

# Intracerebral haemorrhage profiles are changing: results from the Dijon population-based study

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Incidence of intracerebral haemorrhage over the past three decades is reported as stable. This disappointing finding is questionable and suggests that any reduction in intracerebral haemorrhage incidence associated with improvements in primary prevention, namely, better control of blood pressure, might have been offset by an increase in cases of intracerebral haemorrhage owing to other factors, including the use of antithrombotic drugs in the ageing population. Therefore, we aimed to analyse trends in intracerebral haemorrhage incidence from 1985 to 2008 in the population-based registry of Dijon, France, taking into consideration the intracerebral haemorrhage location, the effect of age and the changes in the distribution of risk factors and premorbid treatments. Incidence rates were calculated and temporal trends were analysed by age groups (<60, 60–74 and ≥75 years) and intracerebral haemorrhage location (lobar or deep) according to study periods 1985–92, 1993–2000 and 2001–08. Over the 24 years of the study, 3948 patients with first-ever stroke were recorded. Among these, 441 had intracerebral haemorrhage (48.3% male), including 49% lobar, 37% deep, 9% infratentorial and 5% of undetermined location. Mean age at onset increased from  $67.3 \pm 15.9$  years to  $74.7 \pm 16.7$  years over the study period ( $P < 0.001$ ). Overall crude incidence was 12.4/100 000/year (95% confidence interval: 11.2–13.6) and remained stable over time. However, an ~80% increase in intracerebral haemorrhage incidence among people aged ≥75 years was observed between the first and both second and third study periods, contrasting with a 50% decrease in that in individuals aged <60 years, and stable incidence in those aged 60–74 years. This result was attributed to a 2-fold increase in lobar intracerebral haemorrhage in the elderly, concomitantly with an observed rise in the premorbid use of antithrombotics at this age, whatever the intracerebral haemorrhage location considered. In conclusion, intracerebral haemorrhage profiles have changed in the past 20 years, suggesting that some bleeding-prone vasculopathies in the elderly are more likely to bleed when antithrombotic drugs are used, as illustrated by the rise in the incidence of lobar intracerebral haemorrhage in the elderly, in which cerebral amyloid angiopathy may be strongly implicated. Future research should focus on the impact and management of antithrombotics in patients with intracerebral haemorrhage, which may differ according to the underlying vessel disease.

**Keywords:** stroke; intracerebral haemorrhage; incidence; registry; population-based; epidemiology

**Abbreviation:** ICH = intracerebral haemorrhage; IRR = incidence rate ratio

## Introduction

Intracerebral haemorrhage (ICH) accounts for 10–20% of strokes in Western countries and can reach twice this proportion in Asia (Feigin *et al.*, 2009; van Asch *et al.*, 2010). Although knowledge of the pathophysiology and acute treatment of ischaemic stroke has advanced considerably in the past decade, progress with ICH has been much slower (Mayer and Rincon, 2005; Qureshi *et al.*, 2009). ICH outcomes are still poor, with <40% of patients independent at 1 year (van Asch *et al.*, 2010). Therefore, primary prevention remains the most valuable means to reduce the burden of ICH and its adverse consequences worldwide. However, a recent meta-analysis did not demonstrate any significant decrease in the incidence of ICH over the past three decades (van Asch *et al.*, 2010). This disappointing finding is questionable and suggests that any reduction in ICH incidence associated with improvements in primary prevention, namely, better control of blood pressure, might have been offset by increases in cases of ICH owing to other factors, including the use of antithrombotic drugs in the ageing population (Donnan *et al.*, 2010). Another consideration resulting from these observations is that ICH may not be a single entity, but rather an expression of distinct underlying vasculopathies, with different susceptibility to antithrombotic drugs.

To investigate this hypothesis, we aimed to analyse trends in ICH incidence from 1985 to 2008 in the population-based registry of Dijon, France, taking into consideration the ICH location, the effect of age and the changes in the distribution of risk factors and premorbid treatments.

