

Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data



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Summary

Background Combinations of aspirin, clopidogrel, and vitamin K antagonists are widely used in patients after myocardial infarction. However, data for the safety of combinations are sparse. We examined the risk of hospital admission for bleeding associated with different antithrombotic regimens.

Methods By use of nationwide registers from Denmark, we identified 40 812 patients aged 30 years or older who had been admitted to hospital with first-time myocardial infarction between 2000 and 2005. Claimed prescriptions starting at hospital discharge were used to determine the regimen prescribed according to the following groups: monotherapy with aspirin, clopidogrel, or vitamin K antagonist; dual therapy with aspirin plus clopidogrel, aspirin plus vitamin K antagonist, or clopidogrel plus vitamin K antagonist; or triple therapy including all three drugs. Risk of hospital admission for bleeding, recurrent myocardial infarction, and death were assessed by Cox proportional hazards models with the drug exposure groups as time-varying covariates.

Findings During a mean follow-up of 476·5 days (SD 142·0), 1891 (4·6%) patients were admitted to hospital with bleeding. The yearly incidence of bleeding was 2·6% for the aspirin group, 4·6% for clopidogrel, 4·3% for vitamin K antagonist, 3·7% for aspirin plus clopidogrel, 5·1% for aspirin plus vitamin K antagonist, 12·3% for clopidogrel plus vitamin K antagonist, and 12·0% for triple therapy. With aspirin as reference, adjusted hazard ratios for bleeding were 1·33 (95% CI 1·11–1·59) for clopidogrel, 1·23 (0·94–1·61) for vitamin K antagonist, 1·47 (1·28–1·69) for aspirin plus clopidogrel, 1·84 (1·51–2·23) for aspirin plus vitamin K antagonist, 3·52 (2·42–5·11) for clopidogrel plus vitamin K antagonist, and 4·05 (3·08–5·33) for triple therapy. Numbers needed to harm were 81·2 for aspirin plus clopidogrel, 45·4 for aspirin plus vitamin K antagonist, 15·2 for clopidogrel plus vitamin K antagonist, and 12·5 for triple therapy. 702 (37·9%) of 1852 patients with non-fatal bleeding had recurrent myocardial infarction or died during the study period compared with 7178 (18·4%) of 38 960 patients without non-fatal bleeding (HR 3·00, 2·75–3·27, $p < 0·0001$).

Interpretation In patients with myocardial infarction, risk of hospital admission for bleeding increased with the number of antithrombotic drugs used. Treatment with triple therapy or dual therapy with clopidogrel plus vitamin K antagonist should be prescribed only after thorough individual risk assessment.

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Introduction

Treatment with aspirin and clopidogrel is recommended after acute myocardial infarction to reduce recurrent ischaemic events.^{1–3} Some patients have an additional indication for treatment with a vitamin K antagonist.⁴ Treatment with multiple antithrombotic drugs after myocardial infarction represents a clinical dilemma because risk of bleeding is exacerbated with combination therapy and longer duration of treatment. Although several studies have reported rates of bleeding,^{5–9} research on antithrombotic drugs has generally focused on improving efficacy rather than safety. Additionally, the safety of several drug combinations has not been investigated in clinical trials. Guidelines for the management of patients with myocardial infarction who also have an indication for

vitamin K antagonists are unclear.^{1,2,4,10} Combination treatment is widely used and some guidelines recommend an untested combination of clopidogrel plus vitamin K antagonist as the preferred option for patients with myocardial infarction who are treated with an intracoronary stent.^{4,10} Since bleeding episodes in patients with myocardial infarction are associated with increased morbidity and mortality,^{11,12} the use of undocumented treatment combinations raises concerns.

We undertook a nationwide study of 40 812 unselected patients treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists after myocardial infarction to examine the risk of non-fatal and fatal bleeding in a real-life setting and to identify the safest combinations of antithrombotic drugs.

