourinary cancers were diagnosed in patients with major compared with any genitourinary bleeding (17 versus 72), but the associa-

Table 1. Number of Patients With Bleeding or New Cancer Diagnosis and the Proportion of New Cancers Diagnosed in Patients With Bleeding

Organ System	Patients With Bleeding, n		New Cancer Diagnosis, n (%)		
	Any*	Major	Total Patients	In Patients With Bleeding*	In Patients With Major Bleeding
Any	2678	713	1084	257 (23.8)	79 (7.3)
Gastrointestinal	915	296	212	67 (31.5)	28 (13.2)
Genitourinary	467	82	297	72 (24.2)	17 (5.7)
Urinary	407	64	125	57 (45.6)	15 (12.0)
Other†	1520	346	594	66 (9.4)	14 (2.4)

*Major or minor.
†Nongastrointestinal, nongenitourinary.

tion between major genitourinary bleeding and genitourinary cancer was even stronger than for any genitourinary bleeding (17 of 79 [21.5%] versus 280 of 27 395 [1.0%]; HR, 45.1 [95% CI, 27.4–74.2]).

Table II in the online-only Data Supplement presents data on new cancer diagnosis in relation to urinary bleeding, a subset of genitourinary bleeding. Urinary bleeding was associated with an almost 100-fold higher hazard of new urinary cancer diagnosis (57 of 402 [14.2%] versus 68 of 27 395 [0.2%]; HR, 98.5 [95% CI, 68.0–142.7]) and a 1.8-fold higher hazard of new nonurinary cancer diagnosis (19 of 398 [4.8%] versus 950 of 27 395 [3.5%]; HR, 1.86 [95% CI, 1.18–2.94]). Nonurinary bleeding was not associated with a higher hazard of new urinary cancer diagnosis but was associated with a higher hazard of new nonurinary cancer diagnosis. Fewer urinary cancers were diagnosed after major compared with any urinary bleeding (15 versus 57), but the association between major urinary bleeding and new urinary cancer diagnosis was even stronger than for any urinary bleeding (15 of 63 [23.8%] versus 110 of 27 395 [0.4%]; HR, 111.8 [95% CI, 63.6–196.4]).

Table III in the online-only Data Supplement presents data on new cancer diagnosis in relation to gastrointestinal or genitourinary bleeding. Gastrointestinal or genitourinary bleeding was associated with a 13-fold higher hazard of new gastrointestinal or genitourinary cancer diagnosis (151 of 1323 [11.4%] versus 352 of 27 395 [1.3%]; HR, 13.8 [95% CI, 11.3–16.8]) and a 1.4-fold higher hazard of new nongastrointestinal, nongenitourinary cancer diagnosis (30 of 1331 [2.3%] versus 564 of 27 395 [2.1%]; HR, 1.46 [95% CI, 1.01–2.12]). Bleeding that was neither gastrointestinal nor genitourinary was associated with a 3-fold higher hazard of new diagnosis of cancer that was not gastrointestinal or genitourinary (66 of 1494 [4.4%] versus 528 of 27 395 [1.93%]; HR, 3.02 [95% CI, 2.32–3.91]) and a 1.6-fold higher hazard or cancer that was gastrointestinal or genitourinary (34 of 1502 [2.3%] versus 469 of 27 395 [1.7%]; HR, 1.61 [95% CI 1.13–2.29]).

The Figure demonstrates the timing of new diagnosis of gastrointestinal cancer (Figure, A) and nongastrointestinal cancer (Figure, B) in patients with prior gastrointestinal bleeding, new diagnosis of genitourinary

Table 2. Association Between Bleeding and New Cancer Diagnosis

Population	Patients, n	New Cancers Diagnosed		Hazard Ratio (95% CI)	*P* Value
		n	%		
Any bleeding*					
In patients with bleeding	2609†	257	9.9	4.39 (3.80–5.07)	<0.0001
In patients without prior bleeding	27 395	827	3.0		
Major bleeding					
In patients with bleeding	672†	79	11.8	5.65 (4.48–7.14)	<0.0001
In patients without prior bleeding	27 395	1005	3.7		
Fatal, critical organ, or surgical-site bleeding					
In patients with bleeding	238†	14	5.9	2.72 (1.60–4.62)	0.0002
In patients without prior bleeding	27 395	1070	3.9		
Bleeding leading to hospitalization					
In patients with bleeding	578†	73	12.6	6.09 (4.78–7.75)	<0.0001
In patients without prior bleeding	27 395	1011	3.7		

*Major or minor bleeding
†This number excludes patients who were diagnosed with cancer before bleeding.

