

Association of Aspirin Use With Major Bleeding in Patients With and Without Diabetes

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THERAPY WITH LOW-DOSE ASPIRIN is used for the treatment of cardiovascular disease. It is recommended as a secondary prevention measure for individuals with moderate to high risk of cardiovascular events (ie, for patients with multiple risk factors such as hypertension, dyslipidemia, obesity, diabetes, and family history of ischemic heart disease).^{1,2} The American Diabetes Association recommends low-dose aspirin use (75-162 mg/d) for adults with diabetes and no previous history of vascular disease but who have a 10-year risk of cardiovascular disease events greater than 10% and who do not have an increased risk for bleeding.¹

A meta-analysis based on individual patient data demonstrated that the benefits of low-dose aspirin for the primary prevention of cardiovascular disease are modest.³ Any benefit of low-dose aspirin might be offset by the risk of major bleeding.⁴ It is known that aspirin is associated with gastrointestinal and intracranial hemorrhagic com-

Context The benefit of aspirin for the primary prevention of cardiovascular events is relatively small for individuals with and without diabetes. This benefit could easily be offset by the risk of hemorrhage.

Objective To determine the incidence of major gastrointestinal and intracranial bleeding episodes in individuals with and without diabetes taking aspirin.

Design, Setting, and Participants A population-based cohort study, using administrative data from 4.1 million citizens in 12 local health authorities in Puglia, Italy. Individuals with new prescriptions for low-dose aspirin (≤ 300 mg) were identified during the index period from January 1, 2003, to December 31, 2008, and were propensity-matched on a 1-to-1 basis with individuals who did not take aspirin during this period.

Main Outcome Measures Hospitalizations for major gastrointestinal bleeding or cerebral hemorrhage occurring after the initiation of antiplatelet therapy.

Results There were 186 425 individuals being treated with low-dose aspirin and 186 425 matched controls without aspirin use. During a median follow-up of 5.7 years, the overall incidence rate of hemorrhagic events was 5.58 (95% CI, 5.39-5.77) per 1000 person-years for aspirin users and 3.60 (95% CI, 3.48-3.72) per 1000 person-years for those without aspirin use (incidence rate ratio [IRR], 1.55; 95% CI, 1.48-1.63). The use of aspirin was associated with a greater risk of major bleeding in most of the subgroups investigated but not in individuals with diabetes (IRR, 1.09; 95% CI, 0.97-1.22). Irrespective of aspirin use, diabetes was independently associated with an increased risk of major bleeding episodes (IRR, 1.36; 95% CI, 1.28-1.44).

Conclusions In a population-based cohort, aspirin use was significantly associated with an increased risk of major gastrointestinal or cerebral bleeding episodes. Patients with diabetes had a high rate of bleeding that was not independently associated with aspirin use.

JAMA. 2012;307(21):2286-2294

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plications.⁵ However, randomized controlled trials have shown that these risks are relatively small.^{3,6}

Randomized controlled trials evaluate selected patient groups and do not necessarily generalize to an entire population. They are particularly limited when evaluating relatively rare events.⁷ Observational studies suggest an excess of approximately 1 to 2 major bleeding episodes annually for every 1000 patients treated with low doses of

aspirin. The bleeding risk sharply increases in individuals older than 70 years.⁸

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A meta-analysis by the Antithrombotic Trialists' Collaboration³ suggested that diabetes, in addition to being an independent risk factor for cardiovascular disease, also increases the risk of extracranial hemorrhage. These estimates were derived from a limited number of events within randomized trials. Hence, the risk-to-benefit ratio for the use of low-dose aspirin in the presence of diabetes mellitus remains to be clarified. To increase the number of observations, we used administrative data to determine the bleeding rate attributable to prophylactic aspirin use and how it is influenced by the presence of diabetes. The objectives of this study were to estimate the incidence of major bleeding events in individuals with diabetes and in those without diabetes and how these events were affected by aspirin use.

METHODS

We conducted a population-based cohort study, using a record-linkage analysis of hospital discharge records, prescription databases, and the civil registry, including data on 4.1 million citizens in 12 local health authorities in Puglia, Italy.

Data Sources

All Italian citizens have equal access to health care services and are cared for by a general practitioner as part of the National Health System. Hospital and pharmaceutical services are provided free or at a minimum charge. Aspirin for the prevention of cardiovascular events is available to all citizens at high cardiovascular risk only by prescription and is free of charge. Prescription databases provide data on all the community prescriptions reimbursed by the National Health System with drugs coded according to the Anatomical Therapeutic Chemical classification system.⁹

Hospital discharge records cover all the admissions in public and private hospitals and include information on primary diagnoses and up to 5 coexisting conditions, performed procedures (diagnostic and therapeutic in-

terventions), date of hospital admission and discharge, and in-hospital death. All diagnoses are coded according to the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)*.¹⁰

Data sources, such as hospital discharge records and prescription databases, and the reliability of record linkage to produce epidemiological information have been validated and described elsewhere.¹¹⁻¹⁷ All security and protection measures for data from patients were performed according to national law.¹⁸

Study Design

We identified new users of low-dose aspirin (≤ 300 mg) (Anatomical Therapeutic Chemical code B01AC06) during the index period from January 1, 2003, to December 31, 2008. The date of the first filled prescription for aspirin was considered the patient's index date. Patients had to be at least 30 years old on the index date with no prescription for aspirin in the past year. Current low-dose aspirin users were defined as those who had the last prescription of aspirin at least 75 days before hospitalization for major bleeding events or the end of follow-up; this allowed for a tolerance of 15 days between prescriptions, each covering a period of 60 days of treatment. All those individuals who did not receive aspirin throughout the study period were considered controls, and were assigned an index date corresponding to the same year of the cases.

