Chapter

Relationship Between Hemorrhagic Stroke and Mortality in Chronic Complex Outpatients: Results from a Community Cohort of Patients

González-Henares MA[1], Clua-Espuny JL[2]*, Queralt-Tomas MLL[3], Campo-Tamayo W[4], Muria-Subirats E[5], Panisello-Tafalla A[6], Lucas-Noll J[7], Forcadell-Arenas T[8] and Gil-Guillen VF[9]

[1]EAP-Camarles-Aldea-Ampolla, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, Spain
[2]Department of Research, ICS Terres de l'Ebre, Research Institute University Primary Care (IDIAP) Jordi Gol, Spain
[3]EAP Tortosa 1-Est, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, Spain
[4]EAP Tortosa-2-Oest, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, Catalonian Health Institute, Spain
[5]UUDD Tortosa-Terres de l'Ebre, Resident Medicina Familiary Comunitaria, CAP Temple, EAP Tortosa Est, Institut Català de la Salut, Spain
[6]EAP-Camarles-Aldea-Ampolla, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, Spain
[7]EAP-Alcanar-St Carlos de la Rápita, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, Spain
[8]EAP Tortosa 1-Est, Catalonian Health Institute, SAP Terres de l'Ebre, Health Department, Generalitat de Catalunya, Spain
[9]Cátedra Medicina de Familia, Universidad Miguel Hernández, Spain

***Corresponding Author:** Clua-Espuny JL, Department of Research, ICS Terres de l'Ebre, Research Institute University Primary Care (IDIAP) Jordi Gol, Spain

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Abstract

Question: Around 3-5% of people can be identified as *chronic complex patients(CCP*) and are increasingly at risk of hemorrhagic stroke. The main objective was to explore differences in risk factors and the association with outcome factors on mortality.

Materials and Methods: Multicenter and prospective cohort study from January 1 2013 to September 30 2016 among patients registered as *chronic complex outpatients*. To predict hazard ratios, mean survival time, and survival probabilities, multivariate Cox regression was used.

Results: 932 CCP were included (52.3% women). Average age was 82.5 years (95% CI 81.8-83.2). During a mean follow-up period of 2.8 years, 65 stroke episodes happened [37 (56.9%) ischemic; 28 (43.1%) hemorrhagic]. The percentage of ICH almost doubled (21.0% to 43.1) after CCP diagnosis; 26.1% had polypharmacy (≥10), 57.6% VKA-treated *patients*showed *TTR<60%*, and had a higher incidence of falling (31.9% vs. 19.2%, p 0.002). The average survival time was significantly shorter associated with age [HR 1.03 95% CI 1.14-1.53, p 0.001], previous stroke [HR 13.54 95% CI 9.23-19.81, p <0.001], antiagreggant treatment [HR 1.97 95% CI 1.21-3.21, p 0.006], anticoagulant treatment [HR 1.78 95% CI 1.22-2.60, p 0.002], and Barthel score <60 [HR 1.43 95% CI 1.04-1.97, p 0.024].

Conclusions: Given the co-occurrence of hemorrhagic strokes with poor performance status, multi-morbidity, and polypharmacy, multi-dimensional interventions are needed to improve health outcomes.

Keywords

Hemorrhagic Stroke; Chronic Complex Patient; Mortality; Fall Risk; Disability

Abbreviations

ADL-Activities of Daily Living; BP-Blood Pressure; CCP- Chronic and Complex Pptient; DDD-Defined Daily Dose; HR-Hazard Risk; ICH-Intracerebral Hemorrhage; IDIAP-Primary Care Research Institute Jordi Gol i Gurina; PIIC-Shared Individual Intervention Plan [Pla d'intervenció individualitzat compartit (PIIC)]; SBP-Systolic Blood Pressure; SD-Standard Deviation; SSRI-Selective Serotonin Reuptake Inhibitor; TTR-Time in Therapeutic Range

Introduction

We face an epidemic of multi-morbidity and rising complexity of health needs [1,2] resulting from changing demographics and global circumstances. In developed countries, around 3-5% of the people

can be identified as *chronic complex patients* who are increasingly at risk of stroke [3,4]. Although the European population aged ≥65 years will double by 2050, there are few studies about the epidemiology of hemorrhagic stroke and the burden of multi-morbidity associated with greater health care costs and an increased risk of adverse events as well reduced functional capacity and multiple geriatric syndromes. The statistics about hemorrhagic stroke show high variability: lowering [3,5] against rising of incidence [6,7], or no change [8,9]. However, there is general agreement on the increase related to aging [10].