Table 3. Effect of Gastrointestinal and Nongastrointestinal Bleeding on New Gastrointestinal and Nongastrointestinal Cancer Diagnoses

Event	New Gastrointestinal Cancer		Hazard Ratio (95% CI)	*P* Value	New Nongastrointestinal Cancer		Hazard Ratio (95% CI)	*P* Value
	n/N	%			n/N	%		
Any gastrointestinal bleeding								
New cancer diagnosis in patients with gastrointestinal bleeding	67/905*	7.4	20.6 (15.2–27.8)	<0.0001	34/888	3.8	1.70† (1.20–2.40)	0.003
New cancer diagnosis without prior gastrointestinal bleeding	145/27 395	0.5			844/27 395	3.1		
Any nongastrointestinal bleeding								
New cancer diagnosis with non gastrointestinal bleeding	16/1901*	0.8	1.36 (0.81–2.28)	0.25	156/1872	8.3	4.32 (3.62–5.16)	<0.0001
New cancer diagnosis without prior nongastrointestinal bleeding	196/27 395	0.7			722/27 395	2.6		
Major gastrointestinal bleeding								
New cancer diagnosis in patients with major gastrointestinal bleeding	28/292*	9.6	26.8 (17.7–40.4)	<0.0001	12/279	4.3	2.28 (1.29–4.05)	0.005
New cancer diagnosis without prior major gastrointestinal bleeding	184/27 395	0.7			866/27 395	3.2		
Major nongastrointestinal bleeding								
New cancer diagnosis in patients with major nongastrointestinal bleeding	2/426*	0.5	0.96 (0.24–3.89)	0.96	38/406	9.4	5.32 (3.83–7.39)	<0.0001
New cancer diagnosis without prior major nongastrointestinal bleeding	210/27 395	0.8			840/27 395	3.1		

*The denominator excludes patients who were diagnosed with cancer before experiencing bleeding.

†Significant treatment interaction: rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily: hazard ratio, 1.36 (95% CI, 0.76–2.43); rivaroxaban 5 mg twice daily: hazard ratio, 1.07 (95% CI, 0.53–2.18); and aspirin: hazard ratio, 3.63 (95% CI, 2.11–6.24).

cancer (Figure, C) and nongenitourinary cancer (Figure, D) in patients with prior genitourinary bleeding, and new diagnosis of urinary cancer (Figure, E) and nonurinary cancer (Figure, F) in patients with prior urinary bleeding. Of cancers diagnosed after bleeding, 52 of 67 (77.6%) of new gastrointestinal cancers diagnosed in patients with prior gastrointestinal bleeding were diagnosed within 6 months and 57 of 67 (85.1%) within 12 months after bleeding; 63 of 72 (87.5%) of genitourinary cancers diagnosed in patients with prior genitourinary bleeding were diagnosed within 6 months and 70 of 72 (97.2%) within 12 months after genitourinary bleeding; and 51 of 57 (89.5%) of urinary cancers diagnosed in patients with prior urinary bleeding were diagnosed within 6 months and 57 of 57 (100%) within 12 months after urinary bleeding.

DISCUSSION

The COMPASS trial demonstrated that increased intensity of antithrombotic treatment with the combination of rivaroxaban 2.5 mg twice daily and aspirin 100 mg once daily or with rivaroxaban 5 mg twice daily increased bleeding, with most of the excess bleeding occurring from the gastrointestinal tract.[8–10] Here, we report that gastrointestinal and genitourinary bleeding identified a group at particularly high risk of new cancer diagnosis. Of 1084 patients (4.0%) diagnosed with cancer, 257 cancers (23.8%) were diagnosed in those with prior bleeding, and of those who experienced bleeding, 1 in 11 (9.9%) were subsequently diagnosed with new cancer. When we restricted our analysis to bleeding from the gastrointestinal or genitourinary tracts, 1 in 14 patients (7.4%) with prior gastrointestinal bleeding were diagnosed with gastrointestinal cancer, and 1 in 7 (15.8%) with prior genitourinary bleeding was diagnosed with new genitourinary cancer. Gastrointestinal and genitourinary cancers were associated with a 20- and 30-fold higher hazard for new cancer diagnosis, respectively, in the corresponding organ systems. The associations between bleeding at other sites and new cancer were much weaker; of those with other (nongastrointestinal, nongenitourinary) bleeding, only 1 in 43 (2.3%) was subsequently diagnosed with gastrointestinal or genitourinary cancer.

Our finding that the majority of cancers diagnosed in patients with prior bleeding were diagnosed after any (ie, major or minor) bleeding rather than after major bleeding highlights the potential for minor bleeding to unmask new cancers. Fewer than one-third of all new cancers diagnosed after bleeding were diagnosed in patients with prior major bleeding, and an even lower proportion of all new gastrointestinal, genitourinary, and urinary cancers diagnosed after bleeding were diagnosed in patients with prior major bleeding involving these sites.

