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Incidence and prognosis of first-ever intracerebral hemorrhage on antiplatelet therapy over 10 years in a population-based stroke registry

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The use of antiplatelet therapy (APT) is prevalent among the general population, sometimes without clear indications. We provided updated figures on the incidence and prognosis of first-ever intracerebral hemorrhage occurring on APT (APT-ICH) over 10 years in a population-based stroke registry and investigated the rates of inappropriate APT prescription. We included all cases of first-ever ICH not on anticoagulants from January 2011 to December 2020 in the district of L'Aquila (Southern Italy). Indication to APT was adjudicated according to 2021 European Society of Cardiology (ESC) guidelines for cardiovascular prevention. We included 606 first-ever ICHs, of whom 251 (41.4%) were APT-related. One-hundred-forty-two APT-ICHs (56.6%) occurred in patients without clear indications to APT. While the incidence of non-APT-ICH decreased over time, the incidence of APT-ICH was stable. APT-ICH showed higher 30-day and 1-year case-fatality rates versus non-APT-ICH (44.7% versus 25.6%, 50.6% versus 34.4%; $p < 0.001$). APT intake was independently associated with higher 30-day case-fatality (HR 1.51, 95%CI 1.03–2.14; $p = 0.023$). Our findings suggest that APT-ICH exhibits sustained incidence over time and elevated mortality. Urgent initiatives are needed to enhance adherence to established guidelines for APT use. This effort has the potential to mitigate the risk of ICH and to reduce the associated mortality.

Keywords Intracerebral hemorrhage, Epidemiology, Antiplatelet, Primary cardiovascular prevention, Incidence, Prognosis

Antiplatelet therapy (APT) has been shown to protect against atherothrombosis while increasing the risk of major bleeding[1]. In recent decades, significant efforts have focused on identifying individuals for whom the benefits of APT in preventing a first myocardial infarction or ischemic stroke (primary prevention) outweigh the associated risks of bleeding. Early meta-analyses of primary prevention trials demonstrated that while low-dose aspirin provided modest protection against cardiovascular events, it also increased the risk of major bleeding[2,3]. More recent data show that the number needed to treat with aspirin to prevent one cardiovascular event over 10 years in the general population was 265, comparable to the number needed to cause one major bleeding event (210). Consequently, guidelines recommend low-dose aspirin only for individuals with high cardiovascular risk, where the potential benefits clearly outweigh the risks[4–6].

Despite these recommendations, the evidence-based use of APT for primary prevention of cardiovascular diseases is still far from being consistently applied in clinical practice. A cross-sectional study from the U.S. National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence (PINNACLE) registry revealed that more than 1 in 10 patients were receiving inappropriate aspirin therapy for primary prevention,

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with significant variation across clinical practices[7]. Similarly, a recent Italian study found that inappropriate APT prescription is even more prevalent among acutely hospitalized older adults (> 50%)[8].

Intracerebral hemorrhage (ICH) represents the most feared complication of long-term APT and it has been shown that up to 20–30% of ICHs occur in patients receiving APT[9]. Furthermore, antiplatelet agents could potentially influence the prognosis of ICH by promoting the growth of the hematoma through their inhibitory effects on platelet aggregation and thus raising mortality rates and residual disability[10]. Nevertheless, existing studies have yielded no conclusive evidence regarding the impact of APT on both the occurrence and the prognosis of ICH, particularly in terms of disability and mortality. Prior meta-analyses indicated a higher case-fatality in patients with APT-ICH compared to non-APT-ICH[9–11], though functional outcomes appeared comparable[11]. However, recent cohort studies have failed to confirm these associations[12,13]. In our study we aimed to provide updated figures on the incidence and prognosis of first-ever ICH occurring on prior APT over 10 years in a population-based stroke registry and to investigate the rates of inappropriate APT prescription.

Methods

Study design and population

Results of the present study were presented according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Our research is part of a prospective, population-based stroke registry conducted within the L'Aquila district (mean catchment population of 298,343 residents). The district is characterized by mountainous terrain and is served by 4 public hospitals, all equipped with around-the-clock access to brain CT scans. Two of these hospitals have specialized neurology departments, and one has a dedicated neurosurgical unit. Medical care within this district is provided free of charge, ensuring easy access to medical services during the acute phase of stroke. The registry adheres to epidemiological standards for studying stroke incidence[14]and has received approval from the Internal Review Board at the University of L'Aquila, under protocol numbers 13/2018 and 57/2019. The registry was conducted in accordance with relevant guidelines/regulations and in accordance with the Declaration of Helsinki. It encompasses all instances of cerebrovascular events occurring within the district, which are regularly reported by local physicians, verified by our research team, and followed up. Patients receive treatment in accordance with routine clinical protocols, as well as national and international guidelines. For our investigation, we specifically recorded cases of intracerebral hemorrhage (ICH) that occurred in the L'Aquila district over a ten-year period, spanning from January 1, 2011, to December 31, 2020. The diagnosis of ICH was confirmed based on the presence of localized neurological deficits accompanied by concurrent evidence of intraparenchymal bleeding as shown in brain imaging[15]. We included only patients experiencing their first-ever ICH, excluding those with a history of previous strokes/TIA and those with hemorrhagic transformations of cerebral infarctions. ICH cases occurring on anticoagulation were excluded when the last intake of anticoagulant occurred within the last 48 h of ICH. Similarly, we excluded patients with primary subdural or epidural hematomas, traumatic ICH, or hemorrhage related to a tumor were also excluded.

