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Bleeding and cancer risk in patients with vascular disease

COMPASS Steering Committee and Investigators

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Background

- Community studies have shown that gastrointestinal (GI) and genitourinary (GU) bleeding may be the first sign of underlying cancer[1,2]
- The COMPASS trial[3] demonstrated that rivaroxaban-based treatments compared with aspirin increased GI bleeding
- It is not known whether GI and GU bleeding during long-term antithrombotic therapy may unmask underlying GI and GU cancers, respectively

1. Jones R, et al. BMJ 2007; 334: 1040. 2. Ford AC, et al. Gut 2008; 57; 1545-52.
3. Eikelboom JW, et al. N Engl J Med 2017; 377: 1319-30.

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Hypothesis

- In patients with vascular disease treated with antithrombotic drugs, GI and GU bleeding are associated with increased rates of new GI and GU cancer diagnosis

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Methods

- COMPASS trial randomized 27,395 patients with stable CAD or PAD to receive rivaroxaban 2.5mg bid plus aspirin, rivaroxaban 5mg bid, or aspirin 100mg od
- Major bleeding was defined according to the ISTH criteria (modified). Any bleeding not meeting the criteria for major was classified as minor
- New cancer diagnosis (first-ever, or recurrent in patients with a history of cancer thought to have been eradicated) was recorded at each follow up visit

Bosch J, et al. Can J Cardiol 2017; 33: 1027-1035.

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Analyses

We examined:

- The proportion of new cancers diagnosed before and after bleeding
- The association between bleeding and new cancer diagnosis (using a stratified Cox proportional hazards model with bleeding modelled as a time-dependent covariate)
- The rates of cancer diagnosis according to randomized treatment

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Number of new cancers and proportion diagnosed after bleeding

Site of cancer	Total number of new cancers diagnosed during COMPASS	New cancers diagnosed after bleeding	
		N	%
Any site	1,082*	257	23.8%
Gastrointestinal	307	70	22.8%
Genitourinary	138	62	44.9%
Other sites	655	68	10.4%

*Patients could have had more than one new cancer diagnosis

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Association between GI bleeding and GI cancer

Population	Total N	New GI cancers diagnosed (n=307)		HR (95% CI)	P value
		N	%		
GI bleeding					
After bleeding	901*	70	7.8	12.9 (9.77-17.0)	<0.0001
No prior bleeding	27,395	237	0.9		
Non-GI bleeding					
After bleeding	1,898*	29	1.5	1.77 (1.20-2.61)	0.004
No prior bleeding	27,395	278	1.0		

*Excludes patients with bleeding who were diagnosed with cancer before the bleeding event

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Association between GU bleeding and GU cancer

Population	Total N	New GU cancers diagnoses (n=138)		HR (95% CI)	P value
		N	%		
GU bleeding					
After bleeding	462*	62	13.4	83.4 (58.6-118.6)	<0.0001
No prior bleeding	27,395	76	0.3		
Non-GU bleeding					
After bleeding	2,301*	14	0.6	1.70 (0.97-2.99)	0.06
No prior bleeding	27,395	124	0.5		

*Excludes patients with bleeding who were diagnosed with cancer before the bleeding event

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Timing of cancer diagnosis in relation to bleeding

Site of cancer	Timing of GI and GU cancer diagnosis		
	Within 6 months of bleed	Between 6 and 12 months after bleed	More than 12 months after bleed
Gastrointestinal	54 (77.1%)	6 (8.6%)	10 (14.3%)
Genitourinary	55 (88.7%)	6 (9.7%)	1 (1.6%)

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Frequency of GI bleeding in year 1, 2, and 3+ according to randomized treatment: landmark analysis

Year	Rivaroxaban 2.5mg bid + ASA 100 mg od N (%)	Rivaroxaban 5mg bid N (%)	Aspirin 100mg od N (%)
1	271/9,152 (3.0%)	217/9,117 (2.4%)	115/9,126 (1.3%)
2	74/7,760 (1.0%)	85/7,748 (1.1%)	59/7,823 (0.8%)
3+	35/3,829 (0.9%)	29/3,815 (0.8%)	30/3,917 (0.8%)

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Frequency of GI cancer after GI bleeding in year 1, 2 and 3+

Year	Rivaroxaban 2.5mg bid + ASA 100 mg od N (%)	Rivaroxaban 5mg bid N (%)	Aspirin 100mg od N (%)
1	22/268 (8.2%)	18/216 (8.3%)	8/114 (7.0%)
2	6/72 (8.3%)	6/81 (7.4%)	5/58 (8.6%)
3+	1/34 (2.9%)	2/29 (6.9%)	2/29 (6.9%)

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Conclusions

Among patients with vascular disease on long-term antithrombotic therapy:

- More than 1 in 5 new diagnoses of cancer are preceded by bleeding
- GI bleeding and GU bleeding are powerful predictors of new cancer diagnosis, and more than 50% are diagnosed within 6 months
- Increased GI bleeding with rivaroxaban appears to unmask cancer at an earlier time point

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Implications

- The occurrence of GI or GU bleeding in patients receiving antithrombotic drugs should stimulate a search for cancer in the same organ system
- Extended follow-up of COMPASS trial participants may help to determine whether in vascular patients receiving long-term antithrombotic therapy, unmasking of cancer after bleeding improves cancer outcomes

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Acknowledgments

COMPASS Steering Committee

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Cancer diagnosis by randomized treatment

Cancer	R+A (n=9,152)	R (n=9,117)	A (n=9,126)
Total	366 (4.0%)	365 (4.0%)	351 (3.8%)
GI	109 (1.2%)	111 (1.2%)	87 (1.0%)
GU	47 (0.5%)	42 (0.5%)	49 (0.5%)
GI or GU	155 (1.7%)	150 (1.6%)	136 (1.5%)
Non-GI, non GU	216 (2.4%)	221 (2.4%)	218 (2.4%)

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Frequency of new GI cancer in year 1, 2, and 3+ post randomization according to randomized treatment

Year	Rivaroxaban 2.5mg bid + ASA 100 mg od N (%)	Rivaroxaban 5mg bid N (%)	Aspirin 100mg od N (%)
1	52 (0.6%)	52 (0.6%)	38 (0.4%)
2	41 (0.5%)	41 (0.5%)	30 (0.4%)
3+	16 (0.4%)	18 (0.5%)	19 (0.5%)