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	All patients (n=40 812)	Monotherapy			Dual therapy			Triple therapy
		Aspirin alone (n=18 763)	Clopidogrel alone (n=7250)	Vitamin K antagonist alone (n=1320)	Aspirin plus clopidogrel (n=12 219)	Aspirin plus vitamin K antagonist (n=749)	Clopidogrel plus vitamin K antagonist (n=196)	Aspirin, clopidogrel, and vitamin K antagonist (n=315)
Inclusion date*								
2000–01	12 264 (30%)	8982 (48%)	1173 (16%)	520 (39%)	1215 (10%)	323 (43%)	19 (10%)	32 (10%)
2002–03	14 572 (36%)	6137 (33%)	2621 (36%)	453 (34%)	4900 (40%)	251 (34%)	72 (37%)	138 (44%)
2004–05	13 976 (34%)	3644 (19%)	3456 (48%)	347 (26%)	6104 (50%)	175 (23%)	105 (54%)	145 (46%)
Men	25 721 (63%)	10 853 (58%)	4619 (64%)	791 (60%)	8621 (71%)	470 (63%)	135 (69%)	232 (74%)
Age (men)	65.3 (12.7)	67.7 (13.0)	65.9 (11.7)	70.4 (10.8)	61.4 (12.1)	68.2 (11.3)	67.8 (11.0)	64.0 (11.7)
Age (women)	72.6 (12.7)	75.3 (12.2)	72.1 (11.5)	74.8 (9.6)	66.8 (13.0)	71.3 (12.4)	73.0 (9.8)	67.4 (13.6)
Comorbidity								
Cerebrovascular disease	1841 (5%)	998 (5%)	405 (6%)	158 (12%)	204 (2%)	54 (7%)	14 (7%)	8 (3%)
Diabetes with complication	1853 (5%)	951 (5%)	445 (6%)	84 (6%)	319 (3%)	27 (4%)	14 (7%)	13 (4%)
Cardiac dysrhythmias	4234 (10%)	1908 (10%)	645 (9%)	598 (45%)	631 (5%)	271 (36%)	69 (35%)	112 (36%)
Acute renal failure	295 (1%)	164 (1%)	70 (1%)	23 (2%)	28 (<1%)	8 (1%)	0	2 (1%)
Chronic renal failure	457 (1%)	235 (1%)	113 (2%)	41 (3%)	58 (<1%)	6 (1%)	1 (1%)	3 (1%)
Malignant disease	958 (2%)	587 (3%)	152 (2%)	38 (3%)	166 (1%)	8 (1%)	5 (3%)	2 (1%)
Shock	341 (1%)	180 (1%)	57 (1%)	25 (2%)	62 (1%)	10 (1%)	1 (1%)	6 (2%)
Pulmonary oedema	388 (1%)	230 (1%)	63 (1%)	26 (2%)	59 (<1%)	7 (1%)	3 (2%)	0
Previous bleeding	1846 (5%)	1055 (6%)	335 (5%)	109 (8%)	298 (2%)	24 (3%)	10 (5%)	15 (5%)
PCI	15 082 (37%)	1507 (8%)	4045 (56%)	68 (5%)	9017 (74%)	73 (10%)	119 (61%)	253 (80%)
Concomitant medical treatment†								
β blockers	32 963 (81%)	14 177 (76%)	5900 (81%)	876 (66%)	10 955 (90%)	615 (82%)	157 (80%)	283 (90%)
ARBs	19 425 (48%)	8045 (43%)	3701 (51%)	704 (53%)	6109 (50%)	504 (67%)	133 (68%)	229 (73%)
Statins	27 793 (68%)	9591 (51%)	5802 (80%)	626 (47%)	10 897 (89%)	462 (62%)	149 (76%)	266 (84%)
Loop diuretics	15 686 (38%)	8676 (46%)	2585 (36%)	847 (64%)	2805 (23%)	490 (65%)	120 (61%)	163 (52%)
Glucose-lowering drugs	4948 (12%)	2396 (13%)	1146 (16%)	207 (16%)	1055 (9%)	77 (10%)	37 (19%)	30 (10%)
NSAIDs	4026 (10%)	2030 (11%)	719 (10%)	88 (7%)	1116 (9%)	45 (6%)	11 (6%)	17 (5%)
Proton-pump inhibitors	7784 (19%)	3600 (19%)	1643 (23%)	266 (20%)	2030 (17%)	133 (18%)	41 (21%)	71 (23%)

Data are n (%) or mean (SD). PCI=percutaneous coronary intervention. *Date of discharge from hospital after admission for first myocardial infarction. †The following ATC codes were used: clopidogrel B01AC04; aspirin B01AC06 and N02BA01; vitamin K antagonist B01AA; β blockers C07; angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers (ARBs) C09; statins C10AA; loop diuretics C03C; glucose-lowering therapy A10; non-steroidal anti-inflammatory drugs (NSAIDs) M01A; and proton-pump inhibitors A02BC.

Table 1: Baseline characteristics by first drug exposure group

Methods

Study population

Four nationwide administrative registers were linked on an individual level and used in this study: (1) the Danish National Patient Register, which holds information about all admissions to Danish hospitals since 1978 with diagnoses coded according to the International Classification of Diseases (ICD)-8 and ICD-10; (2) the Danish Register of Medicinal Product Statistics (the national prescription register), which contains information about all prescriptions dispensed in Danish pharmacies since 1995 (date of dispensing, strength, and number of tablets); (3) the civil register, which contains information about vital status of all citizens; and (4) the register of causes of death, which contains the ICD-10 codes for causes of death. Registry studies do not require ethical approval in Denmark. The study was approved by the Danish Data Protection Agency (reference 2003-54-1269).