Former aspirin users, who were those who had prescriptions for aspirin at the beginning of follow-up but had their last prescription of aspirin more than 75 days before an event, were excluded from the analyses.

Outcome Variables

The outcomes of interest were hospitalization for major gastrointestinal bleeding (*ICD-9-CM* codes 531-535 and 578.9) or cerebral hemorrhage (*ICD-9-CM* codes 430-432) occurring after the initiation of antiplatelet therapy. All patients were followed up from their in-

dex date to the earliest hospitalization for gastrointestinal or intracranial hemorrhages, death (derived from the civil registry), or the end of the study period, providing a maximum follow-up of 6 years.

Possible Confounding Factors

To control for confounding, drugs considered either to promote or conversely to be protective against bleeding events were taken into account. Patients with diabetes were defined as individuals exposed to antidiabetic agents in the year before the index date together with those that began to be exposed to antidiabetic agents during the follow-up period. To allow a more accurate definition of individuals with diabetes, those treated before cohort entry but with no antidiabetic prescriptions during follow-up were excluded from the cohort. Cases of gestational diabetes (treated with insulin for only a few months) would have been erroneously considered as cases of diabetes.

Individuals were considered as affected by hypertension if they were exposed to at least 3 prescriptions of antihypertensive agents (eg, centrally acting antiadrenergic agents, α -blockers, thiazide-type diuretics, β -blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists) in the previous year with respect to index date. Previous hospitalizations for cardiovascular events during the year prior to the index date also were considered (*ICD-9-CM* codes for myocardial infarction: 410, 786.51, 786.52, 786.50, 36.0, 36.1, 36.2, and 36.3; for ischemic stroke: 434, 436, 38.11, and 38.12).

Current use of the following medications was identified: other antiplatelet agents, anticoagulants, nonselective nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin as an analgesic agent, systemic corticosteroids, selective serotonin reuptake inhibitors (SSRIs), proton pump inhibitors (PPIs), and statins. In line with previous studies,¹⁹ current use was defined as indi-

viduals with a prescription of such drugs in the previous 3 months from an event or the end of follow-up; for PPIs and statins, a period of 6 months was chosen. Models also were adjusted for occurrence of hospitalization for gastrointestinal complications (ICD-9-CM codes 531-535, 556, and 578) during the year prior to the index date.

Statistical Analyses

From the overall sample of 4.1 million individuals, a sample of 598 418 patients receiving low-dose aspirin was identified. Furthermore, individuals younger than 30 years, those with former aspirin use, and those with diabetes without antidiabetic prescriptions during the study period were excluded from the low-dose aspirin cohort, leaving a sample of 241 844 patients. Following the same exclusion criteria, a sample of 845 707 controls (20% of the overall sample of individuals) was selected at random. To allow

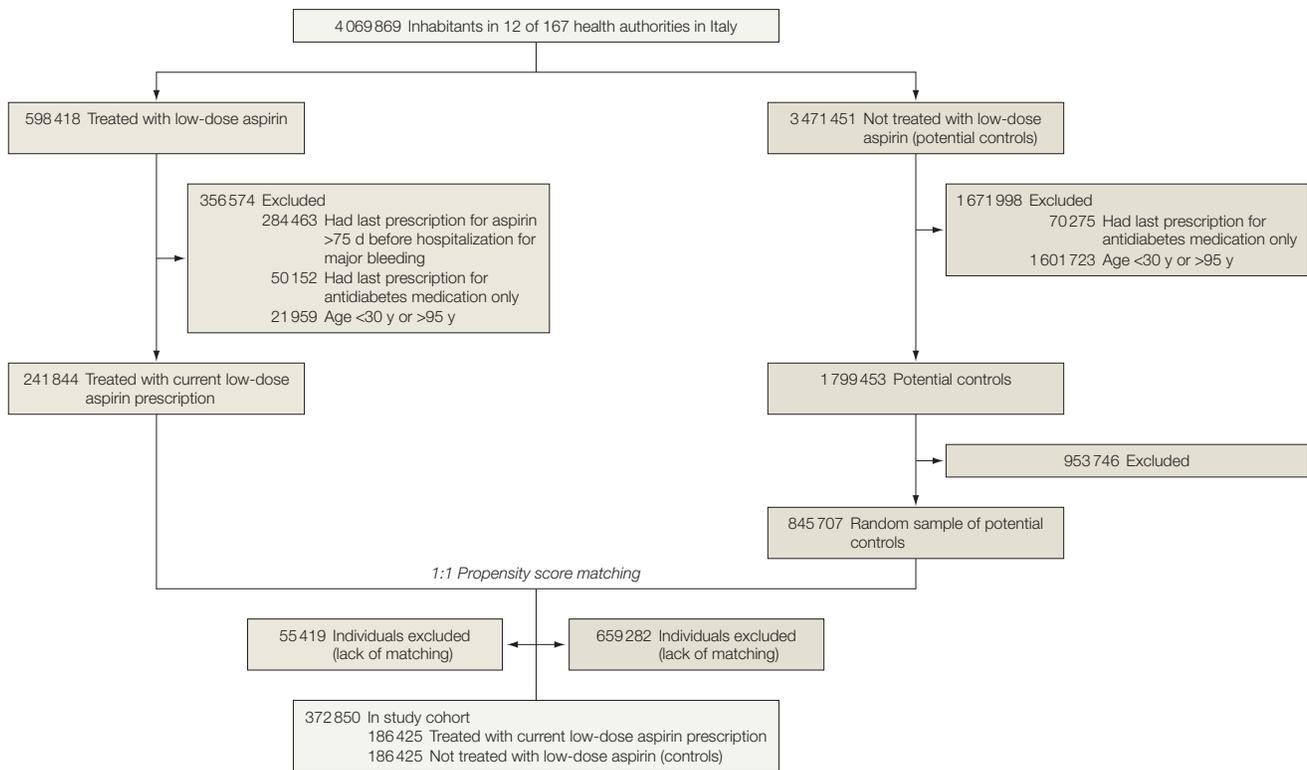
an unbiased comparison between patients currently treated with aspirin and those who never took aspirin, a propensity score–matching algorithm on a 1-to-1 basis was used.^{20,21}