Case-finding procedures

We monitored both inpatient and outpatient healthcare services to detect any ICH event. All cases were initially recognized by a senior physician within 7 days of symptoms onset and subsequently verified by a consulting neurologist. Admission and discharge records were also examined, as well as records from emergency, neuroradiology, neurophysiology, and neurosonology services. Additionally, we conducted a thorough review of patient records that exhibited symptoms potentially indicative of differential diagnoses, including transient ischemic attack (TIA), dizziness, vertigo, confusion, seizures, headaches, and transient global amnesia. We extended our surveillance to encompass neighboring hospitals, rehabilitation centers, and long-term care facilities. On a monthly basis, we scrutinized death certificates, and we included clinical data for all patients who died with an ICH diagnosis, whether their information was not already included in the registry. Comprehensive identification and follow-up was ensured by hot and cold pursuit.

Data collection and follow-up

Demographic and clinical information was systematically collected by reviewing medical records and securely stored in a computerized database in a completely anonymous form, by utilizing Research Electronic Data Capture (REDCap). We recorded data regarding medical history, cardiovascular and neurological assessments. Additionally, we assessed the clinical severity at the onset of ICH using the National Institutes of Health Stroke Scale (NIHSS) score. Furthermore, we evaluated disability or dependence in daily activities by means of the modified Rankin scale (mRS) score. Specifically, we adjudicated the mRS score both prior to the occurrence of the index event and at the time of discharge, with the latter evaluation separately reported for the overall population and for those who survived at discharge. All outcomes were assessed by the treating physician without blinding to APT status. Definitions of vascular risk factors are detailed in **Supplemental Table 1**.

The diagnosis of ICH was confirmed through non-contrast computed tomography (NCCT) scans of the brain at the time of inclusion. We retrospectively assessed the volume and location of the ICH based on the initial available brain NCCT. ICH volumes were estimated by a single operator using the ABC/2 method[16]. ICH location was categorized according to the anatomical site as lobar, deep, infratentorial (brainstem or cerebellum) or mixed (i.e., very large ICH extending into both lobar and non-lobar areas). Any conflict was resolved through consensus before starting the primary analyses. Hematoma expansion was adjudicated retrospectively when ICH volume increased ≥ 6 ml from the first to the second available brain NCCT[17].

APT use

APT-ICH was defined as an ICH occurring in patients on single or dual treatment with aspirin, clopidogrel, ticlopidine, or dipyridamole. We included only patients who developed ICH within 96 h of the last APT intake, based on the maximum time required to recover a normal platelet function after discontinuing aspirin[18].

Based on the adherence to the 2021 European Society of Cardiology (ESC) guidelines for cardiovascular prevention in clinical practice[6], **(Supplemental Table 2)** we categorized patients with APT-ICH into two groups: recommended (R-) and not recommended (NR-) APT. R-APT-ICH was defined if any of the following conditions were met: (1) a history of prior myocardial infarction or revascularization; (2) symptomatic lower extremity artery disease; (3) diabetes mellitus and a high risk of ASCVD. Given that our data collection did not encompass laboratory results, including cholesterol levels, we were unable to calculate the 10-year risk of ASCVD. Therefore, we determined that APT was appropriate for individuals with diabetes mellitus if they presented with at least two of the following conditions: age ≥ 65 years, hypertension, dyslipidemia, current cigarette smoking, or a history of heart failure. Lastly, since we included only first-ever strokes, there were no cases on APT for the secondary prevention of ischemic stroke or TIA.

Statistical analysis

We provided an analysis of the global incidence rate based on catchment population for non-APT and APT-ICH and its trend over the 10-year observation period. To assess the incidence trend and determine confidence intervals (CIs) for the incidence rates, we employed Poisson regression analysis. The Incidence Rate Ratios (IRRs) were calculated based on a Poisson distribution, under the assumption of constant event-rates. We provided separate figures for patients with NR-APT-ICH. Descriptive statistics are provided in terms of absolute numbers with accompanying percentages or as mean values ± standard deviation (SD), as appropriate. Continuous and categorical variables were compared using either the Wilcoxon test or the Pearson 2 test, respectively. We established a two-sided statistical significance level at $P < 0.05$.

We reported 30-day and 1-year case-fatality rates as numbers and percentages with associated confidence intervals (CIs). The overall survival following the index event was estimated using Kaplan-Meier curves, and differences between various groups were assessed using the log-rank test. Univariate estimates of hazard ratios for factors influencing the 30-day and 1-year case-fatality rates were calculated using Cox regression analysis, which included age, sex, risk factors, APT intake, ICH volume and location, intraventricular expansion. Subsequently, we performed a multivariate Cox regression analysis including variables with statistical significance < 0.05 to identify independent predictors of 30-day and 1-year case-fatality in the overall population.

To address missing data in risk factors, we cross-referenced patients' treatment records to enhance data completeness. For Cox regression analyses involving continuous variables, missing values were imputed using the median of the respective variables, where applicable, to maintain consistency in the analyses.

All statistical analyses were performed using R software, version 4.2.