We used the Danish National Patient Register to identify patients aged 30 years or older who had been admitted to hospital with first-time myocardial infarction (ICD-10 code I21 or I22) between 2000 and 2005. Patients were eligible for inclusion if they had claimed a prescription of aspirin, clopidogrel, or vitamin K antagonist within 90 days of discharge from hospital. Inclusion date was the day of hospital discharge. Patients who had emigrated or had invalid dates of death were ineligible. Presence of comorbidity was established according to the modified Ontario acute myocardial infarction mortality prediction rules by identifying discharge diagnoses (ICD-10 codes) during the year before hospital admission.¹³ Because the registers have a low sensitivity for diagnosis of heart failure,¹⁴ we used prescriptions of loop diuretics that were claimed 90 days before hospital admission until 90 days after hospital discharge as a proxy for heart failure.¹⁵ Patients who claimed prescriptions for glucose-lowering drugs were

	Aspirin alone (n=18763)	Clopidogrel alone (n=7250)	Vitamin K antagonist alone (n=1320)	Aspirin plus clopidogrel (n=12 219)	Aspirin plus vitamin K antagonist (n=749)	Vitamin K antagonist plus clopidogrel (n=196)	Triple therapy (n=315)	Total*
Aspirin alone	..	5613	0	11 630	0	0	0	36 006
Clopidogrel alone	1472	..	0	5268	0	0	0	13 990
Vitamin K antagonist alone	1100	537	..	550	584	153	219	4463
Aspirin plus clopidogrel	3485	4632	0	..	0	0	0	20 336
Aspirin plus vitamin K antagonist	1360	553	846	648	..	142	301	4599
Vitamin K antagonist plus clopidogrel	103	291	106	163	44	..	134	1037
Triple therapy	177	254	118	352	115	118	..	1449

*Total number of patients to have claimed prescriptions for each regimen.

Table 2: Subsequent drug exposure groups by first drug exposure group

	Treatment (days, mean [SD])	Time on treatment/ observed time (days, mean [SD])	Duration in treatment group (person-years)	Number of non-fatal and fatal bleeding events*	Proportion of non-fatal and fatal bleeding events (%)†	Time to non-fatal or fatal bleeding event (days, mean [SD])‡	Incidence (% per person-year)	Unadjusted risk ratio (95% CI)	Number needed to harm§	
									Unadjusted	Adjusted¶
Monotherapy										
Aspirin alone	284 (187)	0.59 (0.34)	27 113.0	709	37.5%	220 (161)	2.6%	Reference	Reference	Reference
Clopidogrel alone	96 (111)	0.21 (0.24)	3443.6	158	8.4%	169 (147)	4.6%	1.75 (1.75-1.76)	50.8	115.7
Vitamin K antagonist alone	161 (165)	0.34 (0.32)	1403.3	60	3.2%	275 (162)	4.3%	1.63 (1.62-1.65)	60.2	165.9
Dual therapy										
Aspirin plus clopidogrel	211 (152)	0.44 (0.30)	11 253.7	421	22.3%	181 (141)	3.7%	1.43 (1.43-1.43)	89.3	81.2
Aspirin plus vitamin K antagonist	270 (171)	0.55 (0.31)	2614.4	133	7.0%	243 (151)	5.1%	1.94 (1.94-1.95)	40.5	45.4
Clopidogrel plus vitamin K antagonist	108 (121)	0.24 (0.26)	244.6	30	1.6%	193 (146)	12.3%	4.68 (4.64-4.74)	10.4	15.2
Triple therapy										
Aspirin, clopidogrel, and vitamin K antagonist	155 (140)	0.33 (0.28)	509.5	61	3.2%	178 (139)	12.0%	4.57 (4.55-4.61)	10.7	12.5

*Number of bleeding events occurring during the different treatment regimens. Bleeding events outside these periods (ie, between different treatment periods) are not listed. †(Number of bleeding events in an exposure group÷1891)×100. ‡Time from claiming prescription to hospital admission with bleeding. §Number of patients needed to be treated for 1 year to cause one fatal or non-fatal bleeding. ¶Adjusted for year of admission (in groups of 2 years), age-group, sex, comorbidity, concomitant medical treatment, and percutaneous coronary intervention status.