A logistic regression model including age, sex, diabetes, previous hospitalization for cardiovascular disease, use of antihypertensive agents, NSAIDs, PPIs, SSRIs, and statins as covariates was used to predict the probability (propensity score) to receive aspirin. An 8-to-1 greedy matching algorithm²¹ was eventually used to identify a unique matched control for each aspirin-treated patient according to the propensity score. Adequacy of balance for the covariates in the matched sample was assessed via standardized mean difference between the 2 groups, considering differences less than 10% as good balance, as well as graphical methods (ie, quantile-quantile plots, side-by-side box plots, and nonparametric density plots).²²

Characteristics of the study population are reported as percentages, mean

(standard deviation), or median (interquartile range). Incidence rates (IRs) with 95% confidence intervals of hospitalization per 1000 person-years were estimated for both cohorts. Using Poisson regression, we first estimated crude IR ratios (IRRs) of hospitalization in the cohort with aspirin use compared with the cohort who never took aspirin. The IRRs were then adjusted for all the other covariates within multivariate models. The latter included the following covariates: age, sex, exposure to antidiabetic agents, hospitalization for cardiovascular or gastrointestinal problems in the year prior to study entry, or prescription for antihypertensive agents, other antiplatelet agents, anticoagulants, NSAIDs, aspirin as an analgesic agent, systemic corticosteroids, SSRIs, PPIs, or statins. Both individual (gastrointestinal and intracranial bleeding) and composite end points were assessed; in the latter case, the first occurrence of bleeding event was considered.

Figure 1. Screening and Enrollment of Participants in the Study



Risks were reported as IRRs along with their 95% confidence intervals and *P* values. For subgroup analyses according to sample characteristics, *P* values for interaction also were assessed. A sensitivity analysis also was performed after exclusion of ICD-9-CM code 578.9, which was considered less specific for the identification of upper gastrointestinal bleeding. The cumulative proportion of patients developing major bleeding events during follow-up according to diabetes status and use of aspirin was estimated by life table methods and log-rank tests were reported. *P* values were 2-sided, and values of .05 or less were considered statistically significant. All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc).

RESULTS

From the initial cohort of 241 844 individuals with aspirin use, 186 425 were selected using propensity score matching (FIGURE 1). Prematching characteristics widely differed between those with aspirin use and those without aspirin use, but propensity score matching led to a satisfactory balance for all the characteristics considered (eTable at <http://www.jama.com>). The cohort with aspirin use included patients aged 30 to 95 years who had received the first dose of aspirin in the period considered.

Overall, a total of 1.6 million person-years of observation was accumulated with a median follow-up of 5.7 years (interquartile range, 2.4-6.0 years); the mean (SD) age was 69 (12) years and 53% of cases were female, 57% were identified as affected by hypertension, 15% were treated with hypoglycemic agents, 2.0% had experienced a hospitalization for a cardiovascular event, and 0.9% had experienced a hospitalization for gastrointestinal complications. General characteristics of the study population according to aspirin use are reported in TABLE 1.

Risk of Bleeding Associated With Aspirin Use

During 6 years, 6907 first episodes of major bleeding requiring hospitaliza-

tion were registered; of which there were 4487 episodes of gastrointestinal bleeding and 2464 episodes of intracranial hemorrhage (both events were registered on the same date for 44 individuals). The overall IR of total hemorrhagic events was 5.58 (95% CI, 5.39-5.77) per 1000 person-years for those with aspirin use and 3.60 (95% CI, 3.48-3.72) per 1000 person-years for those without aspirin use (IRR, 1.55; 95% CI, 1.48-1.63). In particular, the use of aspirin was associated with an excess risk of gastrointestinal (IRR, 1.55; 95% CI, 1.46-1.65) and intracranial (IRR, 1.54; 95% CI, 1.43-1.67) bleeding.

