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Hemorrhage and recent oncology diagnosis in individuals with atherosclerosis

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ABSTRACT

Patients receiving antithrombotic therapy are at increased risk of bleeding. In some cases, bleeding may be the first manifestation of an underlying malignancy. We investigated newly diagnosed cancers associated with gastrointestinal or genitourinary bleeding among patients enrolled in the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial and assessed the risk of recent cancer diagnoses following bleeding at these sites. During a 23-month follow-up of 27,395 patients (mean age: 68 years; 21% female), 2,678 patients (9.8%) experienced any bleeding, 713 (2.6%) experienced major bleeding, and 1,084 (4.0%) were diagnosed with cancer. Among the 2,678 patients with bleeding, 257 (9.9%) were subsequently diagnosed with cancer. Gastrointestinal bleeding was 20-fold more common in patients with newly diagnosed gastrointestinal cancers (7.4% *vs*. 0.5%; HR 20.6, 95% CI: 15.2-27.8) and 1.7-fold more common in those with non-gastrointestinal cancers (3.8% *vs*. 3.1%; HR 1.70, 95% CI: 1.20-2.40). Genitourinary bleeding was associated with a 32-fold increased risk of newly diagnosed genitourinary malignancy (15.8% *vs*. 0.8%; HR 32.5, 95% CI: 24.7-42.9), while urinary bleeding was linked to a 98-fold higher risk of newly diagnosed urinary cancer (14.2% *vs*. 0.2%; HR 98.5, 95% CI: 68.0-142.7). Non-gastrointestinal, non-genitourinary bleeding was associated with a threefold higher risk of non-gastrointestinal, non-genitourinary cancers (4.4% *vs*. 1.9%; HR 3.02, 95% CI: 2.32-3.91). Among patients with atherosclerosis receiving antithrombotic therapy, gastrointestinal or genitourinary bleeding was associated with an increased incidence of cancer diagnosis. Any gastrointestinal or genitourinary bleeding should prompt evaluation for possible malignancy at these sites.

INTRODUCTION

Patients with atherosclerosis receiving antithrombotic therapy who develop gastrointestinal (GI) or genitourinary (GU) bleeding are at increased risk of a new cancer diagnosis in these organs. Analyses from the COMPASS trial suggest that gastrointestinal and genitourinary bleeding in patients treated with antithrombotic agents should prompt careful evaluation for previously undiagnosed malignancies, even in cases of minor bleeding [1-3]. Findings from the COMPASS study showed that among more than 27,000 patients followed for a mean period of 23 months, individuals with GI or GU bleeding were approximately 20-32 times more likely to be diagnosed with cancer. Notably, randomization to rivaroxaban 2.5 mg twice daily plus low-dose aspirin, compared with aspirin alone, did not increase the incidence of newly diagnosed cancers or cancer-related mortality [4-7]. Malignancies of the gastrointestinal or genitourinary tract are often highly vascularized and may therefore present with bleeding. In this study, we examined the association between bleeding events and new cancer diagnoses in the COMPASS trial. We also assessed the types of newly diagnosed malignancies identified in patients with bleeding and evaluated the risk of subsequent cancer diagnosis [8-11].

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METHODS

Gastrointestinal and genitourinary bleeding may represent important indicators of newly diagnosed cancer in patients with vascular disease, as suggested by findings from the COMPASS trial presented at the ESC Congress 2018.

In total, 27,395 patients with stable coronary artery disease (CAD) or peripheral artery disease (PAD) were randomized to receive rivaroxaban (2.5 mg twice daily) plus aspirin, rivaroxaban alone (5 mg twice daily), or aspirin alone (100 mg once daily).

The investigators evaluated newly diagnosed cancers occurring before and after bleeding events, the association between bleeding and subsequent malignancy, and cancer detection rates. Among patients with newly diagnosed cancer, 23.8% (n = 257) were diagnosed after a bleeding event. Furthermore, 22.9% of gastrointestinal cancers and 44.9% of genitourinary cancers were diagnosed following bleeding episodes. Most gastrointestinal and genitourinary malignancies were detected within six months after bleeding (77.1% and 88.7%, respectively). Overall, more than one in five malignancies were preceded by bleeding.