Results

From January 1, 2011, to December 31, 2020, we identified 748 first-ever ICH of whom 142 were excluded because occurring on anticoagulation. Among 606 patients with non-anticoagulants-related ICH, 251 (41.4%) were APT-ICH. (Fig. 1) All patients were hospitalized, and hospitalization settings did not differ across subgroups.

Patients' characteristics

As compared to patients with non-APT-ICH, those with APT-ICH were significantly older (79.7 ± 9.5 versus 70.4 ± 15.3 years, $p < 0.001$ Table 1).

Compared to people in non-APT ICH, those with APT-ICH had higher baseline median NIHSS scores (12, IQR 6–20 versus 9, IQR 9–15; $p = 0.014$) and higher median ICH volume at the first brain NCCT scan (13.6 ml, IQR 3.5–36.3 ml versus 6.2, IQR 1.5–23.6 ml, respectively; $p < 0.001$; Table 1). No differences emerged in ICH location, (Table 1) but APT-ICH group had a marginally more frequent lobar presentation (43.0% versus 37.0%; $p = 0.219$) and intraventricular extension (36.3% versus 27.9%; $p = 0.051$) compared to the non-APT-ICH group. (Table 1)

A second brain NCCT was performed in 70.9% and 70.4% with APT-ICH and non-APT-ICH, respectively, after a median time of 1 (IQR 0–1) days from admission ($p = 0.786$). Patients with APT-ICH had a significantly higher frequency of hematoma expansion at the second brain NCCT than those with non-APT-ICH (35.5% versus 20.8%; $p = 0.001$).

Incidence

The crude annual incidence rate per 100,000 person-years of APT-ICH in the 2011–2020 period was 8.4 (95% CI 7.4–9.5), based on a total population of 2,983,430 person-years. Whilst we observed a significant decrease in the annual incidence of non-APT-ICH over time (P for trend = 0.001), there was an overall stable trend in the annual incidence of APT-ICH (P for trend = 0.173). (Fig. 2, **Supplemental Table 3)** Incidence rates of APT-ICH increased with age in both women and men, as well as in the overall population, and become comparable to that of non-APT-ICH in patients aged ≥ 65 years. **(Supplemental Table 4)** Of note, we found a higher annual incidence rate of APT-ICH in women compared to males in the age group 65–74 years. **(Supplemental Table 5).**

Outcomes

Patients with APT-ICH exhibited a significantly higher 30-day and 1-year mortality than those with non-APT-ICH (44.7% versus 25.6% and 50.6% versus 34.4%, respectively; both $p < 0.001$). The distribution of death causes was similar between the two groups ($p = 0.919$ and $p = 0.391$, respectively). (Table 2) Overall, 30-day mortality did not change over time in both patients with APT-ICH and non-APT-ICH. APT-ICH patients

