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Intracranial bleeding: epidemiology and relationships with antithrombotic treatment in 241 cerebral hemorrhages in Reggio Emilia

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Background and Objectives. Anticoagulant (AC) and antiplatelet (AP) drugs are effectively used in the prevention of thromboembolic events, with the trade-off of bleeding side effects, particularly intracranial. The aim of this study was to determine the incidence of intracranial bleeding in the population of Reggio Emilia and to investigate the potential effect of AC and AP drugs.

Design and Methods. We reviewed all the patients admitted for cerebral hemorrhages to our hospital between April 1998 and September 2000. Data were collected with a standardized form. All the patients were followed-up to estimate long-term mortality. χ^2 and t-tests were used as appropriate. Logistic regression analysis was performed to test predictors of mortality. Pharmaceutical department data were employed to estimate the total number of patients receiving AC and AP drugs.

Results. We found 241 cases (107/134 female/male, mean age 61 years, 133/107 spontaneous/traumatic events, 0.32/1000/year overall). Twenty-nine and 47 of these patients were being given AC or AP drugs, respectively (4.9/1000/year and 3.7/1000/year). The relative risk of intracranial bleeding was 11.5 in AP and 15.3 in AC treated patients. Two patients (one underwent neurosurgery and one thrombolytic treatment) were excluded from mortality and risk factors analysis. Six patients were lost from follow-up and excluded from mortality analysis. Overall mortality was 100/233 (42.9%); mortality in traumatic events was 25/103 (24.2%) versus 75/130 (57.7%) in spontaneous events. Mortality was 19/29 (65.5%), 26/47 (55.3%) and 55/157 (35%) in AC recipients, AP recipients, and untreated patients, respectively. This increased risk was mainly confined to traumatic events ($p = 0.06$), without difference between AC and AP recipients. At the time of the event, the mean duration of oral AC treatment was 26.3 months (range 1-120). Mean INR was = 3.1 (range 1.6-8.8). Mortality was significantly predicted by the Glasgow Coma Scale Score (GCS) at admission ($p < 0.0001$), by the type of bleeding (spontaneous versus traumatic) ($p = 0.0026$), and by age ($p < 0.0001$).

Interpretation and Conclusions. Careful selection of patients and prevention of traumatic events are the main candidate mechanisms to reduce intracranial bleeding in patients being treated with AC and AP drugs.
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Key words: cerebral hemorrhage, anticoagulants, platelet aggregation inhibitors.

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Intracranial bleeding is a serious clinical event because of the high rates of fatality and disability that it causes. Spontaneous cerebral hemorrhage (SCH) must be considered separately from post-traumatic cerebral hemorrhage (TCH) mainly extra or epidural hematoma, subdural hematoma (SDH), subarachnoid hemorrhage (SAH) and cerebral contusion. As the clinical presentation of ischemic atherosclerotic events is similar, the differential diagnosis relies on imaging techniques such as computerized tomography (CT) and nuclear magnetic resonance (NMR).

The rate of SCH is about 0.1-0.2 cases/1,000 population/year in the United States,[1] with a trend for progressive increase correlated to the ageing of the population. SCH represents about 15% of stroke cases. SCH can be divided into primary and secondary events. Primary SCH accounts for about 80% of cases and is mainly due to spontaneous rupture of a small vessel wall already damaged by arterial hypertension or amyloid angiopathy.[2] Secondary SCH is due to disruption of congenital arterio-venous fistulas or aneurysms, neoplasia, or inherited or acquired (iatrogenic) coagulation dis-

orders. Risk factors for primary SCH are arterial hypertension, alcohol abuse,[4] heavy meals, emotional stress,[3] physical exertion, prolonged exposure to sun, and pregnancy. Genetic risk factors such as the mutation for the α subunit of factor XIII or lipoprotein E polymorphisms are under study.[5,6]

Cerebral hemorrhages (CH) can be divided into four major categories: (i) capsular or typical, (ii) intracerebral or atypical localized in the frontal lobe or at the level of the parieto-temporal carrefour, (iii) cerebro-meningeal hemorrhage with blood leakage in the ventricular or subarachnoid space, and (iv) small cerebellar, thalamic, pontine or bulbar bleeding. The presentation of post-traumatic cerebral hemorrhages is different: small frontal and temporal contusive hemorrhages, epidural hemorrhage due to direct trauma with bone fracture and section of the median cerebral artery or one of its branches, and SDH, which can be acute, following violent cranial trauma and generally located on the vault, or chronic, due to microtraumatism, and clinically elusive. About 8% of all cerebrovascular events are due to SAH, either traumatic or spontaneous; in 75% of cases spontaneous events are due to rupture of a cerebral aneurysm.