Unfortunately, there are many negative consequences after a hemorrhagic stroke, and high mortality and poor functional, cognitive and psychological outcomes affect a substantial proportion of these people. As the global population of individuals with long-term cardiovascular conditions grows, research and health services will need to increasingly focus on preventing and managing the long-term consequences of stroke. The prevention of these negative effects is of major importance because, nowadays, they are major issues for health and social care providers [11-14]. Over the last 20-30 years, problems related to aging and hemorrhagic stroke have become a prominent issue in global healthcare.

The goals of this study were (i) to provide a description of the epidemiology of hemorrhagic strokeand mortality risk among people registered as *chronic complex outpatients* and (ii) to explore risk factors differences in the association of outcome factors on mortality. This review discusses how primary care might tackle these new challenges of the aging population.

Materials and Methods

We carried out a a multicenter and prospective cohort study of the incidence of mortality from January 1 2013 to September 30 2016 among *chronic complex outpatients* (CCP) attending primary care teams in the *Terres de l'Ebre* health area in Catalonia (Spain). All people were managed by the public health system in Catalonia. Registry information was collected from the government-run healthcare pro-

vider responsible for all inpatient care in the county. The overall number of CCP registered was 3,490 people. We included a randomized sample of 932 adult patients registered in the electronic health records of primary care as CCP in the period from January 1 2013 December 31 2014. Patients were excluded if they resided in a long-term institutional setting. Alpha Risk= 0.05; Precision= 0.03.

Patient outcomes were followed until death or the end of the study (September 30 2016) starting with the reporting date as CCP in the electronic health record. Data included demographics, functional, comorbidity, cognitive and social assessment, and were collected directly from the *Shared Individual Intervention Plan [Pla d'intervenció individualitzat compartit (PIIC)]* written and managed by the nursing service in primary care. In the PIIC, determinants related to personal factors, as well as the social and physical environment are described to provide a tailored personal approach according to the patient's preferences in the case of hospital readmission or emergency care use and the primary caregiver. The report is updated automatically to ensure that relevant information is *shared* across the electronic health record. Currently, 82% of people registered as CCP have this basic information in their PIIC.

Definitions

Chronic Complex Patient *(CCP) definition: those who meet at least four of the following criteria:* 1/Age (≥65 years old), 2/Chronic comorbidities (≥4), 3/Psychosocial disorders (cognitive impairment or psychological disorder with functional disability), 4/Geriatric conditions such as functional disability (Barthel score <55, living in an assisted living facility, nursing home, or with in-home caregivers) or recurrent falls or fall risk, 5/Previous high health care utilization (two unplanned hospitalizations for exacerbation of chronic pathologies or three emergency department visits in the last year), 6/Number of active medications in the last six months (≥4 active medications), 7/ Living alone or with a caregiver ≥75 years old.

The chronic complex patient [14] has been defined as a person with a chronic illness and *complex clinical situations* which make their management significantly far more *difficult.* The group also could include patients who do not meet these criteria, but are affected by other clearly complex conditions, such as schizophrenia or mental illnesses with behavioral disorders.

Stroke: Individuals with current stroke diagnoses in their medical charts after inclusion into the study were considered to have experienced an incident stroke. A previous stroke was considered to be present if the medical charts included a stroke diagnosis or if the individual, a caregiver, or a relative reported the diagnosis and it was found with supporting information on medical charts or other assessments. Records of inpatient care after baseline assessment with International Classification of Diseases (10thversion; ICD-10) code prefixes I60, I61, I63, I64, H34, I67, and G45; subsequent diagnoses of stroke or transient ischemic attack were compiled for all participants. All other diagnoses were based on information from assessments conducted during home visits and records from hospitals, general practitioners, and institutional care facilities. A physician comprehensively reviewed the digital medical charts of individuals.

There are problems in defining fall risk, as many studies fail to specify an operational definition, leaving room for interpretation. A fall is an unintentional event that results in the person coming to rest on the ground or another lower level (W19.9 code in the electronic health record). A fall was defined as the result of any event that caused the patient to end up on the ground against their will, according to the WHO definition [15]. We used *"a clinical report in the electronic health recordthat a person had a fall risk or previous recurrent falls with or without any serious injury*". If a patient is thought to be high risk by medical or nursing staff, allied health, or carers, such patients will be identified as a fall riskin the PIIC. This might include a mention of the patient's level of orientation and cognition, gait and balance, continence status, and number and types of prescribed medications, as well as number of diagnosis.