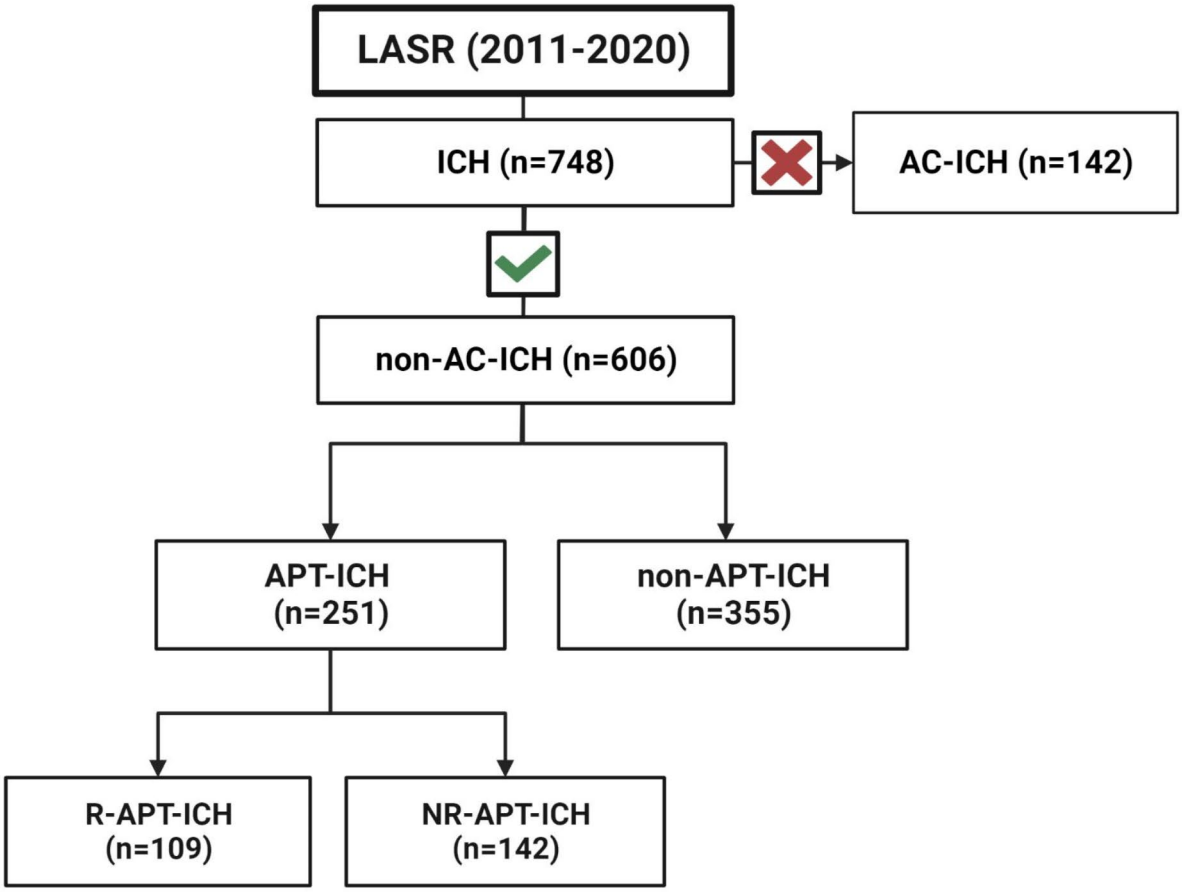

Fig. 1. Study flow-diagram. AC: anticoagulation; APT: antiplatelet; ICH: intracerebral hemorrhage; LASR: L'Aquila Stroke Registry; NR: not recommended; R: recommended.

showed a significant trend toward decreasing 1-year mortality throughout the study period (P for trend = 0.040). (**Supplemental Table 6**) The Kaplan-Meier survival analysis disclosed that most deaths among APT-ICH patients occurred early following ICH; APT-ICH patients showed lower overall survival than non-APT-ICH (log-rank test; $p = 0.016$; Fig. 3). The univariate and multivariate Cox regression analyses showed that the intake of APT (HR 1.51, 95%CI 1.03–2.14; $p = 0.023$), along with increasing age (HR 1.03, 95%CI 1.01–1.05; $p < 0.001$), NIHSS score on admission (1.09, 95%CI 1.06–1.11; $p < 0.001$), infratentorial ICH location (HR 2.44, 95%CI 1.51–3.98; $p < 0.001$) and increasing ICH volume (log HR 2.54, 95%CI 1.43–4.35; $p < 0.001$) were independent predictors of higher 30-day mortality, while APT use did not independently associate with higher 1-year mortality (HR 1.14, 95%CI 0.82–1.59; $p = 0.444$). (Table 3)

R-APT-ICH versus NR-APT-ICH

Within our population, over half of APT-ICH (142/251, 56.6%) occurred in patients who did not meet the ESC 2021 recommendations for the use of APT in cardiovascular prevention (NR-APT-ICH). Baseline characteristics ofR-APT-ICH and NR-APT-ICH patients are reported in **(Supplemental Table 7)**. We found an increasing trend in the incidence of R-APT-ICH (P for trend = 0.028), while the incidence of NR-APT-ICH remained stable throughout the study period (P for trend = 0.925). **Supplemental Table 8**, **Supplemental Fig. 1** Thirty-day and 1-year case-fatality rates were similar betweenR-APT-ICH and NR-APT-ICH patients **Supplemental Tables 9** and the Kaplan-Meier estimates indicated comparable overall survival. **Supplemental Fig. 2**.

Discussion

Our study provides an updated account of the epidemiology and outcomes of APT-ICH over a decade in a well-defined population mostly composed by non-Hispanic white individuals. Around 40% of all ICH occurred in APT users. While the incidence of non-APT-ICH significantly decreased over time, in line with well-known trends, the incidence trend of APT-ICH was stable over the study period. APT-ICH is associated with a worst prognosis in terms of fatalities as compared to those non-APT-ICH. Notably, over half of APT-ICHs occurred in patients who were receiving APT beyond current recommendations for primary or secondary prevention of ASCVD, thus leading to a relevant number of potentially evitable fatalities.