Considerable clinical interest has been given to the relationship between antiplatelet and antithrombotic treatment and cerebral hemorrhage. Oral anticoagulant therapy is the treatment of choice in primary and secondary prevention of venous thromboembolic disease and arterial thrombotic events in patients with atrial fibrillation and valvular prosthesis.[7] Antiplatelet treatment has been shown to be effective in the prevention of arterial thromboembolic events. However, bleeding complications are relatively frequent, difficult to predict, and limit the net clinical benefit of the treatment. The reported incidence of major bleeding events in patients undergoing antithrombotic treatment is 5-11/1,000 patients/year, while the overall range of hemorrhages is about 62/1,000 patients/year.[8-11] The aim of this study was to evaluate the incidence of cerebral hemorrhage in the district of Reggio Emilia, and to evaluate the relationship between cerebral hemorrhage and antiplatelet or antithrombotic treatment.

Design and Methods

All consecutive cases admitted to the Reggio Emilia hospital between April 1998 and September 2000 with the diagnosis of cerebral hemorrhage were retrospectively evaluated. Recruitment was considered for patients admitted to the emergency room with a diagnosis of CH, or for patients discharged, transferred, or deceased and classified with the Diagnosis Related Groups (DRG) codes 430, 431, 432.0, 432.1, or 432.9.

All the patient were followed-up until death or up to September 2001 through evaluation of emergency room admission, hospitalization, or by phone call to the patient or his primary care physician to assess death and time of death.

Intracranial bleedings were classified by cause as SCH or TCH and by typology as CH, SDH, SAH, or ventricular inundation (VI). All cases were screened for predisposing or causal conditions, i.e. antiplatelet or anticoagulant treatment, vascular malformations, congenital or acquired coagulation disease, arterial hypertension, cerebral neoplasia, diabetes mellitus and hyperlipidemias. The GCS was used to rank the clinical severity of the episode on admission. The population referring to the Emergency Department of the Reggio Emilia District comprises about 300,000 people. The number of patients on antiplatelet or anticoagulant treatment was estimated from the database of the Pharmaceutical department of the district. Half of the patients on oral anticoagulant treatment are followed by the Thrombosis Center of Reggio Emilia, which uses the computer-assisted system PARMA 4 (*Program to Archive, Report and Monitor Anticoagulants* version 4), and the other half by general practitioners, cardiologists or by self-prescription. In both cases a single laboratory, through a network of peripheral venipuncture points, is in charge of determining the patients' *International Normalized Ratio* (INR).[7]

Statistic analysis

The data collected for the study were prepared and analyzed using SPSS for Microsoft Windows (ver 10.1.3). Continuous variables (age, INR, time intervals) were evaluated by the mean and t-test procedures. Categorical variables (CH classifications, comorbidity conditions, sex, etc.) were analyzed using the *Tables procedure*, and the marginal percentages (by row or column) were calculated and shown on the respective tables. The comparisons for categorical variables were performed by the χ^2 test, modified according to Fisher when applicable.

The logistic procedure (stepwise method) was employed to test a multivariate model estimating the probability of death. Standard methods were employed for the recalculation of the probability coefficient.

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Results

Population

Overall, 241 patients (107 females and 134 males) were enrolled in this study. Their mean age was 61 years (range 1-91). The mean age of the males was 57.8 years (range 8-90) and that of the females 65.1 years (range 1-91).

Overall rate of CH in the general population

During the study period 241 cases were enrolled, i.e. about 96 per year. The diagnosis was confirmed by CT scan (Toshiba, Tokio) in 239 patients and by the coroner in the remaining two. For the entire population of 300,000 people, the estimated incidence is 0.32 cases/1,000 population/year.

CH typology

There were 133 (55.1%) cases of SCH and 107 (44.9%) of TCH; one episode followed a neurosurgical procedure. There were seven cases of CH following syncopal episodes with a fall and these were assigned to the SCH or TCH group according to a probability base depending on the dynamics of the event.