Table 3: Comparison of antithrombotic drug exposure groups

deemed to have diabetes. Patients were classified with percutaneous coronary intervention (PCI) according to the Danish health-care classification system codes KFNG02 and KFNG05 if a PCI was done within 30 days after discharge from hospital. A previous bleeding was defined as admission to hospital with a diagnosis of bleeding (ICD-10 codes listed below) during the 5-year period before the first myocardial infarction.

We used the national prescription register to identify use of antithrombotic and concomitant drugs. Baseline use was recorded if a prescription was dispensed within 90 days after discharge from hospital; however, for statins, the period was 180 days.¹⁵ Use of loop diuretics and glucose-lowering therapy was identified as previously

described. Claimed prescriptions of aspirin, clopidogrel, or vitamin K antagonists starting at discharge were used to classify patients to one or more of the following drug regimen groups: monotherapy with aspirin, clopidogrel, or vitamin K antagonist; dual therapy with aspirin plus clopidogrel, aspirin plus vitamin K antagonist, or clopidogrel plus vitamin K antagonist; or triple therapy including all three drugs. Duration and doses of treatment were calculated individually.¹⁵ For most patients, treatment regimens changed during the study period. The drug exposure groups were therefore created as time-varying covariates. Patients were allowed in only one drug exposure group at a time, but could change groups during the study period according to claimed prescriptions.

	Non-fatal bleeding (n=1852)	Fatal bleeding (n=115)
Cerebral	152 (8.2%)	35 (30.4%)
Gastrointestinal	733 (39.6%)	34 (29.6%)
Respiratory tract	220 (11.9%)	1 (0.9%)
Urogenital	282 (15.2%)	2 (1.7%)
Treatment for femoral pseudoaneurysm	39 (2.1%)	39 (33.9%)
Anaemia caused by bleeding	426 (23.0%)	4 (3.5%)

Data are n (%).

Table 4: Distribution of non-fatal and fatal bleeding events

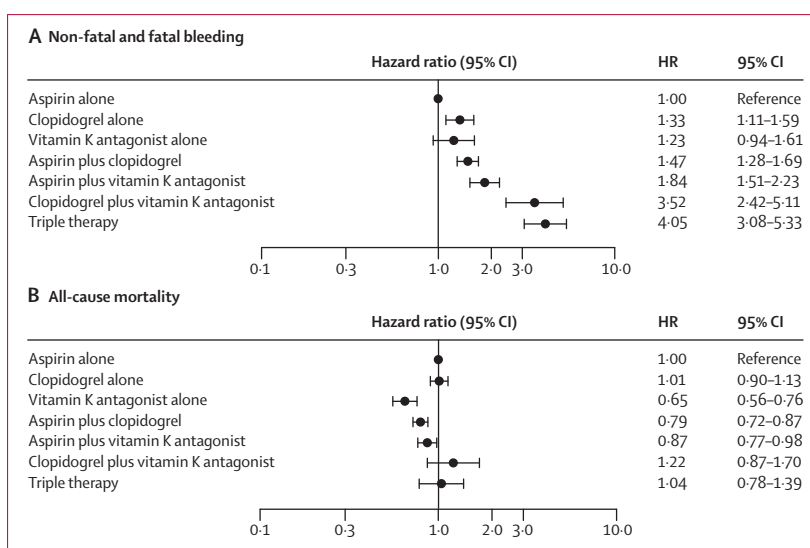


Figure: Adjusted risk of non-fatal and fatal bleeding and all-cause mortality in patients treated with antithrombotic drugs after first myocardial infarction

HR=hazard ratio. Aspirin monotherapy is used as the reference. The Cox proportional hazard models were adjusted for year of admission (in groups of 2 years), age-group, sex, comorbidity (cerebrovascular disease, diabetes with complication, cardiac dysrhythmias, acute renal failure, chronic renal failure, malignant disease, shock, pulmonary oedema), concomitant medical treatment (β blockers, angiotensin-converting enzyme inhibitors plus angiotensin-II receptor blockers, statins, loop diuretics, glucose-lowering drugs, non-steroidal anti-inflammatory drugs, proton-pump inhibitors), and treatment with percutaneous coronary intervention.

Of the antithrombotic drugs examined, aspirin was the only drug that could be bought over-the-counter. Patients on chronic aspirin treatment, however, usually receive aspirin on prescription in order to receive financial reimbursement. This occurrence is substantiated by the high use of aspirin seen in this study. We only included aspirin claimed by prescriptions in our analysis.