Patients receiving rivaroxaban plus aspirin or rivaroxaban alone had a slightly higher incidence of newly diagnosed gastrointestinal cancer during the first year (0.6%) compared with those receiving aspirin alone (0.4%).

These findings suggest that gastrointestinal or genitourinary bleeding in patients receiving antithrombotic therapy should prompt evaluation for possible malignancy in the affected organ. Extended follow-up of participants in the COMPASS trial may further improve cancer detection and clinical outcomes following bleeding events.

Statistical analysis

We analyzed the incidence of malignancies diagnosed before and after episodes of genitourinary or gastrointestinal bleeding. The association between bleeding and the incidence of newly diagnosed cancer was examined using stratified Cox proportional hazards models with bleeding events treated as time-dependent variables. The proportional hazards assumption was assessed by plotting the log of the survival function against time. We also evaluated the association between antithrombotic therapy and time-dependent index bleeding events. The cumulative hazard was calculated as the negative logarithm of the Kaplan-Meier survival function and plotted over time. Two-sided p-values < 0.05 were considered statistically significant, and no adjustments were made for multiple comparisons. All statistical analyses were performed using SAS version 9.4 for Linux (Statistical Analysis System [SAS] Institute Inc., Cary, NC, USA). The COMPASS trial was approved by the relevant institutional review boards, and all participants provided written informed consent.

RESULTS

Randomized treatment with rivaroxaban 2.5 mg twice daily plus aspirin 100 mg once daily had no significant effect on the overall incidence of newly diagnosed cancers compared with aspirin alone (366/9,152 [4.0%] *vs*. 352/9,126 [3.9%]; hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.89-1.20; $p = 0.66$). Similarly, rivaroxaban 5 mg twice daily showed no significant difference compared with aspirin alone (366/9,117 [4.0%] *vs*. 352/9,126 [3.9%]; HR 1.04, 95% CI 0.90-1.21). The randomized treatment also had no significant impact on cancer-related mortality (70/9,152 [0.8%] *vs*. 85/9,126 [0.9%]; HR 0.82, 95% CI 0.60-1.12; $p = 0.21$). Comparable findings were observed for rivaroxaban 5 mg twice daily compared with aspirin alone (87/9,152 [1.0%] *vs*. 85/9,126 [0.9%]; HR 1.03, 95% CI 0.76-1.38).

Baseline characteristics were compared between patients who experienced bleeding and those who did not. Patients with bleeding were generally older, had a lower body mass index (BMI), and were more likely to be current or former smokers, among other differences. Among 25,673 patients without a history of cancer, 910 new malignancies (first-ever or recurrent) were diagnosed, representing 3.5% of the cohort. In contrast, 174 malignancies were identified among 1,722 patients with a prior history of cancer, corresponding to 10%. Table 1 summarizes the number of patients experiencing bleeding in relation to newly diagnosed cancer, as well as the proportions of individuals with gastrointestinal, genitourinary, and urinary bleeding.

Table 1. Number of patients with bleeding and newly diagnosed cancer by bleeding site

Organ system	Patients with bleeding		New cancer diagnosis		
	Any* N	Major N	Total patients N	In patients with bleeding* N (%)	In patients with major bleeding N (%)
Any	2,678	713	1,084	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†	1,520	346	594	66 (9.4%)	14 (2.4%)

* - denotes major or minor, † - denotes nongastrointestinal or nongenitourinary

Overall, 257 of 1,084 (23.7%) new cancer diagnoses occurred prior to bleeding events. Among the 1,084 patients with newly diagnosed cancer, 79 (7.3%) had a history of bleeding. In total, 503 patients were diagnosed with either gastrointestinal or genitourinary cancer, including six patients who had both malignancies. Among the 212 patients diagnosed with a new gastrointestinal malignancy, 67 had a history of gastrointestinal bleeding, and 28 (13.2%) experienced gastrointestinal bleeding at the time of diagnosis. Among the 297 patients with newly diagnosed genitourinary cancer, 72 (24.2%) experienced genitourinary bleeding, while 17 (5.7%) had a prior history of genitourinary bleeding.