The rate for SCH was 0.17 cases/1000 population/year. The number of events in the five predefined categories were: 1) CH =100 (41.5%), 2) SAH = 57 (23.6%), 3) SDH = 27 (11.2%), 4) VI = 26 (10.8%), 5) associated presentation, CH plus SAH = 31 (12.8%); a single episode of epidural hemorrhage was assigned to the SDH group.

Antiplatelet and anticoagulant treatment

Out of the 241 patients enrolled, 27 (11.2%) were on oral anticoagulant therapy (24 on warfarin and 3 on acenocoumarin), 2 on subcutaneous calcium heparin at therapeutic levels, and 47 patients (19.5%) were receiving antiplatelet treatment (40 on acetyl-salicylic acid, 5 on ticlopidine and 2 on indobufen). Two patients (one neurosurgical and one treated with rt-PA for acute myocardial infarction) were excluded from analysis. The remaining 163 (67.7%) patients were not taking any drug active on the coagulation system. In the AC recipients 82% of events were SCH and 18% were TCH: 78% of cases were intracranial (20% of which with VI), 16% SDH and 6% SAH. Sixty-five percent of the SDH events were traumatic. The estimated number of patients in the district of Reggio Emilia on anticoagulant therapy is 2,200/year (7/1,000 in the population) and that on antiplatelet treatment 5,000/year (16/1,000 in the population). Figure 1 shows the relationship between hemorrhage subtypes and therapy.

Congenital or acquired coagulation defects

Of the 163 patients not treated with anticoagulants or antiplatelets, 140 showed a normal laboratory coagulation profile (85.9%), 15 (9.1%) had an isolated thrombocytopenia (platelet count range = 45,000-145,000×1,000 mm^3), 2 patients were found to have disseminated intravascular coagulation, 2 patients an unexplained prolongation of the prothrombin time (PT), 2 of the activated partial thromboplastin time (aPTT) and 1 of both PT and aPTT. One patient was affected by essential thrombocytosis. Six out of the 15 thrombocytopenic patients had chronic liver disease.

Anticoagulant therapy

Twenty-nine patients were on anticoagulant therapy (24 on warfarin, 3 on acenocoumarin and 2 on subcutaneous unfractioned heparin [UFH]). Indications for treatment were: venous thromboembolic disease = 9, atrial fibrillation = 14 (3 of which on secondary prophylaxis for stroke), valvular prosthesis = 6.

The characteristics of the 27 patients who suffered a CH during oral anticoagulant treatment are shown in Table 1. The rate of CH associated with oral anticoagulant therapy was 4.9 cases/1,000 population/year (relative risk = 15.3).

The anticoagulation of 8 (29.6%) of these patients was being managed by the Thrombosis Center in Reggio Emilia, using a computerized-assisted method, while 19 (70.4%) were being managed by general practitioners, cardiologists or by self-administration, using manual methods. One patient was on a combined ASA plus warfarin treatment. The mean duration of oral anticoagulant therapy at the time of the event was 26.3 months (range 1-120). The INR at the event and the mean INR of the three months prior to the event are shown in Table 1.

Mean INR at the time of the event was 3.1 (range 1.6-8.8). INR values at the event and in the three months before were 2.9 vs 3.2 and 2.9 vs 3.1 in the patients treated with computer-assisted and the manual method, respectively. In detail, 2 patients showed an INR < 2, 16 patients showed an INR in the range 2 to 3, 3 patients showed an INR between 3 and 4.5 (within their assigned range), 4 patients showed an INR between 3 and 4.5 (above their assigned range), and two patients showed an INR > 4.5. The mean INR of the previous three months was 3.0 (range 1.9-4.9).