Variables

Sex: female (0) male (1)

Age: <80 years old (1), ≥80years old (2).

Number CCP criteria: <4 (0) ≥4 (1).

Charlson comorbidity index [16]. Short version.

Current medications were asked about during the home visit and confirmed in medical records. Polypharmacy (defined as five or more daily medications): <5 (0), 5-9 (1), and ≥10 (2). Oral anticoagulants (acenocumarol or warfarin)with TTR ≥60% (1), TTR <60% (2), or new oral anticoagulants (NOACs) (0). Antidepressants and/or sedating or other drugs affecting the neurological system: male (1), female (2). If there was a diagnosis of "atrial fibrillation",$CHA_2DS_2VAS_C$HASBLED scores were included.

Recurrent falls or fall risk: no (0), yes (1).

Hypertension not controlledby therapy (≥ 160/90 mmHg): no (0), yes (1).BP was measured as an average of separate follow-up measurements in the last six months.

Alcoholism abuse vs. dependence: no (0), yes (1)

Presence of cognitive impairment[17]: a disease-specific diagnosis of cognitive impairment, without specification of sub-type or severity, was used and mesured by the Pfeiffer test: [0-2 errors] = intact intellectual functioning (1); [≥3 errors] = mild to severe intellectual impairment(2).

Presence of disability: scores (Barthel ≥60 (1), <60 (2) or Rankin <4 (1), 5(2)) were used to assess dependence in ADL.

Sociofamiliar risk: score on the Gijon [18] scale 10-14 (1) ≥15 (2).

We conducted an intention-to-treat analysis. Patients were followed up from cohort entry as CCP to the first event occurrence (death), the end of the study period, or loss to follow-up. Categorical variables were expressed as frequencies (percentage) and quantitative variables as mean (standard deviation) or median (interquartile range). Demographic data were summarized using mean and SD or median and quartiles for continuous variables and percentages for categorical data. Data analysis information was extracted and the adjusted risk estimates and 95% confidence intervals (CI) and all two-sided statistical tests were performed at the 5% significance level. Statistical tests of homogeneity were performed using Cochran's chi-squared test for homogeneity (Q) and the percentage of total variation across studies attributable to heterogeneity (I^2). Using univariate linear regression analysis with medication count as a continuous outcome variable, we identified explanatory variables that had significant ($p \leq 0.05$) univariate linear associations with medication count. Time-to-event analysis was performed using non-parametric methods like the Kaplan-Meier and log-rank test. The multivariate Cox proportional hazards regression model was fitted, adjusting for the following baseline characteristics and confounding and predictive factors of each event: age, sex, Charlson index, factors in the $CHA_2DS_2VAS_C$ and HAS-BLED scales, and active treatments. To predict hazard ratios, mean survival time, and survival probabilities, multivariate Cox regression was used. The variables were included in a multivariable model Cox to identify their influence on mortality. The non-hemorrhagic group and no stroke group were considered as the reference in all analyses. All analyses were performed using IBM SPSS version 19.0.

Ethics approval was granted by the Ethics Research Committee at Institut Primary Care Jordi Gol i Gurina (IDIAP), Health Department, Generalitat de Cataluña.

Results and Discussion

From 2013 to 2014, 932 CCP patients were included (52.3% women) in the study. The baseline characteristics are shown in Table 1 and were not different from those previously described [3]. In the present study, there were 265 stroke episodes among 250 people. The overall stroke incidence was 24.9/1000 person-years. In total, 200 stroke episodes had happened at baseline before patients were registered as CCP [(154 ischemic (79%), 41 hemorrhagic (21.0%)]. The annual crude hemorrhagic stroke rate was 23.5/100,000 person-years. During a mean follow-up period of 2.8 years, 65 stroke episodes happened [37 (56.9%) ischemic; 28 (43.1%) hemorrhagic]. The percentage of hemorrhagic strokes almost doubled (21.0% to 43.1) after diagnosis as CCP. Those that suffered a stroke after registration as CCP had more comorbidities (p 0.012), higher scores in CHA_2DS_2VASC ($p < 0.001$), HAS_BLED ($p < 0.001$), a greater fall risk (40.9% vs. 18.6%,$p < 0.001$), and higher mortality (47.0% vs. 33.3%, p 0.031) than those without a stroke episode.