TABLE 2 shows IRs by aspirin use and their IRRs, according to the different characteristics. Among those without aspirin use, incidence increased

steeply with age. The IRs exceeding the upper limit of the 95% confidence interval for the estimate relative to the whole population were observed in men (IR, 4.50; 95% CI, 4.30-4.70) per 1000 person-years, in individuals with diabetes (IR, 5.35; 95% CI, 4.97-5.76) per 1000 person-years, hypertension (IR, 4.23; 95% CI, 4.06-4.40) per 1000 person-years, previous hospitalization for cardiovascular problems (IR, 5.91; 95% CI, 4.78-7.31) per 1000 person-years or gastrointestinal complications (IR, 12.00; 95% CI, 10.03-14.44) per 1000 person-years, among those treated with other antiplatelet agents (IR, 5.03; 95% CI, 4.55-5.56) per 1000 person-years, anticoagulants (IR, 5.59; 95% CI, 5.10-6.12) per 1000 person-years, systemic corticosteroids (IR, 4.07; 95% CI, 3.65-4.53) per 1000

Table 1. Study Cohort Characteristics

Characteristic	No. (%) of Participants ^a		
	Overall (N = 372 850)	Aspirin Use	
		Never (n = 186 425)	Current (n = 186 425)
Male sex	174 970 (46.93)	85 444 (45.83)	89 526 (48.02)
Age, mean (SD), y	69.37 (11.57)	69.76 (11.29)	68.99 (11.83)
Age group, y			
<50	68 938 (18.49)	34 775 (18.65)	34 163 (18.33)
50-59	122 171 (32.77)	63 542 (34.08)	58 629 (31.45)
60-69	102 071 (27.38)	49 933 (26.78)	52 138 (27.97)
70-79	60 815 (16.31)	31 542 (16.92)	29 273 (15.70)
≥80	18 855 (5.06)	6633 (3.56)	12 222 (6.56)
Previous hospitalization			
Cardiovascular problems	7358 (1.97)	3190 (1.71)	4168 (2.24)
Gastrointestinal problems	3352 (0.90)	2107 (1.13)	1245 (0.67)
Medication use			
Antidiabetic agents	56 118 (15.05)	27 066 (14.52)	29 052 (15.58)
Antihypertensive agents	212 743 (57.06)	109 172 (58.56)	103 571 (55.56)
Other antiplatelet agents	20 218 (5.42)	14 879 (7.98)	5339 (2.86)
Aspirin as analgesic agent	480 (0.13)	258 (0.14)	222 (0.12)
NSAIDs	129 816 (34.82)	67 245 (36.07)	62 571 (33.56)
Oral anticoagulants	25 831 (6.93)	17 046 (9.14)	8785 (4.71)
Systemic corticosteroids	32 803 (8.80)	18 595 (9.97)	14 208 (7.62)
PPIs	169 700 (45.51)	85 184 (45.69)	84 516 (45.34)
SSRIs	18 920 (5.07)	9428 (5.06)	9492 (5.09)
Statins	91 841 (24.63)	43 924 (23.56)	47 917 (25.70)
Events, No.			
Major bleeding	6907	3369	3538
Gastrointestinal bleeding	4487	2193	2294
Intracranial hemorrhage	2464	1197	1267

Abbreviations: NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

^aUnless otherwise indicated.

person-years, PPIs (IR, 4.09; 95% CI, 3.90-4.28) per 1000 person-years, SSRIs (IR, 4.09; 95% CI, 3.90-4.28) per 1000 person-years, and among those not treated with statins (IR, 4.08; 95% CI, 3.93-4.22) per 1000 person-years.

The use of aspirin was associated with a greater risk of bleeding in most of the subgroups evaluated. Significant interactions were detected between the magnitude of risk conferred by aspirin and sex, age, presence of diabetes, hypertension, previous hospital-

ization for cardiovascular or gastrointestinal problems, and use of several concomitant treatments including anticoagulants and PPIs.

The risk of bleeding associated with the use of aspirin was particularly high in individuals younger than 50 years

Table 2. Incidence Rates of Major Bleeding Events and Relative Incidence Rate Ratios by Sample Characteristics