Antiplatelet therapy

Forty-seven patients were on antiplatelet treatment, (40 on ASA, 5 on ticlopidine and 2 on

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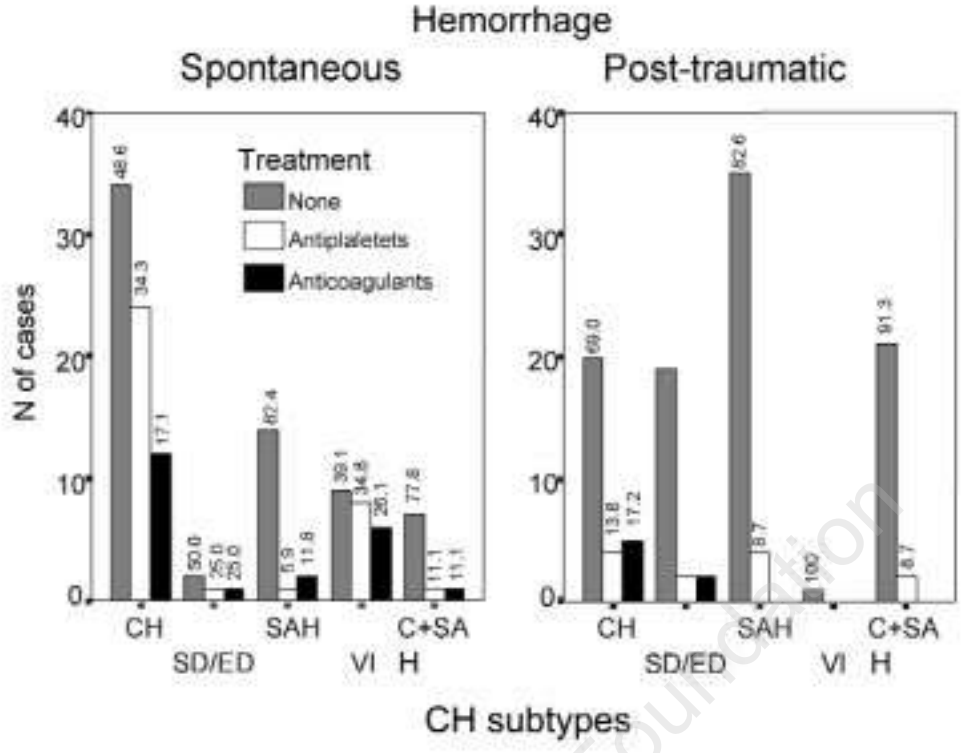

Figure 1. Distribution of the cerebral hemorrhages according to type and treatment. The figure shows separately, for spontaneous (left panel) and post-traumatic (right panel) events, the absolute numbers (column height) and the percentage (intra subtype, numbers on top of column) for each of the subtypes of CH (CH = cerebral hemorrhage, SD / ED = subdural / extradural hematoma, SAH = subarachnoid hemorrhage, VI = ventricular inundation, C+SA = cerebral + subarachnoid hemorrhage) and for the presence / absence / type of anticoagulant treatment (columns gray and black).

indobufen). The estimated rate of CH in antiplatelet-treated patients was 3.7 cases/1,000 population/year (relative risk = 11.5).

Risk factors

The following risk factors were considered in 239 patients: arterial hypertension, diabetes mellitus, hyperlipidemia, primitive or secondary cerebral neoplasia, vascular malformations, comorbidity.

Of the 239 patients, 119 (49.8%) did not show any particular risk factor. Thirty-five patients out of the 132 with SCH (26.5%) and 84 out of the 107 with TCH (78.5%) did not show any particular risk factor. More detailed data are shown in Table 2. Arterial hypertension was found in 28.2% of the patients who had a SCH.

Glasgow coma scale

No significant difference was found between the subgroups of CH. Patients in the TCH group showed a mean value of 11.2, and those in the SCH group 10.4 (p = n.s.). At logistic regression, GCS appeared a strong predictor of mortality ($p < 0.0001$)(Table 3).

Death

The deaths were classified based on the time since the event (within 48 hours, within 30 days and within one year). One hundred patients (42.9%) died, 133 patients were alive at the end of the study period, and 6 were lost from follow-up. In the TCH group, 25/103 (24.2%) patients died and in the SCH group 75/130 (57.7%) did so ($p< 0.0001$); 85% of deaths occurred within 30 days with no difference between the SCH or TCH group. Nineteen of the 29 patients on anticoagulant treatment died (65.5%). Both patients on subcutaneous UFH died. The death rate in patients not on antithrombotic treatment was 55/157 (35.0%), while it was 17/27 (62.9%) and 26/47 (55.3%) in patients treated with anticogulant or antiplatelet agents, respectively (p = ns). The increased risk was mainly confined to traumatic events, for which the difference approached statistical significance ($p = 0.06$), without difference between AC and AP recipients. Detailed data on the distribution of death in rela-

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Table 1. Characteristics of the 27 patients on oral anticoagulant treatment.