## Materials and methods

### Case collection procedure

All first-ever ICH cases that occurred within the city of Dijon, France (2007 census: 151 543 inhabitants), from 1 January 1985 to 31 December 2008 were identified from the Dijon Stroke Registry. This registry complies with epidemiological criteria for stroke incidence studies (Sudlow and Warlow, 1996). Its methodology has been described elsewhere (Béjot *et al.*, 2012). Briefly, multiple overlapping sources of information were used to identify fatal and non-fatal stroke and transient ischaemic attack in hospitalized and non-hospitalized patients:

- (i) a review of medical records from the emergency rooms, and all the clinical and radiological departments of Dijon University Hospital, with a diagnosis of stroke made by one of the neurologists of the department of neurology;
- (ii) a review of medical records from the emergency rooms and all of the clinical departments of the three private hospitals of the city and its suburbs, with diagnosis made by neurologists working in these establishments;
- (iii) a review of computerized hospital diagnostic codes of Dijon University Hospital. The International Classification of Diseases, 10th revision, was used. The following codes were initially searched for: I60 (subarachnoid haemorrhage), I61 (ICH), I62 (non-traumatic intracranial haemorrhage), I63 (ischaemic stroke), I64 (non-determined stroke), G45 (vascular syndromes),

G46 (transient ischaemic attack) and G81 (hemiplegia). Study investigators then consulted the medical records of identified patients to confirm or not the reported diagnosis or to reclassify the patients if a misclassification was noted;

- (iv) a review of computerized hospital diagnostic codes of the private hospitals with the same procedure as described previously was also conducted;
- (v) collaboration with the general practitioners to identify stroke patients managed at home or in nursing homes, with the diagnosis assessed by public or private neurologists from outpatient clinics;
- (vi) a review of the medical records of patients identified from a computer-generated list of all requests for imaging to the private radiological and Doppler ultrasonography centres of the city and its suburbs;
- (vii) regular checking of death certificates obtained from the local Social Security Bureau, which is responsible for the registration of deaths in the community, particularly fatal strokes outside hospital. The quality and the completeness of the registry are certified every 4 years by an audit from the National Institute for Health and Medical Research and the National Public Health Institute.

### Intracerebral haemorrhage definition and location

Stroke was defined according to WHO recommendations (WHO, 2000). In our registry, both ischaemic strokes, subarachnoid haemorrhages and ICH were collected. The diagnosis of stroke subtype was always made on clinical signs, cerebral imaging and complementary examinations. For this study, only first-ever non-traumatic ICH, that is, occurring for the first time in a patient's life, and documented by imaging, were considered for the calculation of incidence. Patients with cerebral haemorrhages related to a tumour, vascular malformation or haemorrhagic transformation of a cerebral infarct were also excluded. ICH diagnosis and determination of ICH locations were based on the findings of CT scans for all patients but one who underwent an MRI. For this study, all brain imaging data were blindly reviewed by two investigators (Y.B. and M.G.) to confirm the location of the ICH. We considered the following locations: (i) lobar (frontal, temporal, parietal and occipital) when the origin of the haemorrhage appeared to be in the cerebral hemispheres superficial to the deep grey matter structures; (ii) deep when it originated from the lenticular or caudate nuclei, thalamus, internal or external capsule; and (iii) infratentorial when it originated from the brainstem or cerebellum. In cases of uncertainty about the ICH location, especially for patients with large ICH, the most probable origin was discussed by the investigators. ICH was classified as undetermined either when the origin could not be reliably identified, as was the case in haemorrhages that overlapped two territories, or when data were missing.