Outcome measures

A bleeding endpoint was defined as an admission to a Danish hospital with a diagnosis of non-fatal bleeding (primary or secondary) or a diagnosis of bleeding as the cause of death (fatal bleeding). The following ICD-10 codes were used: cerebral bleeding I60-62, S06.4-06.6; bleeding from the respiratory tract J94.2, R04; gastrointestinal bleeding K25.0, K25.2, K25.4, K26.0, K26.2, K26.4, K27.0, K27.2, K28.0, K28.2, K92.0-92.2; bleeding from the urinary tract R31; and anaemia from acute or chronic bleeding D62, D50. We recorded patients

treated for bleeding complications in relation to a PCI procedure if the patient underwent PCI within 14 days before the bleeding event (coded as KPEG80 and KPEG10 by the Danish health-care classification system codes). In addition to the bleeding endpoints, we analysed the effect of non-fatal bleeding on the combined risk of recurrent myocardial infarction or death.

Statistical analysis

Baseline variables for each antithrombotic regimen group are presented as percentages, or means with SDs, referring to the patients' first exposure group. Incidence rates, risk ratios, and numbers needed to harm were assessed (adjusted and unadjusted).¹⁶ We analysed adjusted risks of non-fatal bleeding, fatal bleeding, all bleeding (patients were censored at first event), and all-cause mortality by use of Cox proportional hazards models with the drug exposure groups as time-varying covariates. This model implies that patients were only deemed at risk for each exposure group while taking the corresponding antithrombotic drugs. Aspirin monotherapy was used as reference since aspirin is recommended as lifelong treatment for patients with ischaemic heart disease. The analyses were adjusted for year of admission (in groups of 2 years), age-group, sex, comorbidity, concomitant medical treatment, and PCI status. The models were tested for absence of interactions and found to be valid. The risk of recurrent myocardial infarction or death was analysed in a separate Cox model in which non-fatal bleeding was included as a time-varying variable; patients were counted in the non-bleeding group until the date of bleeding and thereafter included in the bleeding group. The model was adjusted for the year of admission, age-group, comorbidity, concomitant cardiovascular drugs, PCI status, and antithrombotic treatment (dichotomous variables). Patients were censored after 18 months; patients included after July 1, 2005, were followed until Dec 31, 2006. Statistical analyses were done with SAS version 9.1.4.

Role of the funding source

The sponsor of the study had no role in study design, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 40812 patients who were admitted to hospital with first-time myocardial infarction in Denmark during 2000-05, and who claimed a prescription of aspirin, clopidogrel, or a vitamin K antagonist within 90 days of hospital discharge. Table 1 shows the baseline characteristics of patients by first drug exposure group. See webappendix p 1 for baseline characteristics of patients according to PCI status.

See Online for webappendix

Several patients changed treatment regimen, and therefore drug exposure group, during the study period (table 2). Table 3 shows mean duration of treatment, ratio between days on treatment and observation time, and total duration of exposure (person-years) for each drug regimen.

During a mean follow-up of 476.5 days (SD 142.0), 1852 (4.5%) patients were admitted to hospital with non-fatal bleeding. The number of events of non-fatal bleeding increased during the study period (log-rank, $p < 0.0001$). We identified 115 (0.3%) events of fatal bleeding; this number did not change during the study period (log-rank, $p = 0.61$). Mean time from claiming a prescription of an antithrombotic treatment to occurrence of a bleeding event varied from 169 days (SD 147) for clopidogrel monotherapy to 275 days (162) for monotherapy with a vitamin K antagonist (table 3). Most non-fatal bleeding events were gastrointestinal, whereas most fatal bleeding events were associated with treatment for femoral pseudoaneurysm (table 4).

The unadjusted incidence of non-fatal and fatal bleeding was lowest in the aspirin monotherapy group (2.6% per year) and highest in the clopidogrel plus vitamin K antagonist (12.3% per year) and triple therapy (12.0% per year) groups. The adjusted numbers needed to harm were substantially lower for dual therapy with clopidogrel plus vitamin K antagonist and for triple therapy than they were for the other drug regimens (table 3).

The figure shows the results of the Cox analyses for the combined endpoint of non-fatal and fatal bleeding and for all-cause mortality. Compared with aspirin alone, all antithrombotic exposure groups were associated with an increased risk of non-fatal and fatal bleeding, apart from monotherapy with vitamin K antagonists (adjusted HR 1.23, 95% CI 0.94–1.61). Increased risk was proportional to the number of drugs used. However, the risk of non-fatal and fatal bleeding associated with dual therapy with clopidogrel plus vitamin K antagonist (HR 3.52, 2.42–5.11) was only slightly lower than the risk associated with triple therapy (HR 4.05, 3.08–5.33). Similar HRs were obtained in a separate model that analysed the risk of non-fatal bleeding alone (data not shown). In a model analysing fatal bleedings alone, we found reduced risk for fatal bleeding with clopidogrel monotherapy (HR 0.12, 0.02–0.85) and increased risk associated with clopidogrel plus vitamin K antagonist treatment (HR 5.37, 1.87–15.5; data not shown). Risk of all-cause mortality was not increased in any of the antithrombotic exposure groups compared with aspirin monotherapy.