	Age	D	HT	INR	pINR	I	Duration (months)	M	Therapy	Outcome
1	73	W	CH/S	2.2	2.4	AF	24	M	K	Death 48 h
2	69	W	VI/S	2.8	3.1	AF	36	M	FFP	Death 48 h
3	64	W	SAH/S	2.6	2.4	PE	3	C	K	Alive
4	79	W	CH/S	2.8	2.7	AF	60	M	K	Death 48 h
5	77	W	CH+SAH/S	2.3	2.5	AF	30	C	FFP	Death 24 h
6	80	W	CH/S	1.7	2.4	VP	120	M	K	Death day 24
7	72	A	CH/S	2.6	2.9	PE	3	M	FFP	Death 48 h
8	86	W	VI/S	2.0	2.4	DVT	11	C	K	Alive
9	65	W	CH/S	8.8	4.9	AF	1	M	FFP	Death day 8
10	84	W	VI/S	2.3	2.4	AF	72	M	K	Death day 30
11	75	W	CH/S	3.4	3.2	AF	1	M	FFP	Alive
12	71	W	CH/S	2.7	3.6	DVT	3	M	FFP	Alive
13	89	A	CH/S	2.9	3.1	DVT	1	C	FFP	Death day 40
14	73	W	CH/T	3.2	3.5	VP	36	C	PC	Alive
15	86	W	CH/S	4.2	3.9	AF	82	M	K	Death day 40
16	71	W	CH/S	1.6	1.9	PE	6	C	K	Death 48 h
17	76	W	CH/S	2.3	2.5	AF	5	M	K	Alive
18	81	W	VI/S	2.7	2.4	AF	41	M	FFP	Death 24 h
19	69	W	CH/T	3.1	3.8	VP	24	C	FFP	Alive
20	81	W	VI/S	2.8	2.9	DVT	3	M	K	Alive
21	83	W	SDH/T	2.9	3.2	VP	97	M	FFP	Death 24 h
22	74	W	VI/S	2.9	3.0	AF	9	M	FFP	Death 24 h
23	74	W	SDH/T	2.6	2.9	DVT	3	M	FFP	Death 6 months
24	71	W	SAH/S	5.4	3.4	AF	1	C	PC	Alive
25	57	W	CH/S	3.5	3.4	AF	6	M	K	Death 24 h
26	74	A	CH/S	3.6	3.3	AF	8	M	K	Death 4 months
27	68	W	CH/S	3.7	3.5	VP	26	M	FFP	Alive

D = Drug (W = warfarin; A = acenocoumarin); HT = hemorrhage type (CH = cerebral hemorrhage; SDH = subdural hematoma; SAH = subarachnoid hemorrhage; VI = ventricular inundation; /S = spontaneous event; /T = traumatic event); INR = INR at the time of the event; p-INR = Mean value of the INR in the three months before the event; I = indication for treatment (AF = atrial fibrillation; PE = pulmonary embolism; DVT = deep venous thrombosis; VP = valvular prosthesis); Duration = time (months) from the beginning of anticoagulant treatment; M = management (M = manual; C = computer assisted); Therapy = therapy of the hemorrhagic event (K = vitamin K1 administration; FFP = fresh frozen plasma; PC = prothrombin concentrates).

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tionship to anticoagulant or antiplatelet treatment are shown in Table 4. The main predictors of mortality at logistic regression analysis were traumatic versus spontaneous events (p = 0.0026), age (p <0.0001) and GCS (p < 0.0001).

Discussion

Intracerebral bleeding is a common and serious clinical emergency. The yearly risk rate for CH in patients treated with oral anticoagulants is 1-2.5 cases/1,000 patients/year.[8-11]

The aim of this retrospective study was to compare the data available in the literature with those assessed in a local population. The retrospective design of the study must be taken carefully into account to give the right weight to the figures and rates of our study. In particular, since we could have lost asymptomatic events and, even worse, fatal events in outpatients, our figure could be an underestimate and should be considered as the lower limit of an undefined range.

Furthermore, as far as concerns AP patients, the total number of treated patients (denominator of the ratio) could have been retrospectively underestimated with the result of even greater uncertainty in the rates. Despite these limitations the data are worth considering and allow some comments.