### Vascular risk factors and pre-stroke treatments

Vascular risk factors were collected with the same methodology over the whole study period (Béjot *et al.*, 2012). Hence, hypertension was defined by a history of known hypertension or antihypertensive treatment. Diabetes mellitus was recorded if a glucose level of  $\geq 7.8$  mmol/l had been reported in the medical record or if the patient was under insulin or oral hypoglycaemic agents. Hypercholesterolaemia was recorded if total cholesterol level  $\geq 5.7$  mmol/l was reported in the medical history of the patient or if patients were treated with

lipid-lowering therapy. We also recorded a history of atrial fibrillation, previous myocardial infarction, and a history of transient ischaemic attack, defined as the sudden development of signs and symptoms affecting motor, sensory, sensorial and speech, brainstem and cerebellum functions lasting <24 h. Smoking was not included in the analysis because of missing data of >10% for the first study period. Pre-stroke therapy was also recorded, including oral anticoagulants (warfarin, acenocoumarol or fluindione), antiplatelet agents (aspirin, clopidogrel, ticlopidine or dipyridamole), antithrombotics (either anticoagulant and/or antiplatelet agent) and antihypertensive treatment.

## Statistical analysis

Proportions and mean values were compared between groups using the chi-square test and the Wilcoxon–Mann–Whitney test respectively. To measure the incidence rates, the National Institute of Statistics provided census data for 1982, 1990, 1999 and 2007 concerning the population in Dijon in 1-year age groups and by sex. The population was estimated from these censuses by linear interpolation. The crude incidence rate per age group and the standardized rate were calculated for every year and according to sex using the direct method with world populations (Ahmad *et al.*, 2001). We assumed Poisson distribution for the annual number of events to calculate 95% confidence intervals (CIs) for the rates. To evaluate the impact of the time on ICH incidence, incidence rate ratios (IRRs) were calculated using a Poisson regression adjusted for sex and/or age according to the analyses performed. The results were presented according to three study periods: 1985–92, 1993–2000 and 2001–08. As significant interactions were found between study periods and both age and ICH location, stratified analyses were performed accordingly. To investigate the reasons for the observed trends in the incidence in patients with lobar and deep ICH, we evaluated changes in the prevalence of vascular risk factors and pre-stroke treatments in supratentorial ICH only. We used a logistic regression in which each risk factor or pre-stroke treatment represented a dichotomous dependent variable, and time (considered as continuous) the independent variable. The odds ratios (ORs) and their related 95% CIs were calculated. *P*-values <0.05 were considered statistically significant. Statistical analysis was performed with STATA® 9.0 software (StataCorp LP).

## Ethics

Our registry was approved by the National Ethics Committee (CNIL) and the French Institute for Public Health Surveillance (InVS).

## Results

### Characteristics of the intracerebral haemorrhage cohort

Over the 24 years of the study, 3948 patients with first-ever stroke were recorded. The majority of patients were admitted to hospital. There was no change in this proportion over the study periods: 90.1% in 1985–92, 90.3% in 1993–2000 and 90.6% in 2001–08 (*P* = 0.91). Out-of-hospital deaths represented 3%, 1% and 4% of non-hospitalized patients for the three study periods, respectively (*P* = 0.30). A total of 441 patients (11%; 95% CI: 10–12) had ICH (213 male, mean age: 72.5 ± 15.8 years): 49% were lobar, 37% deep, 9% infratentorial and 5% had undetermined location. There was no significant temporal change in the

proportion of ICH among overall incident strokes between 1985 and 2008 (*P* = 0.97). Hospital admissions rates remained stable over time (95.2% in 1985–92, 98.7% in 1993–2000 and 95.1% in 2001–08, *P* = 0.18).

### Temporal changes in intracerebral haemorrhage incidence and mean age at onset

From 1985 to 1989, patients suffered their first-ever ICH at a mean age of 67.3 ± 15.9 years versus 74.7 ± 16.7 years in 2004–08 (*P* < 0.001).

Over the whole study period, the crude incidence of ICH was 12.4/100 000/year (95% CI: 11.2–13.6). It was higher in males (12.8/100 000/year; 95% CI: 11.6–14.6) than in females (11.9/100 000/year; 95% CI: 10.4–13.6) (age-adjusted IRR, female:male 0.66; 95% CI: 0.54–0.79, *P* < 0.001). Corresponding incidence rates adjusted to the world population were 9.1/100 000/year (95% CI: 7.8–103) in males, and 6.2/100 000/year (95% CI: 5.3–7.1) in females.

