Benefit of aspirin on mortality reduction of gastrointestinal cancer prevention versus risk of mortality from major bleeding in subjects after *Helicobacter pylori* eradication: a territory-wide study

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Introduction

- Aspirin has been shown to have chemopreventive effect on digestive cancer development
- However, aspirin is associated with increased bleeding risk, including gastrointestinal bleeding (GIB) and intracranial bleeding
- Eradication of *Helicobacter pylori* (*H. pylori*) reduces the risk of aspirin-induced upper GIB
- The chemopreventive benefit to risk ratio of aspirin in *H. pylori*-eradicated subjects may therefore be larger, in particular with concomitant proton pump inhibitor (PPI) use
- We aimed to investigate the benefit-risk profile of aspirin on the mortality from chemopreventin and bleeding in *H. pylori*-eradicated subjects

Methodology

- This was a retrospective cohort study based on a territory-wide healthcare database (CDARS) in Hong Kong.
- All adult patients (age ≥18) who received clarithromycin-based triple therapy for *H. pylori* eradication between January 1, 2003, and December 31, 2016 were identified.
- Exclusion criteria were (1) age <18 years, (2) cancer diagnosed before or within six months after receiving *H. pylori* eradication therapy (as these were likely pre-existing cancers), and (3) failure of *H. pylori* eradication therapy.

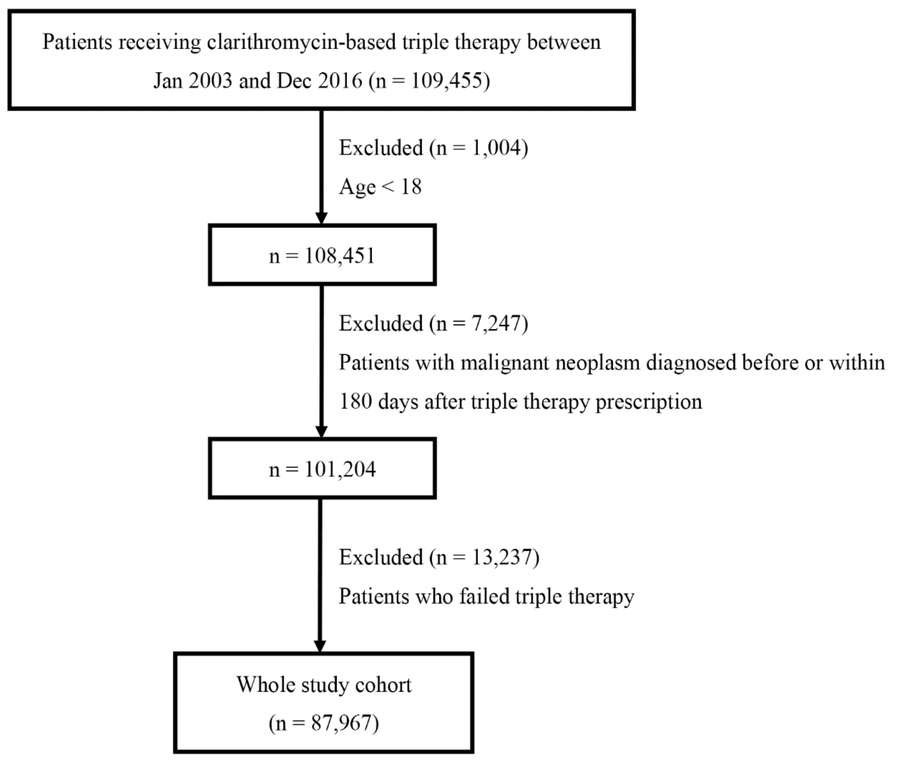

Figure. Patient selection flow diagram

Primary outcome: GI cancer-related mortality (including esophagus, stomach, small intestine, colorectum, hepatobiliary system and pancreas)

Secondary outcome: Major bleeding-related mortality (including GIB and intracranial bleeding)

Exposure: aspirin

Covariates: refer to **Table 1**

Statistical analysis: Multivariable Cox proportional hazards

→adjusted hazard ratio (aHR) of mortality (GI cancer and major bleeding)