Subgroups	Aspirin Use, Incidence Rate per 1000 Person-Years (95% CI)		Incidence Rate Ratio (95% CI)	P Value for Interaction
	Never	Current		
Entire sample	3.60 (3.48-3.72)	5.58 (5.39-5.77)	1.55 (1.48-1.63)	NA
Sex				
Male	4.50 (4.30-4.70)	6.42 (6.14-6.72)	1.43 (1.34-1.52)	.001
Female	2.86 (2.72-3.01)	4.79 (4.55-5.04)	1.67 (1.56-1.80)	
Age group, y				
<50	0.61 (0.41-0.91)	1.93 (1.52-2.45)	3.17 (1.99-5.05)	.009
50-59	1.40 (1.24-1.58)	2.48 (2.19-2.82)	1.77 (1.49-2.11)	
60-69	2.58 (2.40-2.77)	3.94 (3.66-4.24)	1.53 (1.38-1.69)	
70-79	4.61 (4.39-4.85)	6.87 (6.52-7.25)	1.49 (1.38-1.60)	
≥80	6.93 (6.51-7.38)	10.60 (9.91-11.23)	1.52 (1.39-1.66)	
Diabetes				
No	3.32 (3.20-3.45)	5.53 (5.33-5.74)	1.66 (1.58-1.75)	<.001
Yes	5.35 (4.97-5.76)	5.83 (5.36-6.33)	1.09 (0.97-1.22)	
Hypertension				
No	2.74 (2.59-2.90)	5.42 (5.14-5.72)	1.98 (1.83-2.14)	<.001
Yes	4.23 (4.06-4.40)	5.69 (5.44-5.94)	1.34 (1.27-1.43)	
Previous hospitalization for cardiovascular problems				
No	3.56 (3.44-3.68)	5.57 (5.39-5.77)	1.56 (1.49-1.64)	.003
Yes	5.91 (4.78-7.31)	5.76 (4.56-7.26)	0.97 (0.71-1.33)	
Previous hospitalization for gastrointestinal problems				
No	3.51 (3.40-3.63)	5.52 (5.34-5.71)	1.57 (1.50-1.65)	.06
Yes	12.00 (10.03-14.44)	14.00 (10.70-18.24)	1.16 (0.84-1.60)	
Use of other antiplatelet agents				
No	3.48 (3.36-3.60)	5.48 (5.29-5.67)	1.58 (1.50-1.66)	.12
Yes	5.03 (4.55-5.56)	9.30 (7.90-10.94)	1.85 (1.53-2.24)	
Use of aspirin as analgesic agent				
No	3.60 (3.48-3.72)	5.57 (5.39-5.76)	1.55 (1.48-1.62)	.21
Yes	3.25 (1.05-10.07)	11.40 (5.45-24.00)	3.52 (0.91-13.62)	
Use of NSAIDs				
No	3.55 (3.40-3.70)	5.58 (5.35-5.82)	1.57 (1.48-1.67)	.43
Yes	3.68 (3.49-3.89)	5.57 (5.26-5.89)	1.51 (1.40-1.64)	
Use of oral anticoagulants				
No	3.41 (3.29-3.53)	5.51 (5.32-5.70)	1.61 (1.54-1.70)	.007
Yes	5.59 (5.10-6.12)	7.09 (6.15-8.17)	1.27 (1.07-1.50)	
Use of systemic corticosteroids				
No	3.55 (3.43-3.68)	5.58 (5.39-5.78)	1.57 (1.49-1.65)	.10
Yes	4.07 (3.65-4.53)	5.52 (4.86-6.28)	1.36 (1.15-1.61)	
Use of PPIs				
No	3.21 (3.06-3.36)	6.67 (6.40-6.95)	2.08 (1.95-2.21)	<.001
Yes	4.09 (3.90-4.28)	4.24 (4.01-4.50)	1.04 (0.96-1.12)	
Use of SSRIs				
No	3.61 (3.49-3.73)	5.54 (5.35-5.74)	1.54 (1.46-1.61)	.12
Yes	4.09 (3.90-4.28)	4.24 (4.01-4.50)	1.04 (0.96-1.12)	
Use of statins				
No	4.08 (3.93-4.22)	6.42 (6.19-6.67)	1.58 (1.50-1.66)	.95
Yes	2.20 (2.02-2.39)	3.45 (3.18-3.74)	1.57 (1.40-1.76)	

Abbreviations: NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

(IR, 3.17; 95% CI, 1.99-5.05) per 1000 person-years, in individuals not treated for hypertension, and in those treated with aspirin as an analgesic (statistical significance was not reached). On the other hand, the presence of diabetes, a previous hospitalization for cardiovascular events or gastrointestinal problems, or treatment with PPIs or SSRIs were not associated with an increased hemorrhagic risk.

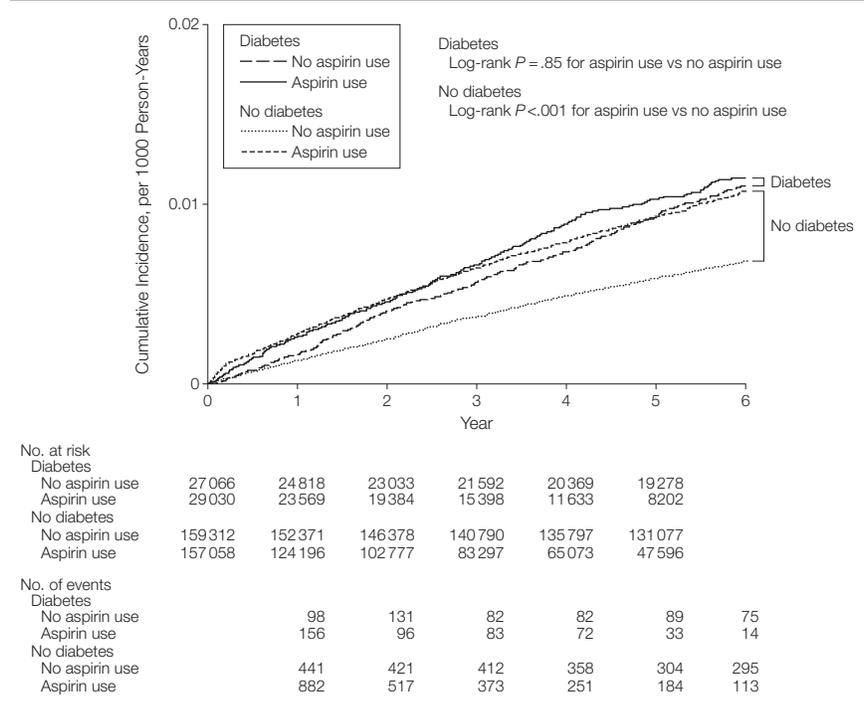
As an additional analysis, we evaluated the risk of bleeding associated with the use of aspirin when administered in combination with other antiplatelet agents and/or anticoagulants. Compared with those without aspirin use, the risk was 2.6 times higher in individuals treated with aspirin and other antiplatelet agents (IRR, 2.56; 95% CI, 2.15-3.04), 2 times higher when aspirin was administered in association with anticoagulants (IRR, 1.92; 95% CI, 1.65-2.24), and almost 3 times higher when all 3 classes were administered in concomitance (IRR, 2.89; 95% CI, 1.71-4.88).