From 1985 to 2008, the global incidence of ICH was stable (sex- and age-adjusted IRR 1.12; 95% CI: 0.88–1.42, *P* = 0.34 for study period 1993–2000 versus period 1985–92, and sex and age IRR 1.08; 95% CI: 0.85–1.36, *P* = 0.53 for study period 2001–08 versus 1985–92) (Table 1). However, some differences in temporal trends in ICH were noted according to the age (Tables 1 and 2). Indeed, whereas the incidence of ICH in people aged ≥75 years increased between study period 1985–92 and both study period 1993–2000 (IRR 1.77; 95% CI: 1.24–2.53, *P* = 0.002) and study period 2001–08 (IRR 1.82; 95% CI: 1.29–2.58, *P* = 0.001), the incidence observed in individuals aged <60 years decreased (IRR 0.50; 95% CI: 0.29–0.87, *P* = 0.014 and IRR 0.57; 95% CI: 0.34–0.96, *P* = 0.036, respectively). In contrast, no change in incidence was noted in individuals aged 60–74 years (IRR 0.95; 95% CI: 0.62–1.44, *P* = 0.806 and IRR 0.80; 95% CI: 0.52–1.24, *P* = 0.321, respectively).

Incidence of infratentorial ICH remained stable over time (0.9/100 000/year, 95% CI: 0.5–1.7 in 1985–92, 0.9/100 000/year, 95% CI: 0.5–1.7 in 1993–2000 and 1.4/100 000/year, 95% CI: 0.8–2.3 in 2001–08; *P* = 0.66 for trend). For supratentorial ICH, stratified analyses by age and ICH location revealed a marginally significant decrease in the incidence of both lobar and deep ICH in individuals aged <60 years (Table 2 and Fig. 1). In contrast, the incidence of lobar ICH in patients aged ≥75 years greatly increased (IRR 2.08; 95% CI: 1.23–3.52, *P* = 0.007 for period 1993–2000 versus period 1985–92, IRR 2.22; 95% CI: 1.33–3.70, *P* = 0.002, for period 2001–08 versus period 1985–92), whereas only a non-significant increasing trend was observed for that of deep ICH. Further analyses revealed that the increase in incidence of lobar ICH in patients aged ≥75 years was found in patients aged 75–84 years (IRR 1.94; 95% CI: 1.06–3.57, *P* = 0.032 for period 1993–2000 versus period 1985–92, IRR 1.97; 95% CI: 1.09–3.55, *P* = 0.024, for period 2001–08 versus period 1985–92), and in those aged ≥85 years (IRR 2.75; 95% CI: 0.91–8.29, *P* = 0.072 for period 1993–2000 versus period 1985–92, IRR 3.21; 95% CI: 1.09–9.45, *P* = 0.034, for period 2001–08 versus period 1985–92). No change

**Table 1** Temporal trends in crude incidence rates of ICH observed in Dijon, France, from 1985 to 2008

Age groups	Period 1985–92			Period 1993–2000			Period 2001–08		
	n	Incidence	95% CI	n	Incidence	95% CI	n	Incidence	95% CI
Total	126	10.8	9.0–12.8	151	12.7	10.7–14.8	164	13.6	11.6–15.8
Age < 60	36	3.8	2.7–5.3	19	2.0	1.2–3.1	23	2.4	1.5–3.6
Age 60–74	44	32.0	23.3–43.0	44	33.0	24.0–44.4	37	27.7	19.5–38.2
Age ≥ 75	46	54.1	39.6–72.1	88	94.0	75.4–115.8	104	94.0	76.8–113.9

Incidence expressed as *n*/100 000/year.