	APT-ICH ($n=251$)	non-APT-ICH ($n=355$)	*P* value
Males, n (%)	138 (55.0)	218 (61.4)	0.134
Age, mean ± SD	79.7 ± 9.5	70.4 ± 15.3	**< 0.001**
Ethnicity, n (%)			0.661
Non-Hispanic White	249 (99.2)	353 (99.4)	
Hispanic White	1 (0.4)	2 (0.6)	
Black	1 (0.4)	0 (0.0)	
Time from symptom onset to hospital arrival, n (%)			0.478
< 1 h	43 (17.1)	49 (13.8)	
1–3 h	65 (25.9)	88 (24.8)	
3–4.5 h	12 (4.8)	18 (5.1)	
>4.5 h	47 (18.7)	82 (23.1)	
Hospitalization setting, n (%)			**0.006**
Stroke Unit	87 (34.7)	116 (32.7)	
Internal Medicine	57 (22.7)	98 (27.6)	
Neurosurgery	41 (16.3)	78 (22.0)	
Intensive Care Unit	41 (16.3)	38 (10.7)	
Other	25 (10.0)	15 (4.2)	
Pre-event mRS, mean ± SD	1.3 ± 1.3	1.1 ± 1.2	**0.019**
NIHSS at ICH onset, median (IQR)	12 (6–20)	9 (5–16)	**0.014**
Risk factors, n (%)			
Arterial hypertension	210 (83.7)	232 (65.4)	**< 0.001**
Dyslipidemia	82 (3.3)	43 (12.1)	**< 0.001**
Diabetes mellitus	65 (25.9)	74 (20.9)	0.174
Atrial fibrillation	11 (4.4)	2 (0.6)	**0.004**
Chronic heart failure	62 (24.7)	57 (16.1)	**0.010**
Lower extremity artery diseases	39 (15.5)	15 (4.2)	**< 0.001**
Obesity	12 (4.8)	29 (8.2)	0.117
Cigarette smoking	17 (6.8)	46 (13.0)	**0.026**
Alcohol abuse	12 (4.8)	23 (6.5)	0.525
Blood pressure on admission, mean ± SD			
SBP	163.5 ± 34.3	166.2 ± 34.6	0.964
DBP	89.3 ± 19.4	92.6 ± 19.6	**0.043**
Ongoing treatment at onset, n (%)			
Lipid lowering drugs	66 (26.3)	28 (7.9)	**< 0.001**
Antihypertensives	177 (70.6)	237 (66.8)	0.373
Ongoing AP at onset, n (%)			
ASA	194 (77.3)	-	
Clopidogrel	31 (12.4)	-	
Ticlopidine	13 (5.2)	-	
Dipyridamole + ASA	2 (8.0)	-	
ASA + Clopidogrel	11 (4.5)	-	
Indication to APT, n (%)*		-	-
Prior myocardial infarction/revascularization	85/251 (33.9)	-	
Symptomatic lower extremity artery disease	39/251 (15.5)	-	
Diabetes mellitus at high risk of ASCVD	62/251 (24.7)	.	
No indication	142/251 (56.6)	-	
ICH volume (ml), median (IQR)			
Baseline brain NCCT	13.6 (3.5–36.3)	6.2 (1.5–23.6)	**< 0.001**
2nd brain NCCT	14.3 (3.8–45.3)	7.8 (2.7–24.6)	**0.002**
Hematoma expansion, n (%)	61/172 (35.5)	52/250 (20.8)	**0.001**
Hemorrhage location, n (%)			0.219
Lobar	108 (43.0)	131 (37.0)	
Deep	89 (35.5)	155 (43.7)	
Infratentorial Mixed	36 (14.3) 18 (7.2)	43 (12.1) 26 (7.3)	
Continued			

	APT-ICH ($n=251$)	non-APT-ICH ($n=355$)	*P* value
Intraventricular extension of ICH, n (%)	91 (36.3)	99 (27.9)	0.051
Acute surgical treatment of ICH, n (%)	15 (6.0)	32 (9.0)	0.194

Table 1. Demographic, clinical and neuroimaging characteristics of patients with APT-ICH versus non-APT-ICH. APT: antiplatelet therapy; ASA: acetylsalicylic acid; ASCVD: atherosclerotic cardiovascular disease; DBP: diastolic blood pressure; ICH: intracerebral hemorrhage; IQR: interquartile range; mRS: modified Rankin scale score; NIHSS: national institute of health stroke scale; SBP: systolic blood pressure; SD: standard deviation; *: according to 2021 European Society of Cardiology guidelines for cardiovascular prevention[6], (patients may have > 1 indication to APT). Statistically significant p-values (< 0.05) are reported in bold.

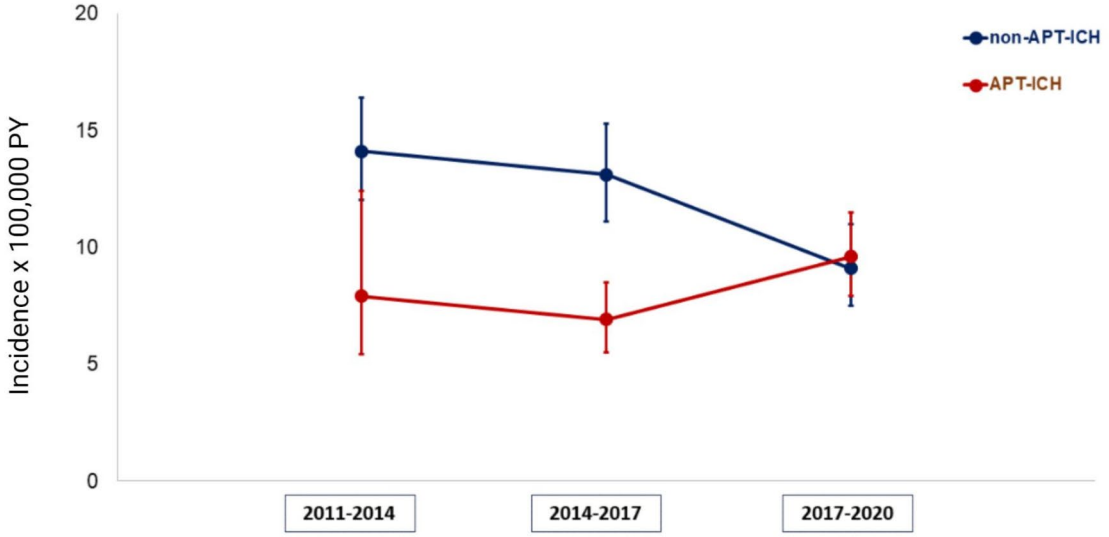

Fig. 2. Incidence trends of APT-ICH and non-APT-ICH, 2011–2020. APT: antiplatelet; ICH: intracerebral hemorrhage; PY: person-years.