Risk of Bleeding Associated With Diabetes

The cumulative IR of major bleeding according to the presence of diabetes and use of aspirin is reported in FIGURE 2. The baseline risk of bleeding in the absence of aspirin therapy was higher among individuals with diabetes than those without diabetes, whereas the use of aspirin was associated with a higher bleeding risk only among individuals without diabetes.

Among individuals not taking aspirin, the IR of major bleeding was 3.32 (95% CI, 3.20-3.45) per 1000 person-years in those without diabetes and 5.35 (95% CI, 4.97-5.76) per 1000 person-years for those with diabetes (IRR, 1.61; 95% CI, 1.49-1.75). Individuals with diabetes had an increased risk of 59% for gastrointestinal bleeding (IRR, 1.59; 95% CI, 1.45-1.79) and 64% for intracranial bleeding (IRR, 1.64; 95% CI, 1.43-1.89). Further adjustment for other covariates within multivariate Poisson regression models confirmed that diabetes was associated with an excess risk

Figure 2. Cumulative Proportion of Patients Developing Major Bleeding Events During Follow-up According to Diabetes Status and Aspirin Use



In the cohort with diabetes, there were 704 major bleeding events in 131 535 person-years for the no aspirin use group (incidence rate [IR], 5.35; 95% CI, 4.97-5.76) and 549 events in 94 232 person-years for the aspirin use group (IR, 5.83; 95% CI, 5.36-6.33). In the cohort without diabetes, there were 2821 major bleeding events in 848 631 person-years for the no aspirin use group (IR, 3.32; 95% CI, 3.20-3.45) and 2818 events in 509 565 person-years for the aspirin use group (IR, 5.53; 95% CI, 5.33-5.74).

of major bleeding (IRR, 1.58; 95% CI, 1.46-1.72), gastrointestinal bleeding (IRR, 1.61; 95% CI, 1.45-1.78), and intracranial bleeding (IRR, 1.54; 95% CI, 1.34-1.77).

Among aspirin users, the IR of major bleeding was 5.53 (95% CI, 5.33-5.74) per 1000 person-years in those without diabetes and 5.83 (95% CI, 5.36-6.33) per 1000 person-years for those with diabetes (IRR, 1.05; 95% CI, 0.96-1.15). Similar estimates were found for both gastrointestinal bleeding (IRR, 1.08; 95% CI, 0.97-1.21) and intracranial bleeding (IRR, 1.01; 95% CI, 0.86-1.18). Further adjustment for other covariates within multivariate Poisson regression models showed that diabetes was associated with a small excess risk of major bleeding (IRR, 1.13; 95% CI, 1.03-1.24) and gastrointestinal bleeding (IRR, 1.15; 95% CI, 1.03-1.29), and a nonsignificant increased

risk of intracranial bleeding (IRR, 1.11; 95% CI, 0.95-1.30).

The sensitivity analyses performed after the exclusion of the less-specific ICD-9-CM code 578.9 increased the risk estimate associated with the use of aspirin. In fact, the IRRs for those with aspirin use vs those without aspirin use were 1.62 (95% CI, 1.53-1.70) for the whole sample, 1.73 (95% CI, 1.63-1.84) for individuals without diabetes, and 1.15 (95% CI, 1.01-1.30) for individuals with diabetes.

Other Factors Associated With the Risk of Bleeding

In addition to aspirin use and the presence of diabetes, the risk of bleeding increased with age and was higher in men, individuals treated with antihypertensive agents, NSAIDs, other antiplatelet and antithrombotic agents, and in those with previous hospitalization for

gastrointestinal and cardiovascular problems. Furthermore, the use of PPIs and statins was associated with a reduction in the risk of hemorrhagic events (TABLE 3).

Of note, the use of statins was associated with a significant reduction of both gastrointestinal (IRR, 0.65; 95% CI, 0.60-0.71) and intracranial (IRR, 0.69; 95% CI, 0.64-0.74) bleeding. The introduction of the aspirin \times diabetes interaction term in the model yielded a statistically significant result ($P < .001$), thus confirming a differential bleeding risk associated with aspirin use and diabetes.