The patients with hemorrhagic stroke were mostly men (62.3%, p 0.008), with more than the average number of CCP criteria [4.1±1.0, p 0.028] and higher scores in the Charlson index ($p < 0.001$), CHA_2DS_2VASC ($p < 0.001$), and HAS_BLED ($p < 0.001$). These patients also had a higher prevalence of hypertension (p 0.004) and worse control (p 0.003), more polypharmacy (p 0.002), a higher prevalence (p 0.034) of moderate dependence (Barthel <60), and a higher prevalence of fall risk (p 0.012). In total, 25% of hemorrhagic episodes happened among patients with ischemic stroke; the significant factors associated consistently with incident hemorrhagic stroke at baseline in univariate model are shown in Table 2. In the basic adjusted multivariate model, the significant factors were: age [HR 1.033 95% CI 1.14-1.053, p 0.001], previous stroke [HR 13.541 95% CI 9.23-19.817, p <0.001], antiagreggant treatment [HR 1.978 95% CI 1.216-3.217, p 0.006], anticoagulant treatment [HR 1.787 95% CI 1.227-2.603, p 0.002], and Barthel score <60 [HR 1.438 95% CI 1.048-1.974, p 0.024].

Table 1: Baseline characteristics of CCP patients and stroke: ischemic vs. hemorrhagic.

CCP PATIENTS	NO STROKE	HEMORRHAGIC STROKE	ISCHEMIC STROKE	p
N (%)	675(72.4)	69 (7.4)	188 (20.17)	
Age (average ±SD)	82.37±10.37	81.62±9.5	83.76±7.9	0.071
Percentage >80 years old n (%)	470 (69.6)	47 (68.1)	138 (73.4)	0.557
Men n (%)	296 (43.9)	43 (62.3)	105 (55.9)	0.001
CCP criteria number (average±SD)	3.72±1.17	4.16±1.05	4.23±1.18	0.645
Hypertension n (%)	549 (81.3)	65 (94.2)	160 (85.1)	0.008
Hypertensionnot controled	71 (10.5)	16 (23.2)	20 (10.6)	0.017
Dyslipemia n (%)	372 (55.1)	38 (55.1)	111 (59.0)	0.623
Diabetes n (%)	371 (55.0)	29 (42.0)	94 (50.0)	0.080
Atrial fibrillation n (%)	226 (33.5)	24 (34.8)	75 (39.9)	0.269
Ischaemic cardiopathy n (%)	135 (20.0)	17 (24.6)	44 (23.4)	0.454
Peripheral artery disease n (%)	107 (15.9)	10 (14.5)	32(17.0)	0.872
Chronic kidney insuficiency	87 (12.9)	10 (14.5)	19 (10.1)	0.503
Heart failure n (%)	283 (32.8)	20 (29.0)	52 (27.7)	0.306
Charlson score (average±SD)	2.31±1.34	3.10±1.37	3.10±1.29	0.998
Stroke before CCP n (%)		48 (63.1)	154 (80.6)	< 0.001
Stroke after CCP n (%)		28 (36.9)	37 (19.4)	< 0.001
$CHA_2DS_2VAS_C$ score (average±SD)	4.61±1.08	6.23±1.11	5.83±1.32	0.201
Stroke risk/year average (average±SD)	5.88±2.25	8.22±1.73	7.87±2.26	0.389
HAS_BLED score (average±SD)	2.74±1.03	4.14±0.88	3.34±1.06	0.002

Bleeding risk/year (average±SD)	4.15±3.22	8.91±3.25	6.11±3.76	0.002
Chronic liver disease n (%)	37 (5.5)	4 (5.8)	10 (5.3)	0.989
Daily medications number (average±SD)	8.83± 3.68	8.06±3.33	9.32±3.30	0.007
Polypharmacy ≥ 5 n (%)	626 (92.7)	65 (94.2)	185 (98.4)	0.005
Polypharmacy ≥ 10 n (%)	299 (44.3)	18 (26.1)	83 (44.1)	0.011
Cognitive impairment n (%)	220 (32.6)	30 (43.9)	88 (46.8)	0.001
Pfeiffer testscore (average±SD)	2.86±3.22	3.2±3.48	3.70±3.31	0.278
Barthel score (average±SD)	68.6±31.58	59.2±31.0	58.97±32.21	0.961
Barthel score <60 n (%)	215 (31.9)	33 (47.8)	95 (50.5)	< 0.001
Fall risk n (%)	117 (17.3)	22 (31.9)	49 (26.1)	0.002
Gijón score (average±SD)	10.53±4.71	10.57±1.81	8.05±4.62	0.177
Antiaggregant treatment n (%)	238 (35.3)	28 (40.6)	119 (63.3)	< 0.001
Anticoagulant treatment n (%)	191 (28.3)	17 (24.6)	62 (33.0)	0.275
Statin treatment n (%)	294 (43.6)	32 (46.4)	97 (51.6)	0.146
Uric acid treatment n (%)	106 (15.7)	16 (23.2)	28 (14.9)	0.272
Proton pump inhibitor treatment n (%)	445 (65.9)	52 (76.8)	15 (77.1)	0.004
Selective serotonin reuptake inhibitors (SSRIs) n (%)	186 (27.6)	24 (34.8)	70 (37.2)	0.028
CNS depressant drugs n (%)	360 (53.3)	42 (60.9)	112 (59.6)	0.190
Death n (%)	215 (31.9)	41 (59.4)	63 (33.5)	< 0.001