Incidence rate

The overall rate of CH, and SCH, the percentage of the patients on oral anticoagulant treatment and the rate of association between CH, SDH and SAH are in agreement with those in the literature.[1,12-14]

The increase in the risk of CH in treated patients is not easily explained. One reason could be linked to the higher mean age and comorbidity of the population on therapy. SCH could derive from microvascular abnormalities[15] and the concomitant anticoagulant or antiplatelet treatment could boost an otherwise self-limiting event to clinical relevance. In this category of patients, the CT or NMR finding of leukoaraiosis is considered to be a risk factor for CH.[14-16] The risk of CH we found

Table 2. Distribution of risk factors according to type of hemorrhage (A) and antithrombotic treatment (B).

	N°of pts	*No risk factor*	*Diabetes and hyperlipidemia*	*Cerebral neoplasia*	*Arterial hypertension*	*Vascular malformations*	*Coagulation defects*	*Comorbidity*
A								
Spontaneous	132	35 (26.5%)	1 (0.8%)	1 (0.8%)	35 (28.2%)	15 (12.1%)	19 (15.3%)	26 (19.7%)
Post-traumatic	107 (78.5%)	84 (4.7%)	5 –	0 (7.5%)	8 –	0 (3.7%)	4 (5.6%)	6
Total	*239*	*119*	*6*	*1*	*43*	*15*	*23*	*32*
B								
Anticoagulants	29 (41.4%)	12 (6.9%)	2 –	0 (41.4%)	12 –	0 –	0 (10.3%)	3
Antiplatelets	47 (48.9%)	23 (6.4%)	3 –	0 (29.8%)	14 (2.1%)	1 –	0 (12.8%)	6
No treatment	163 (51.5%)	84 (0.6%)	1 (0.6%)	1 (10.4%)	17 (8.6%)	14 (14.1%)	23 (14.1%)	23
Total	*239*	*119*	*6*	*1*	*43*	*15*	*23*	*32*

The data are shown as absolute number of patients presenting the conditon and % of the row total.

appears to be higher than that in the ISCOAT database,[11] in which the rate was about 0.5 cases/1000 patients/year and the fatality rate was 60%. A possible explanation for this difference could be that in the ISCOAT study all the patients came from highly specialized oral anticoagulant clinics (FCSA centers).

Anticoagulant therapy

The stratification of the risk for CH is gaining more and more importance as the clinical indications for anticoagulation become widened and the mean age of the population increases.[17] Risk factors for major hemorrhagic complications during anticoagulant therapy were found to be age, sex, active cancer, comorbidity (cardiac, hepatic and renal diseases), positive personal history of hemorrhage and drug use. An integrated use of this set on information can help to distinguish patients at high hemorrhagic risk (> 7%) from those at low risk (< 1%).[18]

The relationship between the risk of CH and the level of anticoagulation is uncertain: some authors found no correlation, suggesting the hypothesis of a low cut-off value phenomenon for the risk,[19] while in other cases excessive anticoagulation appeared to be an important risk factor.[20] In the population of the present study no INR value resulted completely safe. The INR at the event and the mean INR in the three months before the event were, respectively, 3.1 and 3.0 and only two patients (7.4%) had an INR over 5. These data suggest that other coagulation tests could be more sensitive than INR for assessing the individual hemostatic balance in order to optimize the net clinical benefit. Further research is needed about this topic.

Several studies found a correlation between the duration of anticoagulant treatment and the hemorrhagic risk, this risk being high in the first 3-6 months of treatment.[20,21] In the present study the mean treatment duration was 26.3 months, with 9 events (33%) occurring in the first 3 months. In this starting phase the risk is higher for patients requiring rapid anticoagulation: 6/9 patient with early hemorrhage were receiving treament for pulmonary embolism (2 patients) or for deep vein thrombosis (4 patients).

One patient was treated with warfarin plus ASA. This association is used in about 7% of patients on oral anticoagulant treatment in our experience, but we do not have enough data to detect an increase in risk. The association has been generally evaluated for protocols of low level oral anticoagulation associated with aspirin treatment, and a doubling of the CH risk was found for the association, independently from the dose of aspirin.[22,23]

The better outcome observed for patients given the computer-assisted management in the oral anticoagulation clinic compared with those managed manual methods seems related not to the coagulation assisted management itself (INR val-

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Table 4. Mortality and treatment.