	APT-ICH ($n=251$)	Non-APT-ICH ($n=355$)	*P* value
mRS at discharge, mean ± SD			
Overall	4.6 ± 1.7	4.0 ± 1.9	**< 0.001**
Survivors	3.5 ± 1.6	3.2 ± 1.6	0.108
30-day case-fatality rate, n (%)	112 (44.7)	91 (25.6)	**< 0.001**
1-year case-fatality rate, n (%)	127 (50.6)	122 (34.4)	**< 0.001**
30-day causes of death, n (%)			0.919
Fatal hemorrhage	97 (79.5)	77 (84.7)	
Cardiac complications	13 (11.6)	12 (13.2)	
Infections (respiratory tract/urinary)	2 (1.9)	2 (2.1)	
1-year causes of death, n (%)			0.391
Fatal hemorrhage	103 (81.1)	93 (76.2)	
Cardiac complications	18 (14.2)	18 (14.8)	
Infections (respiratory tract/urinary)	6 (4.7)	11 (9.0)	

Table 2. Outcomes of APT-ICH versus non-APT-ICH. APT: antiplatelet; IQR: interquartile range; mRS: modified Rankin scale score; SD: standard deviation. Statistically significant p-values ($p < 0.05$) are reported in bold.

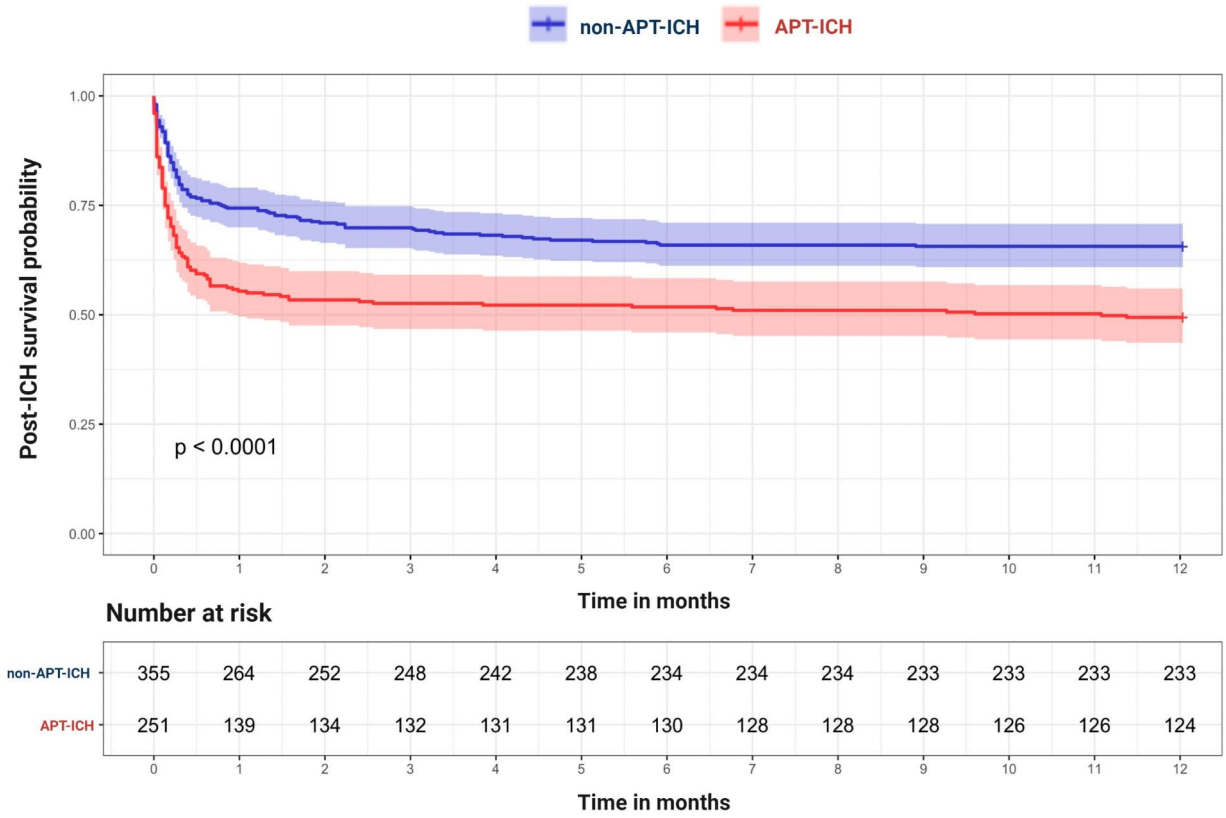

Fig. 3. Kaplan Meier estimates of 1-year survival probability after APT-ICH and non-APT-ICH. APT: antiplatelet; ICH: intracerebral hemorrhage; p: log-rank test p-value. Shaded areas indicate 95% confidence intervals.