Table 4. Effect of Genitourinary and Nongenitourinary Bleeding on New Genitourinary and Nongenitourinary Cancer Diagnoses

	New Genitourinary Cancer		Hazard Ratio (95% CI)	*P* Value	New Nongenitourinary Cancer		Hazard Ratio (95% CI)	*P* Value
	n/N	%			n/N	%		
Any genitourinary bleeding								
New cancer diagnosis in patients with genitourinary bleeding	72/457*	15.8	32.5 (24.7–42.9)	<0.0001	15/462	3.2	1.50 (0.90–2.51)	0.12
New cancer diagnosis in patients without prior genitourinary bleeding	225/27 395	0.8			789/27 395	2.9		
Any nongenitourinary bleeding								
New cancer diagnosis in patients with non genitourinary bleeding	34/2292*	1.5	1.96 (0.36–2.82)	0.0003	156/2257	6.9	3.83 (3.20–4.59)	<0.0001
New cancer diagnosis without prior nongenitourinary bleeding	263/27 395	1.0			648/27 395	2.4		
Major genitourinary bleeding								
New cancer diagnosis in patients with major genitourinary bleeding	17/79*	21.5	45.1 (27.4–74.2)	<0.0001	4/82	4.9	2.72 (1.02–7.29)	0.05
New cancer diagnosis without prior major genitourinary bleeding	280/27 395	1.0			800/27 395	2.9		
Major nongenitourinary bleeding								
New cancer diagnosis in patients with major nongenitourinary bleeding	7/623*	1.1	1.70 (0.80–3.62)	0.17	51/602	8.5	5.37 (4.03–7.17)	<0.0001
New cancer diagnosis without prior major nongenitourinary bleeding	290/27 395	1.1			753/27 395	2.7		

*The denominator excludes patients who were diagnosed with cancer before experiencing bleeding.

Clinicians have long been aware of the potential for bleeding to unmask underlying cancer, but most reports of the association between bleeding and cancer diagnosis are based on retrospective analyses, small case series, or analyses of databases designed to address other questions and do not provide reliable measures of the strength of association.[1–7] In patients with venous thromboembolism who are treated with anticoagulants, clinicians routinely consider the possibility of underlying cancer (regardless of bleeding) because of the known association between cancer and hypercoagulability.[13] Although there is no known direct association between cardiovascular disease and cancer, our findings of a strong and relatively specific link between gastrointestinal bleeding and new gastrointestinal cancer diagnosis and between genitourinary bleeding and new genitourinary cancer diagnosis highlight the importance of searching for occult cancer at the site of bleeding in patients who experience gastrointestinal or genitourinary bleeding.

Although bleeding is undesirable, patients may be less concerned about this risk if it unmasks gastrointestinal and genitourinary cancers that would otherwise potentially remain undiagnosed for a longer period. Earlier diagnosis of cancer in patients with bleeding might lead to improved outcomes, depending on the site and the stage of cancer at the time of diagnosis. Although we did not observe a survival benefit among patients who were diagnosed with cancer in patients with prior bleeding compared with those who were diagnosed with cancer without prior bleeding, the mean duration of follow-up in the trial was only 23 months, the mean duration of follow-up after a diagnosis of cancer was only 10.7 months, and the number of cases with cancers diagnosed in the gastrointestinal or genitourinary tracts was not large enough to detect even a 2-fold difference in mortality. The CHARISMA trial (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) investigators reported that moderate or severe bleeding was associated with increased cancer mortality, but it is unclear whether the increased mortality that they observed was in relation to existing or newly diagnosed cancers.[14]

A strength of the present investigation is that it is based on a large patient cohort with nearly complete (>99%) follow-up and prospective collection of both bleeding and cancer outcomes based on predefined criteria. A potential limitation is that the findings are restricted to patients with chronic coronary or peripheral artery disease treated with aspirin, rivaroxaban, or the combination and to patients who were enrolled in a randomized controlled trial setting. The majority of patients enrolled in the COMPASS trial were not naive to antithrombotic therapy, having been treated with aspirin before study entry, and the effect of bleeding on new cancer diagnoses that we observed may be different in the general population. Our findings may underestimate the effect of bleeding on new cancer diag-