	No treatment		*Antiplatelets*		*Anticoagulants*	
	Spontaneous	*Traumatic*	*Spontaneous*	*Traumatic*	*Spontaneous*	*Traumatic*
Outcome						
Death within 24 hrs	12 (17.9%)	8 (8.9%)	10 (28.6%)	2 (16.7%)	4 (16.7%)	1 (20.0%)
Death within 30 days	21 (31.3%)	8 (8.9%)	7 (20.0%)	2 (16.7%)	8 (33.3%)	1 (20.0%)
Death beyond 30 days	5 (7.5%)	1 (1.1%)	4 (11.4%)	1 (8.3%)	4 (16.7%)	1 (20.0%)
Alive	29 (43.3%)	73 (81.1%)	14 (40.0%)	7 (58.3%)	8 (33.3%)	2 (40.0%)

Overall the Pearson's χ^2 test (Fisher's adaptation) for the table is 0.014. Considering separately spontaneous and traumatic events the values are .807 and .009, respectively. No single comparison resulted statistically significant at the p corrected for multiple comparisons. The absolute number of patients and the percentage of the column total are shown stratified for treatment (no treatment, anticoagulants, antiplatelet agents), spontaneous or traumatic nature of the event and time of death (within 24 hrs, before and after 30 days, or alive).

Table 3. Mortality and Glasgow coma scale.

Treatment	*Outcome*	*N° of pts*	*Mean*	*SD*
No treatment	Death within 24 hrs	20	5.8	4.1
	Death within 30 days	29	8.9	4.0
	Death beyond 30 days	6	14.3	0.5
	Alive	102	11.7	3.4
	Total	157	10.4	4.2
Antiplatelets	Death within 24 hrs	12	7.4	3.6
	Death within 30 days	9	9.0	3.3
	Death beyond 30 days	5	13.4	2.5
	Alive	21	12.6	3.1
	Total	47	10.6	3.9
Anticoagulants	Death within 24 hrs	5	6.0	3.7
	Death within 30 days	9	9.0	5.0
	Death beyond 30 days	5	14.0	0.7
	Alive	10	12.8	2.2
	Total	29	10.8	4.3
Overall	Death within 24 hrs	37	6.3	3.9
	Death within 30 days	47	8.9	4.0
	Death beyond 30 days	16	13.9	1.4
	Alive	133	12.0	3.3
	Total	233	10.5	4.2

ANOVA for the effect of Glasgow coma scale (GCS) value on outcome variable p < 0.0001. Mean and standard deviation (SD) values for GCS at admission are shown for patients stratified according to treatment with anticoagulants, antiplatelet agents or no treatment and for outcome (death within 24 hrs, before and after 30 days, or alive). The GCS is based on the score obtained by evaluating three clinical parameters: eye, language and movement response to stimuli. The GCS score ranges from 15 (alert patient) to 3 (deep coma).

ues, both at the event and in the three months before, were similar), but more likely to a more efficient clinical evaluation of hemorrhagic risk when selecting patients.[24] Moreover, the two populations have different characteristics (compliance, comorbidity, indication for treatment) and a selection bias could exist.

Antiplatelet therapy

A study performed in Australia showed that the use of low dose ASA or other non-steroidal anti-inflammatory drugs does not increase the risk of CH over that in untreated patients.[25] In the Antiplatelet Trialists' Collaboration[26] the absolute excess of intracranial hemorrhages was found to be lower than 1 case/1,000 patients/year in high risk groups with a higher risk in hypertensive and cerebrovascular patients.

These data are in disagreement with ours, in which the absolute risk is 3.4 cases/1,000 patients/year. There are two possible explanations for this difference: first, in our retrospective study we could have underestimated the number of AP patients and second, the risk of CH could be lower in the selected populations of randomized controlled trials than in the general population.

Effects on mortality

The mortality data are in agreement with those in the literature, which show a similar death rate at one and at six months, ranging from 14 to 62% for SCH, and death within 48 hours in 50% of patients.[18,27-29] Considering post-traumatic SDH, for example, the death rate varies between 13 and 20% in published papers[16] and was 15% in our study.

