



Supplementary Figure 1. ACCF/ACG/AHA 2008 Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

Supplementary Table 1. Baseline Characteristics by Risk Groups for All Antiplatelet ± Anticoagulant /NSAID Patients Users

Variables	Cohort dataset (n=98,404)	High-risk group (n=73,691 (74.9%))	Low-risk group (n=24,713 (25.1%))
Age, median (IQR)	62 (53-70)	66 (60-72)	51 (45-56)
Sex, n (%)			
Male	54,789 (55.7%)	40,323 (54.7%)	14,466 (58.5%)
Female	43,615 (44.3%)	33,368 (45.3%)	10,247 (41.5%)
Mucosal DAs, n (%)			
Aspirin	90,766 (92.2%)	68,151 (92.5%)	22,615 (91.5%)
Clopidogrel	34,921 (35.5%)	32,387 (43.9%)	2,534 (10.3%)
Warfarin	6,869 (7.0%)	6,671 (9.1%)	198 (0.8%)
NSAIDS	3,944 (4.0%)	3,529 (4.8%)	415 (1.7%)
DOAC	3,003 (3.1%)	2,874 (3.9%)	129 (0.5%)
PAs co-administered with DAs, n (%)			
PPI	13,337 (13.6%)	11,394 (15.5%)	3 (0%)
Rebamipide	5,890 (6.0%)	4,854 (6.6%)	1,036 (4.2%)
H2RA	19,919 (20.2%)	17,023 (23.1%)	2,896 (11.7%)
Others	3,647 (3.7%)	2,720 (3.7%)	927 (3.8%)

IQR, inter-quartile range; DA, damaging agent; NSAID, non-steroidal anti-inflammatory drug; DOAC, direct oral anticoagulant; PA, protective agent; H2RA, H2-receptor antagonist; PPI, proton pump inhibitor; Others, agents such as sodium alginate, ecabet sodium hydrate, polaprezinc, and Stillen (an ethanol extract of *Artemisiae Argyi Herba*).

Supplementary Table 2. Effect of PA Uses on SHD Incidences by Risk groups for Antiplatelet-alone Users in SCCS analyses

Exposure period	Number of SHD incidence	Total (n = 755)		High-risk group (n = 654)			Low-risk group (n = 101)		
		IRR* (95% CI)	P-value	Number of SHD incidence	IRR* (95% CI)	P-value	Number of SHD incidence	IRR* (95% CI)	P-value
a. All SHD events									
Mucosal DA alone	619	Reference		533	Reference		86	Reference	
PPI	161	0.39 (0.30-0.51)	<0.001	150	0.38 (0.29-0.51)	<0.001	11	0.51 (0.19-1.36)	0.176
PPI & Rebamipide	2	0.10 (0.02-0.47)	0.003	2	0.10 (0.02-0.47)	0.003	0		
PPI & H2RA	4	0.22 (0.08-0.63)	0.005	4	0.23 (0.08-0.67)	0.007	0		
PPI & Others	4	0.11 (0.02-0.67)	0.017	4	0.10 (0.02-0.66)	0.017	0		
Rebamipide	68	0.92 (0.62-1.38)	0.698	56	0.93 (0.59-1.47)	0.756	12	0.94 (0.40-2.22)	0.890
Rebamipide & H2RA	4	0.32 (0.10-1.00)	0.050	4	0.38 (0.12-1.25)	0.111	0		
H2RA	237	0.75 (0.60-0.94)	0.012	214	0.77 (0.61-0.98)	0.031	23	0.67 (0.35-1.28)	0.225
H2RA & Others	2	0.41 (0.07-2.31)	0.314	2	0.72 (0.11-4.68)	0.730	0		
Others	22	0.48 (0.26-0.88)	0.017	16	0.38 (0.19-0.77)	0.008	6	1.03 (0.27-3.85)	0.967
b. First SHD event only									
Mucosal DA alone	618	Reference		532	Reference		86	Reference	
PPI	152	0.39 (0.30-0.52)	<0.001	141	0.39 (0.29-0.51)	<0.001	11	0.48 (0.18-1.27)	0.137
PPI & Rebamipide	2	0.10 (0.02-0.45)	0.003	2	0.10 (0.02-0.45)	0.003	0		
PPI & H2RA	4	0.28 (0.10-0.83)	0.021	4	0.31 (0.10-0.90)	0.031	0		
PPI & Others	4	0.11 (0.02-0.69)	0.019	4	0.11 (0.02-0.69)	0.018	0		
Rebamipide	67	0.94 (0.63-1.42)	0.779	55	0.94 (0.59-1.49)	0.792	12	0.99 (0.41-2.36)	0.978
Rebamipide & H2RA	2	0.21 (0.05-0.94)	0.042	2	0.26 (0.06-1.21)	0.086	0		
H2RA	226	0.79 (0.63-0.99)	0.041	204	0.82 (0.64-1.04)	0.094	22	0.68 (0.35-1.31)	0.245
H2RA & PPI	4	0.28 (0.10-0.83)	0.021	4	0.31 (0.10-0.90)	0.031	0		
H2RA & Others	2	0.43 (0.08-2.43)	0.339	2	0.77 (0.12-5.15)	0.790	0		
Others	22	0.51 (0.28-0.94)	0.030	16	0.41 (0.20-0.84)	0.015	6	0.93 (0.24-3.53)	0.914

PA, protective agent; SHD, significant hemoglobin drop; HR, hazard ratio; CI, confidence interval; DA, damaging agent; PPI, proton pump inhibitor; H2RA, H2-receptor antagonist; Others, agents such as sodium alginate, ecabet sodium hydrate, polaprezinc, and Stillen (an ethanol extract)

of *Artemisiae Argyi Herba*.

* Adjusted IRRs were estimated after adjusting prescription period for PAs and DAs.

Supplementary Table 3. Effect of PA uses on SHD Incidences by Risk groups for All Antiplatelet ± Anticoagulant /NSAID Patients in Matched Landmark Analyses

Exposure group	Total (n = 6821)		High-risk group (n = 6029)		Low-risk group (n = 792)	
	HR* (95% CI)	p-value	HR* (95% CI)	p-value	HR* (95% CI)	p-value
a. All SHD events						
Mucosal DA alone	Reference		Reference		Reference	
PPI	0.77 (0.28-2.13)	0.617	1.01 (0.37-2.81)	0.981	0.01 (0.00-3.80)	0.125
Rebamipide	0.36 (0.12-1.08)	0.069	0.48 (0.16-1.47)	0.199	0.00 (0.00-1.85)	0.076
H2RA	0.62 (0.20-1.92)	0.412	0.79 (0.25-2.51)	0.695	0.01 (0.00-6.02)	0.157
b. First SHD event only						
Mucosal DA alone	Reference		Reference		Reference	
PPI	0.79 (0.29-2.13)	0.642	1.03 (0.38-2.84)	0.948	0.01 (0.00-3.80)	0.115
Rebamipide	0.37 (0.13-1.07)	0.066	0.49 (0.16-1.47)	0.203	0.00 (0.00-1.85)	0.063
H2RA	0.64 (0.23-1.79)	0.395	0.81 (0.28-2.32)	0.696	0.01 (0.00-6.02)	0.128

PA, protective agent; SHD, significant hemoglobin drop; HR, hazard ratio; CI, confidence interval; DA, damaging agent; PPI, proton pump inhibitor; H2RA, H2-receptor antagonist; Others, agents such as sodium alginate, ecabet sodium hydrate, polaprezinc, and Stillen (an ethanol extract of Artemisiae Argyi Herba).

*Adjusted HRs were estimated after adjusting prescription period for PAs and DAs.