**Table 2** Sex-adjusted incidence rate ratios of ICH by age groups and location

Age groups	Overall ICH		Lobar ICH		Deep ICH	
	IRR (95% CI)	P	IRR (95% CI)	P	IRR (95% CI)	P
Age < 60						
Period 2 versus Period 1	0.50 (0.29–0.87)	0.014	0.45 (0.20–1.00)	0.050	0.47 (0.19–1.15)	0.099
Period 3 versus Period 1	0.57 (0.34–0.96)	0.036	0.52 (0.25–1.10)	0.089	0.62 (0.28–1.41)	0.526
Period 3 versus Period 2	1.14 (0.62–2.10)	0.666	1.16 (0.48–2.80)	0.740	1.34 (0.51–3.53)	0.551
Age 60–74						
Period 2 versus Period 1	0.95 (0.62–1.44)	0.806	1.12 (0.61–2.08)	0.716	1.12 (0.55–2.28)	0.755
Period 3 versus Period 1	0.80 (0.52–1.24)	0.321	0.77 (0.39–1.52)	0.454	1.12 (0.55–2.27)	0.763
Period 3 versus Period 2	0.84 (0.55–1.31)	0.448	0.69 (0.36–1.33)	0.264	1.00 (0.51–1.95)	0.991
Age ≥ 75						
Period 2 versus Period 1	1.77 (1.24–2.53)	0.002	2.08 (1.23–3.52)	0.007	1.55 (0.86–2.78)	0.142
Period 3 versus Period 1	1.82 (1.29–2.58)	0.001	2.22 (1.33–3.70)	0.002	1.70 (0.97–2.98)	0.064
Period 3 versus Period 2	1.03 (0.78–1.37)	0.838	1.07 (0.72–1.58)	0.744	1.10 (0.68–1.77)	0.706

Period 1 = 1985–92; Period 2 = 1993–2000; Period 3 = 2001–08.

in incidence was noted for the age group 60–74 years, whatever the location considered. In addition, the incidence was stable between 1993–2000 and 2001–08 for overall age groups and ICH locations.

## Changes in vascular risk factors and premorbid treatments

To investigate the increase in ICH incidence over time in patients aged ≥ 75 years, we analysed the distribution of vascular risk factors and premorbid treatments and their temporal trends by age and ICH location. In the overall cohort, the distribution of vascular risk factors and premorbid treatments did not differ according to the ICH location (Table 3). The absence of any difference was consistent in patients aged < 75 and ≥ 75 years (Supplementary Table 1).

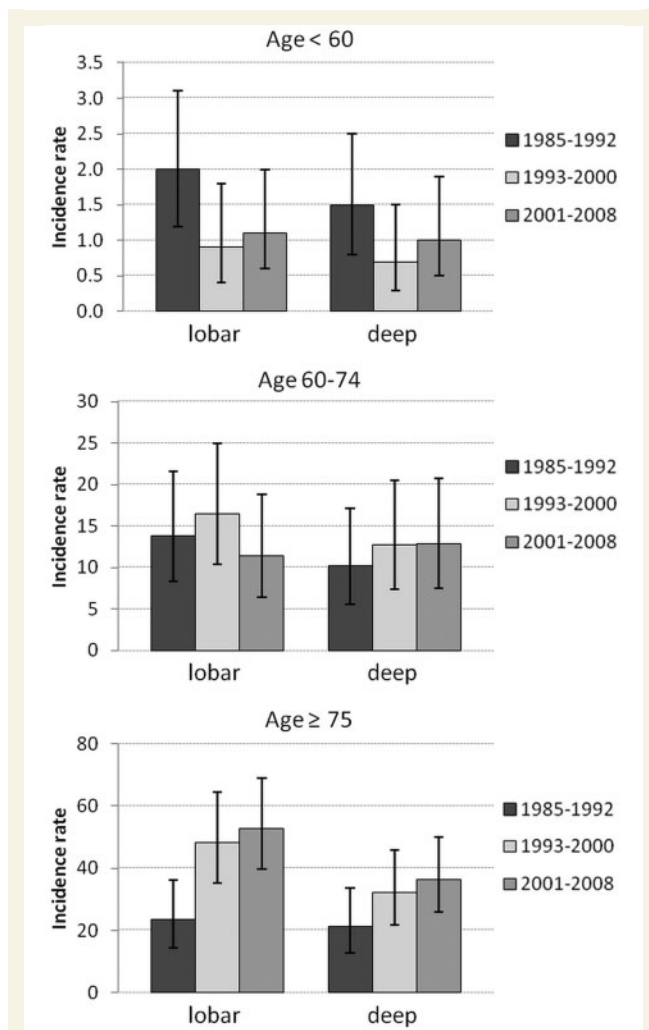
In the overall cohort, the prevalence of the premorbid use of antithrombotics increased with time in both patients with lobar ICH (OR = 1.10/year increase in time, 95% CI: 1.05–1.16, *P* < 0.001) and those with deep ICH (OR = 1.09/year increase in time, 95% CI: 1.03–1.15, *P* = 0.002) (Supplementary Table 2). In contrast, there was no change in either the prevalence of hypertension or the premorbid use of antihypertensive treatment, whatever the location considered. When considering age, the rise in the use of antithrombotics was observed in individuals aged ≥ 75 years with either lobar or deep ICH (Table 4), whereas only a non-significant trend was observed in those aged < 75 years (Supplementary Table 3).