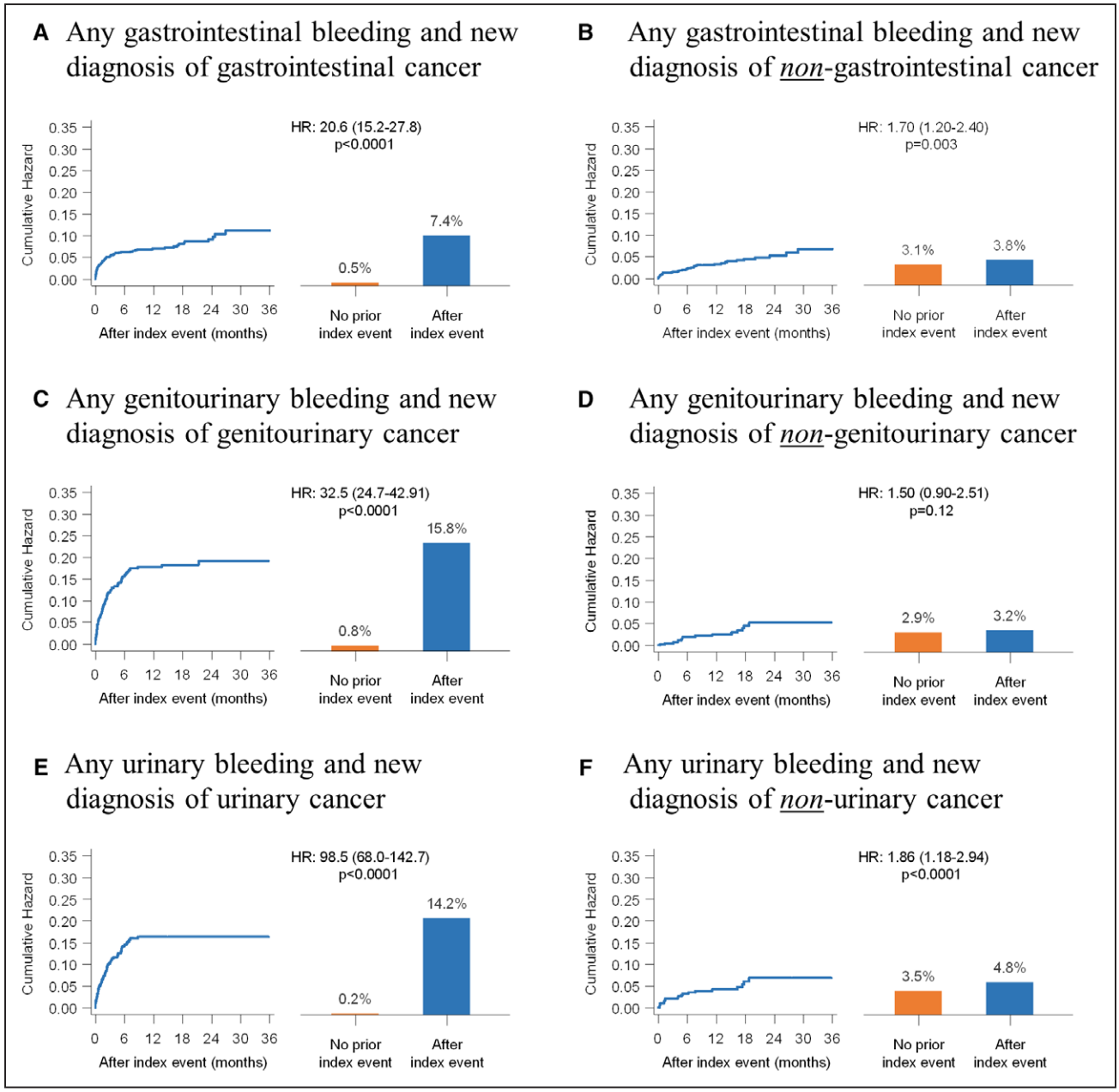

Figure. Frequency and timing of new cancer diagnosis in relation to bleeding New diagnosis of gastrointestinal (A) and nongastrointestinal (B) cancer after any gastrointestinal bleeding; new diagnosis of genitourinary (C) and nongenitourinary (D) cancer after any genitourinary bleeding; and new diagnosis of urinary (E) and nonurinary (F) cancer after any urinary bleeding.
Bars present proportion of patients with the new diagnosis of cancer after bleeding or without prior bleeding. HR indicates hazard ratio.

nosis because presumably there will have been bleeds after first exposure to aspirin that led to new cancer diagnosis. The association between bleeding and cancer should be further explored in studies involving patients who are naive to antithrombotic therapy and in those exposed to different antithrombotic or antiplatelet regimen and in studies with longer follow-up to determine whether earlier diagnosis of cancer may be associated with improved cancer survival. A second potential limitation is that the protocol did not mandate investigation of patients for cancer but left this to the discretion of the investigator.

CONCLUSIONS

Among patients with chronic coronary artery disease or peripheral artery disease treated with antithrombotic drugs, both gastrointestinal bleeding and genitourinary tract bleeding are strongly and relatively specifically associated with new diagnosis of cancer within the respective organ systems. These data indicate that gastrointestinal and genitourinary bleeding in patients receiving antithrombotic drugs should prompt a careful search for undiagnosed cancer, even when the bleeding is minor. Extended follow-up of patients in the COM-

PASS trial may help to determine whether diagnosis of cancer in patients who develop bleeding after starting more intensive antithrombotic therapy can improve long-term cancer outcomes.

ARTICLE INFORMATION

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