Table 5 shows the effect of patient characteristics on risk of bleeding. Increased risk of bleeding was associated with previous bleeding, older age, diabetes, and heart failure.

702 (37.9%) of 1852 patients with non-fatal bleeding had recurrent myocardial infarction or died during the study period compared with 7178 (18.4%) of 38960 patients

without non-fatal bleeding (HR 3.00, 2.75–3.27, $p < 0.0001$).

Table 6 shows the results of the sensitivity analyses. HRs for non-fatal or fatal bleeding when patients were analysed according to the first regimen they received, or when patients with or without PCI were analysed separately, were similar to the HRs seen in the main analysis. We undertook two stratified propensity analyses: the first included the propensity for bleeding and the second included the propensity for first treatment with aspirin plus clopidogrel. Again, the results were consistent with those in the main analysis.

Discussion

We examined the association between occurrence of non-fatal and fatal bleeding and treatment with combinations of aspirin, clopidogrel, and vitamin K antagonists in a nationwide cohort of patients with first-time myocardial infarction. All drug combinations were associated with an increased risk of hospital admission for non-fatal and fatal bleeding, apart from monotherapy with a vitamin K antagonist. Increased risk of bleeding

	No bleeding (n=38 921)	Bleeding (n=1891)	Hazard ratio (95% CI)*
Sex			
Women	14 391 (37.0%)	700 (37.0%)	Reference
Men	24 530 (63.0%)	1191 (63.0%)	1.33 (1.21–1.47)
Age (years)			
<60	11 016 (28.3%)	224 (11.8%)	Reference
60–69	9 406 (24.2%)	326 (17.2%)	1.47 (1.24–1.74)
70–79	10 300 (26.5%)	387 (20.5%)	2.49 (2.13–2.92)
≥80	8 199 (21.1%)	654 (34.6%)	2.81 (2.37–3.35)
Comorbidity			
Cerebrovascular disease	1 708 (4.4%)	133 (7.0%)	1.12 (0.94–1.34)
Diabetes with complication	1 729 (4.4%)	124 (6.6%)	1.03 (0.83–1.27)
Cardiac dysrhythmias	3 949 (10.1%)	285 (15.1%)	0.93 (0.81–1.07)
Acute renal failure	267 (0.7%)	28 (1.5%)	1.26 (0.85–1.87)
Chronic renal failure	410 (1.1%)	47 (2.5%)	1.35 (0.99–1.83)
Malignant disease	876 (2.3%)	82 (4.3%)	1.52 (1.22–1.90)
Shock	319 (0.8%)	22 (1.2%)	0.94 (0.61–1.43)
Pulmonary oedema	363 (0.9%)	25 (1.3%)	0.89 (0.60–1.33)
Previous bleeding	1 575 (4.0%)	271 (14.3%)	2.46 (2.15–2.81)
PCI	14 532 (37.3%)	550 (29.1%)	0.88 (0.78–0.99)
Concomitant medical treatment			
β blockers	31 515 (81.0%)	1 448 (76.6%)	0.99 (0.89–1.11)
ARBs	19 425 (47.4%)	703 (37.2%)	1.03 (0.94–1.13)
Statins	26 722 (68.7%)	1 071 (56.6%)	0.72 (0.64–0.81)
Loop diuretics	14 599 (37.5%)	1 087 (57.5%)	1.49 (1.34–1.65)
Glucose-lowering drugs	4 644 (11.9%)	304 (16.1%)	1.21 (1.05–1.40)
NSAIDs†	3 780 (9.7%)	246 (13.0%)	1.34 (1.17–1.54)
Proton-pump inhibitors	7 112 (18.3%)	672 (35.5%)	1.87 (1.69–2.06)

PCI=percutaneous coronary intervention. ARBs=angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers. NSAIDs=non-steroidal anti-inflammatory drugs. *Hazard ratios from the Cox proportional hazard model for non-fatal and fatal bleeding.