## Discussion

Despite the apparent stable incidence of ICH observed from 1985 to 2008, important changes occurred in the profile of patients with ICH. Patients suffered their first ICH at an older age at the end of the study (75 years) than they did at the beginning of the study (67 years), indicating some improvement in primary prevention. However, an 80% increase in the incidence of ICH among people aged ≥ 75 years, contrasting with a 50% decrease in that in individuals aged < 60 years, may suggest that some bleeding-prone vasculopathies in the elderly are more likely to bleed when antithrombotic drugs are used, as illustrated by the rise in the incidence of lobar ICH in the elderly, in which cerebral amyloid angiopathy may be strongly implicated.

The major advantage of this study is the continuous and prospective ascertainment from 1985 to 2008 in a geographically well-defined population. To the best of our knowledge, this is the largest study on ICH conducted on a population-based registry ever described. Thanks to the overlapping sources of information to identify both hospitalized and non-hospitalized patients, case ascertainment was exhaustive. In addition, the population of Dijon was very stable, with < 5% migration, which avoided bias due to changes in ethnic mix, and there was no change in the economic status of local residents. Several limitations have to be acknowledged. Changes in the diagnostic procedures offered to stroke patients in our registry over time may have slightly influenced our findings about overall ICH incidence. Even though





**Figure 1** Temporal trends in crude incidence of ICH stratified by age groups and ICH location. Incidence rates expressed as  $n/100\,000/\text{year}$ .

access to brain imaging has been excellent since the beginning of the Dijon Stroke Registry, some temporal changes were observed. Indeed, 89.3% of patients had brain imaging in 1985–92, compared with 96.5% in 1993–2000, and 99.5% in 2001–08. Corresponding proportions were: (i) 100%, 99.4% and 99.6% in patients aged <60 years; (ii) 95%, 97.8% and 99.7% in patients aged 60–74 years; and (iii) 83.6%, 95.1% and 99.4% in patients aged  $\geq 75$  years. Therefore, it could be assumed that the better imaging coverage in the elderly in our registry may have contributed in part to an increase in overall ICH incidence in this age group as well as in lobar ICH. Moreover, only one ICH patient was identified by MRI, and CT scans were used to determine ICH location for the others. Therefore, our divergent findings for trends in incidence (i.e. only limited increase in deep ICH incidence contrasting with great increase in lobar ICH incidence) cannot be explained by a better detection due to changes in diagnostic procedures. In addition, this limited access to MRI data, which is often the case in population-based studies, precluded assessment of MRI biomarkers such as brain microbleeds. Another potential

limitation is that the severity of arterial hypertension was not documented. These data would have been useful to study the potential influence of the severity of arterial hypertension according to the underlying vasculopathy. Finally, the number of cases with pre-stroke use of antithrombotics was small in patients aged  $\geq 75$  years during the first study period, which may have underpowered our analyses.