Table 2: Significant factors consistently associated with incident hemorrhagic stroke at baseline in the univariate model.

Variables	Hazard Ratio	95% CI	p
Age	1.034	1.017-1.052	< 0.001
Charlson score	1.349	1.223-1.487	< 0.001
Previous ischemic stroke	17.20	11.9-24.66	< 0.001
Atrial fibrillation	1.389	1.037-1.862	0.028
$CHA_2DS_2VAS_c$score	1.652	1.383-1.972	< 0.001
HAS-BLED score	1.148	1.158-1.738	< 0.001
Selective serotonin reuptake inhibitors (SSRIs)	1.354	1.007-1.822	0.045
Fall risk	1.401	1.010-1.942	0.044
Pfeiffer score	1.11	1.071-1.163	< 0.001
Barthel score<60	2.706	2.028-3.611	<0.001

Among the women with hemorrhagic stroke, the percentage of cognitive impairment was higher than among men (65.4% vs. 30.2%, p 0.006). These patients also had higher scores on the Pfeiffer test (p 0.007) and Gijon scores (0.020), and were more often users of CNS depressant drugs (84.6% vs. 46.5%, p 0.002).

The overall mortality was significantly higher among those with hemorrhagic stroke (59.4% vs. 32.2%, p < 0.001). The average survival time was significantly shorter (Figure 1) among those with hemorrhagic stroke. In the basic multivariate analyses, the outcome independent factors were: Charlson score [HR 1.13395% CI 1.043-1.23, p 0.003], cognitive impairment (Figure 2) [HR 1.051 95% CI1.012-1.093, p 0.011], Barthel score <60 [HR 1.921 95% CI 1.473-2.505, p < 0.001], age [HR 1.037 95% CI 1.021-1.053, p <0.001], heart failure [HR 1.822 95% CI 1.448-2.293, p < 0.001], and Charlson score [HR 1.133 CI 95% 1.043-1.230, p 0.003]. In the univariate model, the protective factors were polypharmacy [HR 0.962 95% CI 0.932-0.992, p 0.015] and the statin treament[HR 0.677 95% CI 0.540-0.850, p 0.001]. Regarding hemorrhagic stroke, the factors associated with mortality were atrial fibrillation [HR 2.082 95% CI 1.110-3.908, p 0.022], Charlson score [HR 1.263 95% CI 1.012-1.577, p 0.039], and anticoagulant treatment [HR 2.962 95% CI 1.510-5.813, p 0.002]. Only the Pfeiffer

score [HR 1.094 95% CI 1.001-1.196, p 0.047] remained significant in the multivariate model.

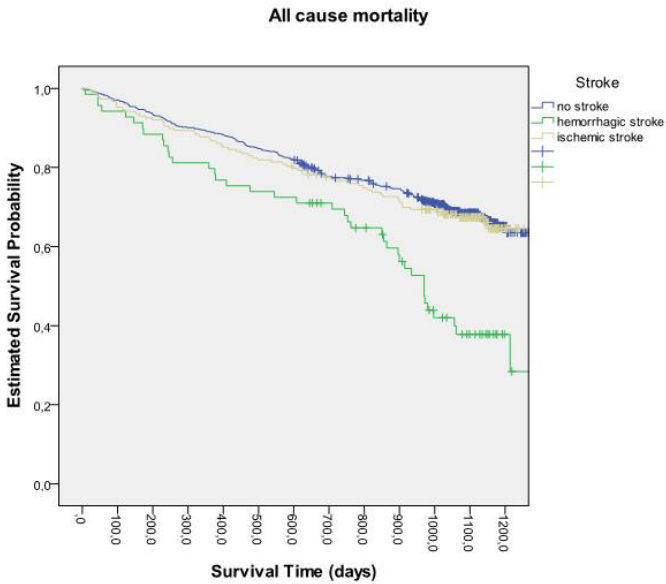

Figure 1: Kaplan-Meier estimates of survival during follow-up according to the type of stroke at baseline.