Table 2 presents bleeding events associated with newly diagnosed cancers. Among patients without a prior cancer diagnosis, 257 of 2,609 (9.9%) patients who experienced bleeding were subsequently diagnosed with cancer, compared with 827 of 27,395 (3.0%) patients without bleeding (hazard ratio [HR] 4.39; 95% confidence interval [CI] 3.80-5.07; $p < 0.0001$). Among patients with major bleeding and no prior malignancy, 79 of 672 (11.8%) were diagnosed with a new cancer, compared with 1,005 of 27,395 (3.7%) patients without major bleeding (HR 5.65; 95% CI 4.48-7.14; $p < 0.0001$).

Table 3 presents data on newly diagnosed cancers associated with gastrointestinal bleeding. Gastrointestinal bleeding was associated with a 20-fold increased risk of newly diagnosed gastrointestinal cancer (67/905 [7.4%] among patients with prior gastrointestinal bleeding *vs*. 145/27,395 [0.5%] among those without prior gastrointestinal bleeding; HR 20.6, 95% CI 15.2-27.8). In contrast, the risk of newly diagnosed non-gastrointestinal cancers was only modestly increased (34/888 [3.8%] *vs*. 844/27,395 [3.1%]; HR 1.70, 95% CI 1.20-2.40).

Table 2. Correlation between hemorrhage and the diagnosis of novel malignancy

Population	Number of patients	New cancers diagnosed (95% CI)		HR	*p* value
		N	%		
Any bleeding*					
In patients with bleeding	2,609†	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 patient without prior bleeding	27,395	1,005	3.7		
Fatal, critical organ or surgical site bleeding					
In patient with bleeding	238†	14	5.9	2.72 (1.60-4.62)	0.0002
In patient without prior bleeding	27,395	1070	3.9		
Bleeding leading to Hospitalization					
In patient with bleeding	578†	73	12.6	6.09 (4.78-7.75)	<0.0001
In patient without prior bleeding	27,395	1,011	3.7		

* - denotes major or minor, † - denotes nongastrointestinal or nongenitourinary

Although fewer gastrointestinal cancers were identified after gastrointestinal bleeding (28 *vs*. 67), the association between gastrointestinal bleeding and gastrointestinal cancer remained substantially stronger than that observed for bleeding overall (28/292 [9.6%] *vs*. 184/27,395 [0.7%]; HR 26.8, 95% CI 17.7-40.4).

Table 4 presents data on newly diagnosed cancers associated with genitourinary bleeding. Genitourinary bleeding was associated with an approximately 30-fold increased risk of newly diagnosed genitourinary cancer (72/457 [15.8%] *vs*. 225/27,395 [0.8%]; HR 32.5, 95% CI 24.7-42.9). In contrast, no significant difference was observed in the risk of newly diagnosed non-genitourinary cancers (15/462 [3.2%] *vs*. 789/27,395 [2.9%]; HR 1.50, 95% CI 0.90-2.51).

Non-genitourinary bleeding was not associated with an increased risk of newly diagnosed genitourinary cancer. However, it was previously linked to an elevated risk of newly diagnosed non-genitourinary cancers and was observed in some patients with genitourinary bleeding (17 *vs*. 72 cases).

Notably, the association between primary genitourinary bleeding and genitourinary cancer was even stronger when considering any episode of genitourinary bleeding (17/79 [21.5%] *vs*. 280/27,395 [1.0%]; HR 45.1, 95% CI 27.4-74.2).