COMMENT

This study provides information for the evaluation of the risk-benefit balance of aspirin use in a real-world setting. Our study demonstrated that the incidence of major bleeding events is much higher than that recorded in randomized, prospective clinical trials. Data from the meta-analysis by the Anti-thrombotic Trialists' Collaboration³ reported an IR of major gastrointestinal and other extracranial bleeding of 0.10% per year in patients treated with aspirin and 0.07% in those not treated with aspirin in a population with a comparable age range (ie, 19-94 years). In

comparison with these estimates, we found a 5-time higher incidence of major bleeding leading to hospitalization among both aspirin users and those without aspirin use.

In line with existing evidence,^{3,23} the use of aspirin was associated with a 55% relative risk increase in major bleeding; this translates to 2 excess cases for 1000 patients treated per year. In other words, the excess number of major bleeding events associated with the use of aspirin is of the same magnitude of the number of major cardiovascular events avoided in the primary prevention setting for individuals with a 10-year risk of between 10% and 20%.³

The increase in the risk of hemorrhages associated with the use of aspirin was present in the majority of subgroups evaluated; the exceptions were patients with diabetes and those previously admitted to the hospital for gastrointestinal or cardiovascular problems. In the latter 2 subgroups, the lack of excess risk of bleeding can at least partially be attributable to the concomitant use of PPIs in line with existing recommendations,²⁴ whereas diabetes deserves additional consideration.

To our knowledge, this is the first longitudinal study that specifically examined the role of diabetes in the incidence of major bleeding in a cohort of individuals, irrespective of the use of aspirin. In a systematic review, Feigin et al²⁵ reported a protective effect of diabetes on the incidence of subarachnoid hemorrhages; the authors justified this unexpected finding by pointing out the high risk of death from other causes in the population with diabetes and therefore the chance of developing such hemorrhages was smaller than in individuals without diabetes.

A case-control study in Japan reported similar results showing that diabetes decreased the risk of subarachnoid hemorrhage in older women.²⁶ As for gastrointestinal bleeding, a British case-control study on patients with bleeding peptic ulcers indicated that diabetes was associated with an increased relative risk for this condition

Table 3. Factors Associated With Hospitalization for Major Bleeding Events From Multivariate Analysis

	No. of Events	Person-Years	Incidence Rate (95% CI)	Incidence Rate Ratio (95% CI)
Age	NA	NA	NA	1.05 (1.05-1.05)
Sex				
Female	3044	852 958	3.57 (3.44-3.70)	1 [Reference]
Male	3848	731 006	5.26 (5.10-5.43)	1.69 (1.61-1.79)
Aspirin use				
Never	3525	980 166	3.60 (3.48-3.72)	1 [Reference]
Current	3367	603 797	5.58 (5.39-5.77)	1.61 (1.54-1.69)
Diabetes				
No	5639	1 358 196	4.15 (4.04-4.26)	1 [Reference]
Yes	1253	225 767	5.55 (5.25-5.87)	1.36 (1.28-1.44)
Use of antihypertensive agents				
No	2524	671 690	3.76 (3.61-3.91)	1 [Reference]
Yes	4368	912 273	4.79 (4.65-4.93)	1.14 (1.08-1.19)
Previous hospitalization for cardiovascular problems				
No	6736	1 557 250	4.33 (4.22-4.43)	1 [Reference]
Yes	156	26 713	5.84 (4.99-6.83)	1.29 (1.10-1.51)
Previous hospitalization for gastrointestinal problems				
No	6722	1 570 458	4.28 (4.18-4.38)	1 [Reference]
Yes	170	13 505	12.60 (10.83-14.63)	2.87 (2.46-3.35)
Use of other antiplatelet agents				
No	6363	1 492 032	4.26 (4.16-4.37)	1 [Reference]
Yes	529	91 931	5.75 (5.28-6.27)	1.42 (1.29-1.56)
Use of NSAIDs				
No	4415	1 020 188	4.33 (4.20-4.46)	1 [Reference]
Yes	2477	563 775	4.39 (4.22-4.57)	1.10 (1.05-1.16)
Use of oral anticoagulants				
No	6237	1 473 858	4.23 (4.13-4.34)	1 [Reference]
Yes	655	110 105	5.95 (5.51-6.42)	1.31 (1.21-1.43)
Use of PPIs				
No	3960	876 914	4.52 (4.38-4.66)	1 [Reference]
Yes	2932	707 049	4.15 (4.00-4.30)	0.84 (0.80-0.88)
Use of statins				
No	5750	1 162 005	4.95 (4.82-5.08)	1 [Reference]
Yes	1142	421 958	2.71 (2.55-2.87)	0.67 (0.62-0.71)

Abbreviations: NA, not applicable because data are per year; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor.