Table 5: Effect of patient baseline characteristics on risk of bleeding

	Cox proportional hazard model			Propensity score	
	First drug regimen only	Patients with PCI*	Patients without PCI*	Stratified for bleeding†	Stratified for aspirin plus clopidogrel‡
Aspirin alone	Reference	Reference	Reference	Reference	Reference
Clopidogrel alone	1.12 (0.87–1.42)	1.42 (1.02–1.98)	1.27 (1.01–1.60)	1.29 (1.15–1.40)	1.32 (1.10–1.58)
Vitamin K antagonist alone	0.94 (0.64–1.36)	1.95 (0.94–4.05)	1.16 (0.87–1.55)	1.23 (0.94–1.61)	1.22 (0.93–1.60)
Aspirin plus clopidogrel	1.26 (1.04–1.54)	1.52 (1.16–1.99)	1.48 (1.24–1.76)	1.42 (1.24–1.63)	1.47 (1.28–1.69)
Aspirin plus vitamin K antagonist	2.50 (1.81–3.45)	1.58 (0.95–2.64)	1.87 (1.52–2.30)	1.83 (1.51–2.22)	1.82 (1.50–2.20)
Vitamin K antagonist plus clopidogrel	2.47 (1.10–5.55)	3.81 (2.16–6.74)	3.26 (1.94–5.46)	3.41 (2.35–4.95)	3.51 (2.42–5.09)
Triple therapy	3.60 (2.16–6.00)	3.31 (2.13–5.14)	4.90 (3.38–7.10)	3.86 (2.94–5.07)	4.05 (3.08–5.34)

Data are hazard ratios for non-fatal and fatal bleeding (95% CI). PCI=percutaneous coronary intervention. *All treatment periods included. †C statistic=0.71. ‡C statistic=0.84.

Table 6: Sensitivity analyses

was proportional to the number of drugs used. Notably, dual therapy with clopidogrel plus vitamin K antagonist was nearly as hazardous as triple therapy. The risk of the combined endpoint of recurrent myocardial infarction or death was higher in patients with non-fatal bleeding than in patients without non-fatal bleeding.

Several studies have reported frequency of bleeding in patients with acute coronary syndromes who were treated with different antithrombotic drugs. However, these studies have been difficult to compare because of diverse definitions of the bleeding diagnoses.^{5–8,17} Two examples of frequently used definitions of bleeding are measurements of declining haemoglobin concentration and use of blood transfusions.^{9,18,19} However, such information is often missing for bleeding events that occur after hospital discharge. To overcome this drawback, we used a definition that was based on readmission to hospital with a diagnosis of bleeding, since this event constitutes bleeding that is clinically serious enough to warrant hospital admission and therefore gives high specificity. This definition has previously been used,^{17,20} and is a logical choice in countries with complete nationwide registers of all hospital admissions.

Previous studies of bleeding risks have been related to specific antithrombotic regimens. To our knowledge, only two studies have compared incidence of bleeding associated with different combinations of aspirin, clopidogrel, and vitamin K antagonists by use of data for dispensed prescriptions, hospital admissions, and causes of death.^{17,21} The study by Buresly and colleagues¹⁷ included elderly patients with myocardial infarction admitted to hospital between 1996 and 2000, when antithrombotic drugs were used for shorter periods and with limited use of combination therapy. However, the results reported were similar to our findings.

The risk of bleeding associated with treatment with clopidogrel monotherapy has previously been shown to be similar to the risk associated with high-dose aspirin monotherapy.²² By contrast, we found an increased risk of bleeding in patients treated with clopidogrel alone. In Denmark, low-dose aspirin is recommended for all patients with myocardial infarction and this could

account for the differences in risk, since high-dose aspirin is associated with a higher incidence of bleeding than is low-dose aspirin.²³

The efficacy of a combination of aspirin plus clopidogrel has been studied thoroughly in patients with acute coronary syndromes, and some studies have reported rates of bleeding.^{6–8,24,25} The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study showed major and minor bleeding in 3.7% and 5.1% of patients treated with this combination,⁶ with no excess of life-threatening bleeding compared with aspirin alone. In the CURE study, patients were ineligible for inclusion if they were at high risk of bleeding or taking vitamin K antagonists. An observational study of real-life patients meeting the inclusion criteria of the CURE study reported an incidence of life-threatening bleeding that was four times higher than that seen in the CURE trial.⁸ One study of patients with ST-segment elevation myocardial infarction reported that patients assigned to aspirin plus clopidogrel had similar rates of bleeding to those assigned to placebo,²⁴ whereas another showed a higher incidence of minor bleeding in patients assigned to the dual therapy (3.6%) than in patients assigned to aspirin monotherapy (3.1%; $p=0.005$).²⁵ The unadjusted incidence of non-fatal and fatal bleeding in patients treated with aspirin plus clopidogrel recorded in our study (3.7%) is similar to results in two of the cited studies.^{6,25} Correspondingly, we found an increased risk of bleeding associated with aspirin plus clopidogrel compared with aspirin alone. The estimates were similar when patients with or without PCI were analysed separately.

