



Bleeding and cancer risk in patients with vascular disease

COMPASS Steering Committee and Investigators

Declaration of interest

- Consulting/Royalties/Owner/ Stockholder of a healthcare company (honoraria and research support)



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 demonstrated in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) that rivaroxaban-based treatments compared with aspirin increased GI bleeding³
- It is not known whether GI and GU bleeding also unmasks GI and GU cancers in vascular patients receiving long-term antithrombotic therapy

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

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
- Bleeding was defined according to the ISTH criteria (modified)
- New cancer diagnosis (first-ever cancer, or recurrent cancer in patients with a previous diagnosis in whom the cancer was thought to have been eradicated) was recorded at each follow up visit

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

Number of new cancers and proportion diagnosed before or after bleeding

Site	Total number of new cancers diagnosed during COMPASS	New cancers diagnosed after bleeding	
		N	%
All	1,082*	257	23.8%
Gastrointestinal	307	70	22.8%
Genitourinary	138	62	44.9%

*Patients could have had more than one new cancer diagnosis

Association between GI bleeding and GI cancer

Population	Total N	New GI cancers (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

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

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%)

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%)

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%)

Conclusions

Among COMPASS 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 GI and GU cancer diagnosis, respectively, and more than 75% of these cancers are diagnosed within 6 months of the bleed
- The early increase in GI bleeding with rivaroxaban-based treatments appears to be associated with earlier diagnosis of GI cancer

Implications

- The occurrence of GI or GU bleeding in patients receiving antithrombotic drugs should stimulate a vigorous search for cancer in the same organ system
- Extended follow-up of COMPASS trial participants may help to determine whether earlier diagnosis of GI cancer in patients with GI bleeding improves cancer outcomes

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COMPASS Steering Committee
National Leaders Offices
COMPASS Investigators
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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%)

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%)