It is not clear whether the anticoagulant or antiplatelet treatment plays a role in terms of prognosis. In our population the death rate was higher in treated patients than in untreated ones (59.2 vs 35%), both within 24 hours and thereafter without difference, at any time, between anticoagulant- and antiplatelet-treated patients. The difference was completely accounted for by TCH, while there was no difference for SCH. It is not clear whether the hemorrhages were more extensive and prolonged in anticoagulated patients, although this

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is biologically plausible.[19] On the other hand it is not surprising that the difference in mortality between treated and untreated patients was lower in SCH, when the amount of bleeding *per se* is relevant, versus TCH, when the coagulation status of the patient can play a major role in determining the entity of the bleeding. Factors able to predict mortality were reported to be a low GCS value, a low volume of hematoma as assessed by CT or NMR imaging and VI.[30]

Patients with a GCS < 9 and > 60 mL of blood showed a death rate of 90% at 30 days, while patients with GCS > 9 and < 30 mL of blood had a death rate of 17%. In our study GCS carries a predictive value for the risk of early death (Table 3). VI was confirmed to be a negative prognostic factor as well: 75% of the subjects died independently of the origin of the hemorrhage. The mean age of the patients who died was significantly different from that of patients who survived, both for SCH and for TCH, with mean values of 68.5 and 55.8 years, respectively ($p < 0.0001$).

Other risk factors

Arterial hypertension represents the foremost risk factor, particularly in patients under 55 years old, smokers and those with uncontrolled hypertension.[27] Moreover, this condition is widely present in the general population. We found abnormal values of arterial blood pressure in 41.4% of anticoagulated patients, 29.8% of antiplatelet-treated patients and 18% of the general population.

The correction of abnormal blood pressure levels lowers the risk of CH: in the *Hypertension Detection and Follow-up Program*, antihypertensive therapy reduced the risk of CH by 46% in patients below 65 years old.[31] In the *Systolic Hypertension in the Elderly Program* the rate of ischemic and/or hemorrhagic stroke in patients above 60 years old was 8.2% in the placebo group and 5.2% in the treated group.[32]

Vascular malformations in our population were significantly represented only in SCH (12% of patients), and only in patients not on anticoagulant/antiplatelet treatment; a single patient on aspirin bled from a cerebral aneurysm. These data are in disagreement with those from studies in which neurovascular imaging tecniques were more widely used to evaluate the indication for neurosurgery.[33] Diabetes mellitus was present (as single disease or in comorbidity) in 5.4% of the patients and in 7.2% of those with SCH, not dissimilar from rates in a Swedish population of patients with SCH.[12]

Emergency treatment of CH

In 50% of the cases the initial clinical course of CH was slow for the first 24 hours. Even in the absence of clear guidelines, rapid treatment is commonly considered critical in order to normalize any alteration in blood coagulation as soon as possible.

Fredriksson *et al.* showed, on a retrospective basis in 17 cases, that prothrombin concentrates revert coagulation abnormalities more quickly than fresh frozen plasma.[34] In our experience, and lacking local guidelines, we used only vitamin K in 12 patients, fresh-frozen plasma in 13 cases and prothrombin concentrates in 2 cases, based on clinical and laboratory judgement. No conclusion on difference of efficacy between different treatments could be drawn.

Conclusions

Based on the results of our retrospective study an accurate selection of patients, periodic re-evaluation of the hemorrhagic risk and prevention of traumatic events could be the main tools to increase the net benefit of antithrombotic treatment in the management of patients affected by arterial or venous thromboembolic diseases. A prospective confirmation of these results is needed and is possibly worth being performed.

Contributions and Acknowledgments

AN: data collection (emergency area); AG: data collection (anticoagulant therapy); AI: statistical analysis and data collection; MS: bibliography search; GM: data collection neurology; GB: conception and planning.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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Peer Review Outcomes

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Professor Vicente Vicente, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Professor Vicente and the Editors. Manuscript received May 7, 2002; accepted July 9, 2002.

What is already known on this topic

Bleeding complications related to antithrombotic therapy are relatively frequent.

What this study adds

This retrospective study evaluates the relationship between cerebral hemorrhage and antithrombotic treatment.

Potential implications for clinical practice

An accurate patient selection and traumatic event prevention are the main candidate mechanisms to reduce intracranial bleeding complications in individuals under long-term antithrombotic therapy.

Vicente Vicente, Deputy Editor

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