The treatment guidelines for patients with myocardial infarction who have an indication for treatment with a vitamin K antagonist reflect the scarcity of data for this patient population.^{1,2,4,10} For patients treated with a stent, some guidelines recommend dual therapy with clopidogrel plus vitamin K antagonist for 9–12 months,⁴ whereas others recommend triple therapy for a short period depending on the type of stent used.^{1,10} If the patient is at risk of bleeding, clopidogrel plus vitamin K antagonist is recommended.¹⁰ These guidelines result in diverse clinical practices.^{5,9,26,27} The unadjusted incidence

rates of non-fatal and fatal bleeding in patients treated with a vitamin K antagonist alone (4·3% per year) and a vitamin K antagonist plus aspirin (5·1% per year) are similar to findings of a randomised trial of patients with myocardial infarction with a mean age of approximately 60 years.²⁸ Treatment with a vitamin K antagonist alone was not associated with increased risk of bleeding compared with aspirin monotherapy; this finding is supported by results from one trial,²⁹ but opposed by those from another.²⁸ Our result might be accounted for by selection of the patients, since many of the patients taking vitamin K antagonist monotherapy were chronic users, and were therefore taking the drug at the time of their myocardial infarction.

Some small studies have examined dual therapy of vitamin K antagonists with either aspirin or clopidogrel and found similar risks of bleeding associated with both regimens.^{5,9} In our study, risk of non-fatal and fatal bleeding was far higher when vitamin K antagonist was combined with clopidogrel than when combined with aspirin. Indeed, the risk associated with vitamin K antagonist plus clopidogrel was nearly as high as the risk associated with triple therapy. The adjusted numbers needed to harm were substantially lower for dual therapy with clopidogrel plus vitamin K antagonist and for triple therapy than they were for treatment with aspirin plus vitamin K antagonist. Some studies on risk of bleeding associated with triple therapy have found an increased risk,²⁷ whereas others have found an unchanged risk.^{5,9,26} These conflicting results might be attributable to not considering duration of treatment in the analyses.^{5,9,26,27} Our results show a clear association in both unadjusted and adjusted analyses between exposure to triple antithrombotic treatment and increased risk of bleeding.

The wide distribution of times to bleeding indicate that there might be no safe treatment period and bleeding can occur at any time after treatment. A close relation between bleeding episodes and adverse outcomes, including death, stroke, and recurrent myocardial infarction, has previously been reported.^{11,12} The risk of recurrent myocardial infarction or death was substantially higher in patients with a non-fatal bleeding event than in patients without, emphasising the serious nature of bleeding events.

The main strength of our study was the completeness of data, with a nationwide unselected cohort of patients with myocardial infarction followed in a real-life setting and with complete data for dispensed prescriptions. The data in the registers have previously been validated.^{30,31} The main limitations of our study are inherent in its observational nature. We also had no knowledge of the factors affecting the decision by physicians to prescribe different combinations of antithrombotic treatment, although monotherapy or perceived safe combinations of drugs were most likely prescribed to patients judged at increased risk of bleeding. Selection bias would therefore most probably affect our results conservatively. We have not reported the risk of thrombosis because we expect that

patients receiving more than one drug or non-recommended combinations have a higher baseline risk of thrombosis. Additionally, an ischaemic event might occur several months after change of regimen, which makes the time-varying analysis less relevant. We included comorbidity and concomitant drugs in the Cox models to eliminate confounding by these variables, but effect of residual confounding cannot be excluded. To ensure robustness of our findings we applied several sensitivity analyses, all showing consistent results. Furthermore, we had no knowledge of bleeding events occurring outside the hospital, but since these did not lead to admission, it is unlikely that they would have had a major effect on our results.

Thus, in patients with first-time myocardial infarction, all combinations of aspirin, clopidogrel, and vitamin K antagonists are associated with increased risk of non-fatal and fatal bleeding, apart from monotherapy with a vitamin K antagonist, compared with aspirin alone. Increased risk of bleeding was proportional to the number of drugs used. Non-fatal bleeding is an independent predictor associated with increased risk of recurrent myocardial infarction or death. We propose that treatment with triple therapy or dual therapy with clopidogrel plus vitamin K antagonist should be prescribed only after thorough individual risk assessment and careful consideration of the risk–benefit ratio.

Contributors

RS, MLH, SZA, CT-P, and GHG participated in study design and data analysis. RS obtained funding and wrote the report. All authors interpreted the results, revised the report, and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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