According to gender, severity (NIHSS men 8.3±7.3 vs. women 8.7±6.8, (p 0.816) was not significantly different, but women stayed in hospital longer (p 0.030). The functional capacity was better among men after discharge: a higher average Barthel score [70.2±31.2vs. 62.3±32.1, $p < 0.001$] as well a higher Rankin score [3.1±1.4 vs. 2.6±1.5] and a lower percentage with moderate dependence [Barthel ≤60 men 43.1% vs. women 56.9% p 0.021]. In the basic adjusted multivariate model, age, previous disability, and female gender were independent factors associated with poor functional outcome at dis-

charge. The women used more CNS depressant drugs (p <0.001) than men. However, mortality was higher among men (68.3% vs. 50.0%, p 0.162). The case-fatality rates were 44% at 28 days and 57% at one year.

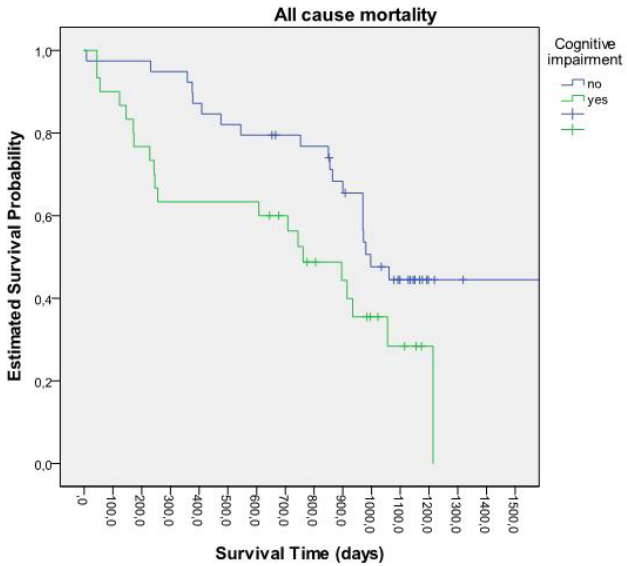

Figure 2: Kaplan-Meier estimates of survival during follow-up according to cognitive impairment at baseline in hemorrhagic stroke cases.

The overall mortality among the CCP people with a fall risk was38.5%. In the unadjusted analysis, the patients who had a previous ischemic stroke were at a significantly higher risk of death (Figure 3) if they had been registered as a fall risk, but not in the case of hemorrhagic stroke (p 0.784). However, the fall risk was higher (31.9% vs. 19.2%, p 0.012) among those with hemorrhagic stroke, but without an impact on long-term survival. Routine clinical questioning about previous falls may, thus, be a key strategy to identify at-risk individuals so preventive interventions can be introduced.

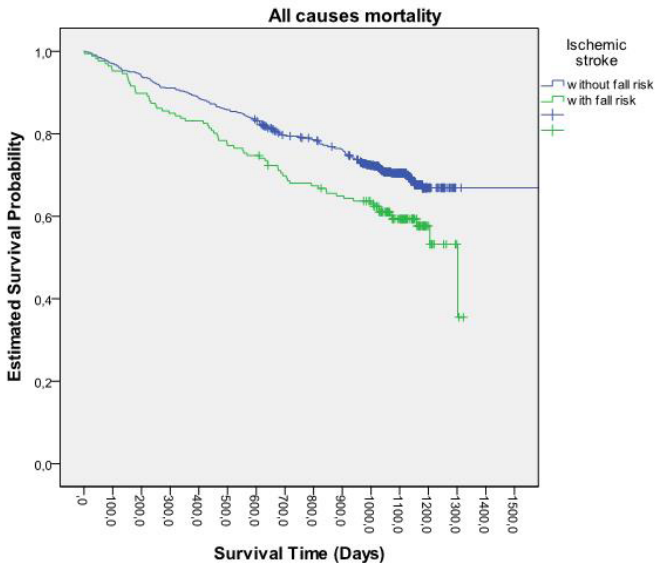

Figure 3: Kaplan-Meier estimates of survival during follow-up of ischemic stroke cases according to the presence of fall risk or not at baseline.