Table 3. Influence of gastrointestinal and non-gastrointestinal hemorrhaging on the diagnosis of new gastrointestinal and non-gastrointestinal malignancies

Event	New gastrointestinal cancer		HR (95% CI)	*p* value	New non-gastrointestinal cancer		HR (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 non-gastrointestinal bleeding								
New cancer diagnosis with non-gastrointestinal bleeding	16/1,901*	0.8	1.36 (0.81-2.28)	0.25	156/1,872	8.3	4.32 (3.62-5.16)	<0.0001
New cancer diagnosis without prior non-gastrointestinal bleeding	196/27,395	0.7			722/27,395	2.6		

* - denotes major or minor, † - denotes nongastrointestinal or nongenitourinary

Table 4. Influence of genitourinary and non-genitourinary hemorrhaging on the diagnosis of new genitourinary and non-genitourinary malignancies

Event	New genitourinary cancer		HR (95% CI)	*p* value	New non-genitourinary cancer		HR (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 non-genitourinary bleeding								
New cancer diagnosis in patients with non- genitourinary bleeding	34/2,292*	1.5	1.96 (0.36-2.82)	0.0003	156/2,257	6.9	3.83 (3.20-4.59)	<0.0001
New cancer diagnosis without prior non-genitourinary bleeding	263/27,395	1.0			648/27,395	2.4		

* - denotes major or minor, † - denotes nongastrointestinal or nongenitourinary

DISCUSSION

Effective collaboration across multiple clinical departments is essential to address these issues and to establish systems that enable the prompt identification of patients presenting with bleeding and their immediate referral for further evaluation. Although bleeding events occur relatively infrequently, they may represent important clinical signals that warrant careful investigation, similar to warning signs used in many cancer screening strategies recommended by national organizations [12,13].

Bleeding in patients receiving anticoagulant or antiplatelet therapy should therefore not be regarded merely as an adverse event but may serve as a clinical indicator prompting evaluation for potential underlying malignancy. In the overall COMPASS population, 9.8% of patients experienced gastrointestinal or genitourinary bleeding [14]. Among these patients, 9.9% were diagnosed with cancer during the 23-month follow-up period after an episode of major or minor bleeding.

The findings of this study indicate that gastrointestinal bleeding is associated with more than a 20-fold increased likelihood of receiving a new diagnosis of gastrointestinal cancer (7.4% *vs*. 0.5%; HR 20.6; 95% CI 15.2-27.8) and a 1.7-fold higher risk of newly diagnosed

non-gastrointestinal cancers (3.8% *vs*. 3.1%; HR 1.7; 95% CI 1.2-2.4) compared with individuals without gastrointestinal bleeding [15].

CONCLUSIONS

Similar findings were observed for genitourinary bleeding, which was associated with a 32.5-fold increased risk of newly diagnosed genitourinary cancer (15.8% *vs*. 0.8%; HR 32.5; 95% CI 24.7-42.9). In patients with urinary bleeding, the risk of new urinary cancer was markedly elevated (14.2% *vs*. 0.2%; HR 98.5; 95% CI 68.0-142.7). Overall, gastrointestinal or genitourinary bleeding was associated with a 13.8-fold higher risk of newly diagnosed gastrointestinal or genitourinary malignancies (11.4% *vs*. 1.3%; 95% CI 11.3-16.8) and a 1.46-fold increased risk of newly diagnosed non-gastrointestinal and non-genitourinary cancers (2.3% *vs*. 2.1%; 95% CI 1.01-2.12).

Our data indicate that a substantial proportion of malignancies in patients with bleeding can be detected even with relatively minor hemorrhagic events. Major bleeding highlights that even modest bleeding may reveal underlying malignancy. Less than one-third of newly diagnosed cancers following bleeding occurred in patients with prior major bleeding, and this proportion was lower for gastrointestinal, genitourinary, and urinary cancers specifically.

It should be noted that this study did not evaluate whether earlier detection of cancer among patients presenting with bleeding improved survival, which may be limited by the relatively short follow-up period. The cardiovascular community has yet to fully incorporate COMPASS trial findings into clinical practice, although emerging evidence supports the use of gastrointestinal and genitourinary bleeding as a potential signal for undiagnosed malignancies.

These findings underscore the growing relevance of low-dose systemic anticoagulation in high-risk patients and highlight the need for integrated care strategies. They suggest that monitoring for bleeding in patients on antithrombotic therapy may facilitate earlier cancer detection and could potentially improve clinical outcomes if integrated into patient management.

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