	Univariate Cox regression analysis						Multivariate Cox regression analysis					
	30-day			1-year			30-day			1-year		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, per year	1.03	1.02–1.04	**<0.001**	1.03	1.02–1.04	**<0.001**	1.03	1.01–1.05	**<0.001**	1.03	1.02–1.05	**<0.001**
Female sex	2.00	0.91–1.58	0.200	1.33	1.04–1.70	**0.026**	1.22	0.83–1.78	0.316	1.29	0.92–1.79	0.138
NIHSS score, per point	1.10	1.08–1.11	**<0.001**	1.09	1.08–1.10	**<0.001**	1.09	1.06–1.11	**<0.001**	1.08	1.06–1.10	**<0.001**
Arterial hypertension	0.95	0.70–1.29	0.926	1.06	0.79–1.40	0.706	-	-	-	-	-	-
Dyslipidemia	1.19	0.86–1.65	0.308	1.27	0.83–1.52	0.438	-	-	-	-	-	-
Diabetes mellitus	1.01	0.73–1.39	0.977	1.09	0.82–1.46	0.560	-	-	-	-	-	-
Atrial fibrillation	2.51	1.24–5.10	**0.011**	2.10	1.03–4.25	**0.039**	1.17	0.46–2.94	0.742	0.90	0.36–2.22	0.804
Obesity	0.72	0.38–1.37	0.287	0.75	0.42–1.32	0.321	-	-	-	-	-	-
Cigarette smoking	0.54	0.31–0.95	**0.020**	0.49	0.29–0.83	**0.008**	0.94	0.44–2.00	0.869	0.82	0.41–1.62	0.564
Alcohol abuse	1.03	0.57–1.84	0.926	0.89	0.51–1.56	0.687	-	-	-	-	-	-
APT-ICH	2.02	1.53–2.67	**<0.001**	1.75	1.37–2.24	**<0.001**	1.51	1.03–2.14	**0.023**	1.14	0.82–1.59	0.444
ICH volume, per ml (log)	3.78	2.85–5.01	**<0.001**	3.37	2.63–4.31	**<0.001**	2.54	1.43–4.35	**<0.001**	2.26	1.71–5.58	**<0.001**
ICH location – lobar	1	Ref.	-	1	Ref.	-	1	Ref.	-	1	Ref.	-
ICH location – deep	0.65	0.46–0.90	**0.010**	0.67	0.50–0.90	**0.008**	0.75	0.48–1.19	0.219	0.23	0.48–1.07	0.104
ICH location – infratentorial	1.44	0.97–2.13	0.068	1.31	0.90–1.88	0.151	2.44	1.51–3.98	**<0.001**	2.23	1.43–3.49	**<0.001**
ICH location – uncertain	2.06	1.32–3.23	**0.002**	2	1.32–3.02	**<0.001**	1.03	0.51–2.07	0.942	1.03	0.56–1.88	0.931
Intraventricular expansion	2.52	1.91–3.43	**<0.001**	2.55	1.98–3.29	**<0.001**	1.38	0.93–2.03	0.105	1.53	1.09–2.15	**0.014**

Table 3. Univariate Cox regression analysis of 30-day and 1-year case-fatality in the overall population. APT: antiplatelet; GCS: Glasgow Coma Scale; HR: hazard ratio; ICH: intracerebral hemorrhage; NIHSS: National Institutes of Health Stroke Scale; *: according to 2021 European Society of Cardiology guidelines for cardiovascular prevention[6] (only in patients on APT at the time of ICH). Statistically significant p-values ($p < 0.005$) are reported in bold.

Within our study population APT-ICH accounted for 41.4% of all cases. When considering first-ever ICH cases occurring during oral anticoagulation therapy in our registry ($n=142$; Fig. 1), the proportion of APT-ICH in our population sets at 33.6%. This prevalence is at the upper end of the range reported in previous cohort studies (spanning from 17.9 to 36.0%)[9–12,19–22]. The relatively high proportion of patients with APT-ICH in our cohort may be explained by the advanced age of the population in our study area and the high prevalence of comorbidities among our patients. We found a stable trend in the incidence of APT-ICH over time. Conversely, there was a significant decrease in the incidence of non-APT-ICH. We can speculate that substantial improvements in primary preventive practices over the last decades might have reduced the risk of developing ICH in patients not receiving APT. In contrast, the persistence of high ICH incidence in patients on APT might be attributed to several factors. The use of APT may have consistently increased within the general population due to higher life expectancy, which has expanded the older demographic segments within the resident populations in high-income countries[23]. It has been also shown that the inhibitory effects of APT on platelet aggregation might vary depending on genetic and acquired determinants[24]. Hence, the non-linear trend of APT-ICH observed in our population might stem from the complex interplay of all these factors within our population. On the one hand, advancing age and the widespread use of APT agents may be elevating the risk of APT-ICH over time. On the other hand, improved healthcare, and individual susceptibility to bleeding events on APT may also be at play. It is worth noting that while the incidence of APT-ICH increased with age in both sexes, it was significantly higher in women aged 65–84 years compared to males belonging to the same age groups. This sex-related difference may rely on a number of possible explanations including increased vulnerability to ICH due to estrogens decline in women after menopause, different response to antiplatelets, or dissimilarities in lifestyle and behavioral risk factors[25–27].

As regards prognosis, we found significantly higher 30-day and 1-year mortality rates in patients with APT-ICH compared to patients not on APT at the time of ICH. Additionally, ongoing APT was an independent predictor of higher 30-day mortality in our population, along with increasing age, higher clinical severity at ICH presentation, increasing ICH volume and infratentorial ICH location. Prior studies have shown that APT intake is associated with increased inhospital and 90-day mortality[10–12,24]. This worse prognosis has been attributed to different mechanisms such as increased frailty due to older age of APT users[28], early hematoma enlargement[29]and more frequent infratentorial location[10]. In our cohort, we found no significant difference in hematoma location, although patients with APT-ICH showed a slightly higher frequency of lobar ICH compared to those with non-APT-ICH. However, patients on APT had significantly higher baseline hematoma volumes and showed a significantly higher frequency of hematoma expansion. Of interest, while 30-day mortality did not change over time, we found a decreasing trend in 1-year mortality among APT-ICH patients. This finding suggests that current treatment strategies for acute APT-ICH are still relatively ineffective (i.e., for the lack of effective reversal procedures), whereas measures to prevent complications occurring in the chronic phase may have improved over time. Lastly, we found similar mRS scores in APT-ICH and non-APT-ICH patients who survived at discharge, thus confirming observations from prior retrospective studies[12,13,30].