(odds ratio [OR], 3.1; 95% CI, 1.2-4.3).²⁷ Possible mechanisms include vascular disease impairing mucosal integrity in diabetes.²⁷

The meta-analysis by the Antithrombotic Trialists' Collaboration reported that some of the risk factors for cardiovascular disease also increase the risk of extracranial hemorrhages, suggesting that those at higher cardiovascular risk are also at higher risk of bleeding. Individuals with diabetes showed a more than 50% increased risk compared with those without diabetes.³

Our study shows, for the first time, to our knowledge, that aspirin therapy only marginally increases the risk of bleeding in individuals with diabetes. These findings were confirmed in multivariate analyses taking into account a number of potential confounders and further reinforced by the highly significant interaction term tested within the multivariate model. These results can represent indirect evidence that the efficacy of aspirin in suppressing platelet function is reduced in this population. An accelerated platelet turnover in diabetes²⁸ could explain the reduced incidence of adverse effects related to aspirin, as well as its limited efficacy in preventing major cardiovascular events.^{1,29}

Our study also provides important information regarding bleeding risk factors other than aspirin use. In line with existing literature, individuals with a previous hospital admission for gastrointestinal problems^{19,30,31} show the highest risk of major bleeding. Increasing age,^{8,19} male sex,^{3,19,32} diabetes,³ hypertension,^{3,25} and previous cardiovascular problems^{3,19} also were confirmed as independent risk factors for major bleeding. As for other medications, the use of both antiplatelet agents or oral anticoagulants was associated with a significant increase in the risk of bleeding, whereas the use of NSAIDs only marginally affected such a risk.

Our data are in line with an Italian population-based study showing an inverse association between an increased consumption of PPIs and reduction of hospitalization for gastro-

intestinal events.³³ However, the cost-effectiveness of PPIs associated with aspirin use needs to be verified. A recent study demonstrated that the addition of a PPI to aspirin is cost-effective only for men at increased risk for gastrointestinal bleeding.³⁴ On the other hand, recent data suggest that use of PPIs might increase the risk of cardiovascular events in patients treated with antiplatelet agents.³⁵⁻³⁷

Another important finding of our study is the substantially lower risk of both gastrointestinal and intracranial hemorrhages associated with the use of statins. As for gastrointestinal bleeding, an apparent protective effect of statins was postulated in a post hoc analysis of the Orbofiban in Patients with Unstable coronary Syndromes—Thrombolysis in Myocardial Infarction 16 (OPUS-TIMI 16) trial.³⁸ In this trial of patients with acute coronary syndromes who were treated with aspirin alone or in combination with orbofiban, the use of statins was associated with a lower risk of major bleeding (OR, 0.71; 95% CI, 0.44-1.14) and total gastrointestinal bleeding (OR, 0.68; 95% CI, 0.45-1.04). Such a protective effect was not confirmed in a population-based case-control study, although a borderline significant protective effect was observed in users of low-dose aspirin (OR, 0.43; 95% CI, 0.18-1.05).³⁹ An increase in systemic prostacyclin and prostaglandin E₂ production by statins has been advocated as the possible protective effect on gastric mucosa.³⁹

The effect of statins on intracranial bleeding is more controversial. A large, randomized trial suggested that statins may increase the risk of intracranial hemorrhage.⁴⁰ More recently, a meta-analysis of published and unpublished data was unable to confirm a significantly increased risk for intracerebral hemorrhage in relation to statins.⁴¹ Our results, based on more than 2000 episodes of intracranial bleeding, strongly suggest a protective effect of statins and call for further investigation in this area.

Our study has limitations. Despite adjustment for a wide range of potential bleeding risk factors, it was not possible to consider variables not routinely captured in the claims database, including lifestyle factors such as obesity, smoking, high alcohol consumption, or use of over-the-counter NSAIDs. Also, we could not take into account over-the-counter aspirin use. Nevertheless, misclassification of exposure status is unlikely because long-term use of aspirin for cardiovascular protection is reimbursed by the national health care system.

In conclusion, weighing the benefits of aspirin therapy against the potential harms is of particular relevance in the primary prevention setting, in which benefits seem to be lower than expected based on results in high-risk populations. In this population-based cohort, aspirin use was significantly associated with an increased risk of major bleeding, but this association was not observed for patients with diabetes. In this respect, diabetes might represent a different population in terms of both expected benefits and risks associated with antiplatelet therapy.

Author Contributions: Dr Nicolucci had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data: De Berardis, Lucisano, Pellegrini, Lepore, Tognoni, Nicolucci.

Drafting of the manuscript: De Berardis, Lucisano, D'Ettorre, Nicolucci.

Critical revision of the manuscript for important intellectual content: Pellegrini, Lepore, Tognoni.

Statistical analysis: De Berardis, Lucisano, Pellegrini, Nicolucci.

Administrative, technical, or material support: D'Ettorre.

Study supervision: Lepore, Tognoni.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Mr D'Ettorre reported receiving consulting fees from Bristol-Myers Squibb. Dr Tognoni reported receiving a research grant from Bayer. Dr Nicolucci reported receiving a research grant and fees for lectures including service on speakers bureaus from Bayer. Ms De Berardis, Messrs Lucisano and Pellegrini, and Dr Lepore did not report any financial disclosures.

Online-Only Material: The eTable is available at <http://www.jama.com>.

Additional Contributions: We thank the Regional Health Agency and the Department of Health of the Puglia Region for the cooperation, general interest, and provision of data.

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