Although 92.7% cases had ≥5 active medications, the percentage of polypharmacy (≥10 active medications) among the hemorrhagic cases was lower (26.1% vs. 44.3%, p 0.002). This fact was associated was higher mortality (log rank 0.043) in the presence of a fall risk (Figure 4), but without a difference in the average Charlson score or prevalence of comorbidities.

We found a higher percentage of CCP using SSRIs among those with a fall risk, but without difference (p 0.2211) in mortality risk. Isolation and loneliness have been shown to be a risk factor for falls. The percentage in our study was 22.3% among people ≥75 years old.

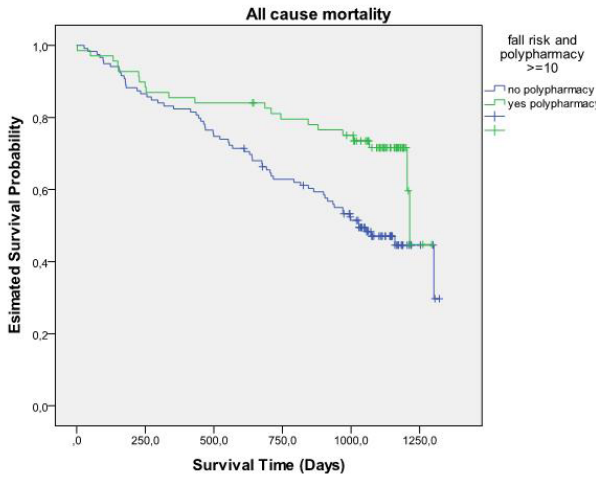

Figure 4: Kaplan-Meier estimates of survival during follow-up of stroke cases according to the presence of polypharmacy (≥10) or not at baseline.

Discussion

This study describes some epidemiological differences in hemorrhagic strokes in the general population. Contrary to previous results [4], in CCP, hemorrhagic strokes happen younger subject than ischemic stroke, without differences in comorbidities. Moreover, the risk of ICH mortality appears to be marginally greater in men. Cardiovascular comorbidities, functional impairment, male gender, high basal hypertension, fall risk, and polypharmacy were associated with incident stroke, but not independently of each other. Some of these factors may increase mortality risk, individually or collectively as a measure of geriatric multimorbidity, but we could not establish them as independent risk factors. It is possible that mortality depends on other factors [20] such as hemorrhage size, which could be less manageable clinically. Clearly, there is an increased incidence associated

with aging and these features should be related to prevention proposals.

In this cohort, 25% of hemorrhagic episodes happened among patients with ischemic stroke at baseline. Following an acute stroke, breakdown of the blood brain barrier occurs, resulting in a friable intracranial vasculature. This breakdown theoretically increases the risk of intracerebral bleeding, specifically in the area of ischemia. The study provides interesting descriptive data about treating older patients on OAC. Antiplatelet drugs confer an increased risk of bleeding, but unfortunately, little data exist to suggest how long this friability lasts or what other factors may contribute [21].

The unadjusted incidence rate was 23.5/105/year, increasing from 55 years in men and from 75 years in women. The incidence rate adjusted to the standard world population and European population were respectively 7.3/105/year and 18.4/105/year. Although there was an increase in the percentage of ICH related to overall stroke from 7.9% [2006-2008] to 14.8% [December 2014, $p < 0.001$], the incidence throughout the period shows a stabilization in the last decade [4] between 9.06/105/year and 33.2/105/year; this has also been seen in other studies [19] on incidence trends. The warfarin *defined daily dose (DDD)*/1000 people/day in *Terres Ebre* increased by 43.1% during the period of 2006 to 2014, but the use of antiaggregants was not significantly changed. Patients with polypharmacy had a significantly higher risk of major and medically relevant non-major bleeding than patients without polypharmacy [22]. In our study, 26.1% of hemorrhagic patients had polypharmacy (≥10); 57.6% of hemorrhagic patients spent more time in the subtherapeutic INR range vs. 46.7% of ischemic cases, and had a significantly higher ($p < 0.001$) bleeding risk/year than ischemic patients; the hemorrhagic patients had a higher incidence of falling (31.9% vs. 19.2%).

Given that elderly patients who receive vitamin K antagonists and multiple drug treatments [4] have a higher bleeding risk, such patients could potentially benefit from more intensive anticoagulation

monitoring. It seems prudent to critically review medications and to stop concomitant treatment with medications with an increased risk of interactions, sedation, or orthostatic hypotension, if feasible. Further studies are needed to examine whether new oral anticoagulants can be used more safely in elderly patients receiving multiple drug treatments [22].