Within our population, we found that over half of patients with APT-ICH were treated beyond recommendations for long-term APT from the 2021 ESC guidelines on cardiovascular prevention[6]. We are aware that, over the study period, there were three updates[4–6]to the ESC guidelines, therefore we cannot exclude that some patients were treated in accordance with recommendations that were in effect at that time. Nevertheless, the very high proportion of APT-ICH patients without clear indication to APT within our cohort point toward a widespread prophylactic use of antiplatelets, which is largely unsupported by the small benefit-risk ratio for the primary prevention of ASCVD. Indeed, in a recent meta-analysis of randomized clinical trials[30], the use of aspirin for primary cardiovascular prevention has been associated with a small reduction in the risk of cardiovascular events (HR 0.89, 95%CI 0.84–0.94). This potential benefit needs to be weighed against a slightly higher increase in the risk of major bleedings (HR 1.43, 95%CI 1.30–1.56)[30]. As a result, the decision to use aspirin for primary prevention should be approached on an individual basis, considering an accurate evaluation of the balance between risk and benefit. Furthermore, the stable incidence of NR-APT-ICH in our cohort may suggest that the selection of patients who are prescribed with long-term APT by treating physicians did not improve over years.

Strengths of our study include the well-defined population of ICH patients and the long-term insight into ICH trends as provided by our 10-year span of investigation. Given the population-based design of our study, we assume that our results can be generalized to the non-Hispanic white population of Western countries. Furthermore, we applied standardized criteria for ICH on a population of 2,983,430 person-years.

Our study also has several limitations. Firstly, it is possible that some cases of ICH were not identified due to early fatalities or a lack of medical attention. However, we addressed these concerns by conducting a thorough search for cases from multiple sources. Secondly, our definition of APT-associated ICH included all patients taking AP drugs within 96 h of the onset of ICH, regardless of their dosage, their actual antiplatelet activity, or other potential factors contributing to ICH. Thirdly, we tried to establish appropriateness of APT use. However, there is not a unique guideline, but several guidelines form different societies with changes over time. To provide a rough estimate we selected the 2021 ESC guideline. We cannot exclude that by applying criteria from other guidelines figures would have been different. Moreover, our dataset did not provide the means for a precise estimation of the 10-year risk of ASCVD in our cohort. Consequently, in patients with diabetes mellitus, the appropriateness of APT was determined based on the presence of additional risk factors. Due to the lack of cardiac imaging data, we were also unable to identify patients on APT who had indication because of asymptomatic coronary artery disease. Therefore, we cannot rule out the possibility that APT was actually appropriate for some of these patients. Fourthly, we cannot rule out the possibility of confounding by indication when comparing outcomes between APT-ICH and non-APT-ICH groups. Specifically, patients prescribed APT likely had worse cardiovascular health than those not on APT, and this underlying difference may have influenced their outcomes

independently of the effects of APT. While we adjusted for various confounders in our multivariate regression model, this inherent difference in health status may not have been fully accounted for, potentially leading to residual confounding in our analysis. Additionally, all outcomes were adjudicated by the treating physician without blinding to APT status, which may have influenced the assessment of certain measures, such as NIHSS and mRS scores. Fifthly, we did not document the percentage of patients who underwent more intensive bundle of care for ICH acute management, nor did we collect data on the withdrawal of life-sustaining treatments. Nevertheless, it is local practice to maintain such treatments until consensus is reached between the treating physician and the patient's caregiver. Lastly, the use of median imputation for missing data in Cox regressions can be considered as a limitation of the study. However, among tested variables, we recorded only a small number of missing values in NIHSS on admission (< 5%).

In conclusion, APT-ICH emerges as a substantial concern within the population, exhibiting a sustained incidence over time, in contrast to the overall decline in ICH rates. Notably, APT-ICH is linked to a considerably elevated mortality rate. In many patients with ICH, the use of APTs is inappropriate. Urgent initiatives are needed to enhance adherence to established guidelines for APT use to mitigate inappropriate use of APT in primary prevention. This effort has the potential to not only mitigate the risk of ICH but also reduce the associated mortality. Furthermore, research is needed to identify safe and effective treatments for arresting bleeding in patients with APT-ICH.

Data availability

The complete dataset used for this study will be shared upon reasonable request from any qualified researcher to the corresponding author.

Received: 5 March 2024; Accepted: 27 November 2024
Published online: 29 November 2024

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Acknowledgements
None.

Author contributions
M.F. and R.O. performed the analyses, drafted the manuscript and created tables and figures. S.S. designed and coordinated the study and revised the manuscript for intellectual content. F.G., M.R., F.D.S., F.C., F.D.S. and B.O. majorly contributed to data retrieval and revised the manuscript for intellectual content. All Authors gave final approval.

Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
the study has obtained approval from the Ethical Committee of the University of L'Aquila (protocol numbers 13/2018 and 57/2019). All subjects gave written informed consent for being included in the study.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-81526-4.

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