Stratified analysis: PPI use versus PPI non-use

Table 2. Association between aspirin use and bleeding-related mortality

	Major bleeding-related mortality		Gastrointestinal cancer-related mortality	
	aHR (95% CI)	Adjusted absolute risk difference (per 10,000 person-years)	aHR (95% CI)	Adjusted absolute risk difference (per 10,000 person-years)
Overall (aspirin use vs non-use)	1.52 (1.11 to 2.08)	1 (0.3 to 3)	0.51 (0.42 to 0.61)	-7 (-8 to -5)
Aspirin without PPI/H2RA use (vs aspirin non-use)	2.12 (1.04 to 4.35)	3 (0.1 to 8)	0.76 (0.47 to 1.24)	-3 (-7 to 3)
Aspirin + H2RA use (vs aspirin non-use)	1.96 (1.26 to 3.06)	2 (1 to 5)	0.72 (0.57 to 0.92)	-4 (-6 to -1)
Aspirin + PPI use (vs aspirin non-use)	1.06 (0.70 to 1.63)	0 (-1 to 2)	0.32 (0.24 to 0.42)	-9 (-10 to -8)

Table 1. Characteristics of aspirin users and non-users

	Aspirin users (n = 20332)		Aspirin non-users (n = 67635)	
	N	%	N	%
Age at triple therapy (median, years)	65.2	55.9 – 74.5	52.1	43.5 - 61.0
Male sex	11155	54.9	29703	43.9
Smoking	1247	6.1	1221	1.8
Alcoholism	362	1.8	1053	1.6
Dyspepsia	1319	6.5	4112	6.1
GORD	769	3.8	1804	2.7
History of GU	1346	6.6	2636	3.9
History of DU	1769	8.7	5841	8.6
DM	5828	28.7	5135	7.6
Hypertension	10182	50.1	9123	13.5
Dyslipidaemia	4710	23.2	2690	4.0
Obesity	432	2.1	638	0.9
IHD	7179	35.3	979	1.4
AF	3056	15.0	905	1.3
CHF	3187	15.7	1084	1.6
Stroke	3963	19.5	685	1.0
CRF	1777	8.7	923	1.4
Cirrhosis	356	1.8	1405	2.1
Metformin	6290	30.9	8779	13.0
NA-NSAIDs	11552	56.8	38867	57.5
Statins	15004	73.8	13919	20.6
PPIs	10131	49.8	15486	22.9
H2RAs	18756	92.2	55208	81.6
Bisphosphonate	874	4.3	1185	1.8
SSRIs	2244	11.0	4849	7.2
Corticosteroids	7196	35.4	11275	16.7
Anticoagulants	5216	25.7	1527	2.3
Other antiplatelets	5880	28.9	521	0.8

Results

- 87,967 eligible patients were followed for a median of 10.3 years
- 1,294 (1.5%) GI cancer-related deaths and 304 (0.3%) major bleeding-related deaths
- Aspirin use was associated with lower GI cancer-related mortality (aHR:0.51;95% CI:0.42–0.61), but higher major bleeding-related mortality (aHR:1.52;95% CI:1.11–2.08) which was mainly due to intracranial bleeding (aHR:2.02;95% CI:1.38–2.96) but not GIB (aHR:0.78;95% CI:0.78–1.36) (**Table 2**).
- The aHR of major bleeding-related mortality with aspirin use among PPI users, H2RA users and non-users of H2RA/PPIs was 1.06 (95% CI: 0.70–1.63), 1.96 (95% CI:1.26–3.06) and 2.12 (95% CI:1.04–4.35), respectively (**Table 2**).
- For the whole cohort, the adjusted absolute risk difference between all aspirin users and non-users was 7 (95% CI:5–8) fewer GI cancer-related deaths and 1 (95% CI:0.3–3) more major bleeding-related death per 10,000 person-years (**Table 3**).
- For the subgroup with concomitant PPI-aspirin use, the difference between aspirin users and non–aspirin users increased to 9 (95% CI:8–10) fewer GI cancer-related deaths per 10,000 person-years without increase in major bleeding-related deaths (**Table 3**).

***Table 3.* Comparison of mortality from gastrointestinal cancer chemoprevention and major bleeding between aspirin users and non-users, stratified by the use of gastroprotective agents**

	Adjusted absolute risk difference (95% CI) per 10,000 person-years		
	GI cancer-related deaths	Major bleeding-related deaths	GI bleeding-related deaths
Aspirin use (vs aspirin non-use)	-7 (-8 to -5)	1 (0.3 to 3)	0 (0 to 0)
Aspirin + PPI use (vs aspirin non-use)	-9 (-10 to -8)	0 (-1 to 2)	-0.5 (-1 to -0.1)
Aspirin + H2RA use (vs aspirin non-use)	-4 (-6 to -1)	2 (1 to 5)	0 (0 to 1)

Conclusion

- The benefit of aspirin in reducing GI cancer-related mortality outweighs its risk on major bleeding related mortality in HP-eradicated subjects. The benefit-risk profile could be further enhanced by concomitant use of PPIs