Ethnic/racial disparities related to hypertension and ICH have been reported [23], and untreated hypertension confers a greater ICH risk in blacks and Hispanics relative to whites across all anatomic locations of ICH. High SBP (≥160mmHg) and atrial fibrillation appeared to be risk factors for incident stroke among very old people [24-27]. In the present study, SBP at least 160mmHg was not associated with incident stroke in the univariate model, but was associated with higher mortality risk. We highlight the importance of BP management in patients with risk factors for intracerebral hemorrhage. Efforts are needed to improve overall hypertension treatment and rates; the prevention and control of hypertension must address both social determinants of health and lifestyle changes, which cannot be managed through clinical care alone. We also need to reduce fragmented care and provide greater follow-up. Coordination among clinicians and caregivers and the periodic critical review of all the medications taken, and establishing a close relationship with the family, primary care physician, and social workers are essential. Our study includes very old people with cognitive and/or physical disability, and whether hypertension truly increases stroke risk in representative populations of very old people remains unclear because the prevalence of SBP ≥160 mmHg is similar (12.0% vs. 11.2%, p 0.407) [28-30] in people with and without ADL dependence and cognitive impairment. Confounding factors may obscure the association between BP and incident stroke unless accounted for. However, women with cognitive impairment could be a target population for care interventions.

Researchers have arbitrarily chosen various cut-off points in the definition of polypharmacy. Therefore, an elderly patient with at least two disease states will usually exceed this arbitrary threshold. In

total, 91.6% of CCP had ≥4 active medications, 52.4% between 4-9, and 32.9% ≥10. The average use of 9.0 daily medications by our study participants is consistent with the existing literature [31,32], but it is high and concerning. This study identified that the hemorrhagic stroke group had less polypharmacy. Perhaps this could be because of worse outcomes or *end-of-life* considerations [33] involving bedside decisions about whether an individual patient will or will not receive a prescription according its usefulness. Rationing tends to occur informally, with decisions often delegated to the healthcare team as opposed to open societal debate and formal governmental policy [34]. On the other hand, polypharmacy is not just the use of multiple medications, but also and/or the administration of more medications than are clinically indicated, representing unnecessary drug use [35,36]. For this definition, medications that are not indicated, not effective, or constitute a therapeutic duplication would be considered polypharmacy. In our study, the most used therapeutic groups are coincident with those commonly involved in inappropriate prescription: treatment of peptic ulcers, cardiovascular medications, antidepressants, and hypnotics [37]. Future research should document more evidence regarding the reality of rationing in CCP, adverse drug-drug interactions, and the increased risk of falling.

The method used to define "fall risk" could be a little clearer. Clinicians are often unaware of the many existing scales used for identifying fall risk and are uncertain about how to select the appropriate one. Given that the majority of falls do not come to the attention of any medical service, the use of the evaluation of fall risk in the community could improve knowledge translation into clinical practice. Eventually, for risk factor assessment to make a difference, all risk factors identified in the risk assessment need to be addressed in the care plans, and the care plans need to be acted on.

There is confusion over whether the risk of hemorrhagic stroke is increased in people taking statins. Several meta-analyses have shown

either no increase, or a non-significant increase, in the risk of hemorrhagic stroke when statins are used for primary or secondary prevention [38,39]. Despite having similar rates of cardiovascular comorbidities, hemorrhagic patients who receive statins are significantly more likely to survive after stroke onset compared with non-users [4] and continuing statins after ICH may not only be safe but could also be beneficial [40]. In our study, statins were the second drug in terms of frequency of prescription in 46.4% of hemorrhagic patients. The decision to stop or continue [41] statin treatment in patients after hemorrhagic stroke remains controversial, and needs randomized trials investigating statin use in patients with acute intracerebral hemorrhage to inform patient management.

Conclusion

In our study, 26.1% of hemorrhagic patients had polypharmacy; 57.6% of hemorrhagic patients spent more time in the subtherapeutic INR range vs. 46.7% of ischemic cases, and had significantly higher bleeding risk/year than ischemic patients. Hemorrhagic patients had a higher incidence of falling and there was a high percentage of cognitive impairment among women. The patients who had a previous ischemic stroke were at a significantly higher risk of death if they have been registered as a fall risk. Given the co-occurrence of hemorrhagic strokes with poor performance status, multi-morbidity, and polypharmacy, multi-dimensional interventions are needed to improve health outcomes.

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