We found that the global incidence of ICH remained stable overtime, but incidence rates in people aged >75 years ( $n = 238$  patients) increased dramatically. Contrary to our results, the Oxfordshire population-based stroke registry reported, in a cohort of 107 patients with ICH, a 40% decrease in the incidence of ICH among people aged <75 years ( $n = 46$  patients) between 1981–86 and 2002–06, whereas the incidence was stable in individuals aged >75 years ( $n = 61$  patients) (Lovelock *et al.*, 2007). It cannot be excluded that differences in healthcare policy with regard to access to brain imaging for elderly people, and the smaller number of patients included in the Oxfordshire cohorts, may account for the discrepancies between these results and ours. In line with our results, in the Greater Cincinnati/Northern Kentucky area, an increase in the incidence of ICH was observed in people older than 70 years (Flaherty *et al.*, 2007). However, the study was limited by being hospital-based.

Because the suspected underlying vasculopathies in deep and lobar ICH may differ, we assessed the changes in the risk factors and premorbid treatment profiles of patients with ICH according to the anatomical distribution of ICH. As a first result, we did not find any major differences in the distribution of vascular risk factors, including that of arterial hypertension. Although arterial hypertension is a major risk factor for ICH in the general population, it has long been considered more frequently associated with deep ICH (Ariesen *et al.*, 2003). In a meta-analysis, Jackson and Sudlow (2006) found a higher prevalence of arterial hypertension in patients with deep versus lobar ICH, but they underlined the fact that this result could be due to methodological biases of selected studies. Our results underline the fact that arterial hypertension is a frequent risk factor that contributes to ICH whatever the location and not only to deep ICH. Moreover, this proportion of hypertensive patients in different locations remained stable over time. We found similar temporal trends in the prevalence of the premorbid use of antithrombotic agents in both lobar and deep ICH. Hence, we demonstrated that the use of antithrombotic agents increased between 1985–92 and 1993–2008 to the same extent in patients aged  $\geq 75$  years with lobar or deep ICH. Concomitantly, only the incidence of lobar ICH increased significantly in this age group, whereas a simple trend was observed for deep ICH, despite a decrease in the use of antihypertensive treatment in patients with ICH in this location. As a result, it can be assumed that some patients aged  $\geq 75$  years using antithrombotic agents were more susceptible to lobar ICH because of a specific underlying disease, such as cerebral amyloid angiopathy (Vernooij *et al.*, 2009; Lovelock *et al.*, 2010).

Our findings have some implications for clinicians or policymakers. Despite the overall stable incidence of ICH, some preventive strategies have been effective. The age at onset of first-ever ICH has increased and this is encouraging for public health. However, the decrease in the incidence of ICH in younger

**Table 3** Distribution of risk factors and premorbid treatments in patients with lobar and deep ICH in Dijon, France, from 1985 to 2008

Risk factors and treatments	Lobar ICH		Deep ICH		P
	n (%)	95% CI	n (%)	95% CI	
Hypertension	122 (56.7)	50.1–63.4	107 (64.8)	57.5–72.2	0.110
Diabetes	33 (15.3)	10.5–20.2	23 (13.9)	8.6–19.3	0.701
Hypercholesterolaemia	44 (20.5)	15.0–25.9	29 (17.6)	11.7–23.4	0.479
Atrial fibrillation	39 (18.1)	12.9–23.3	32 (19.4)	13.3–25.5	0.756
Myocardial infarction	28 (13.0)	8.5–17.6	16 (9.7)	5.1–14.3	0.315
Transient ischaemic attack	21 (9.8)	5.8–13.8	22 (13.3)	8.1–18.6	0.277
Premorbid treatments					
Antiplatelet agents	37 (17.2)	12.1–22.3	28 (17.0)	11.2–22.8	0.951
Anticoagulants	21 (9.8)	5.8–13.8	23 (13.9)	8.6–19.3	0.208
Any antithrombotic treatment	55 (25.6)	19.7–31.5	51 (30.9)	23.8–38.0	0.251
Antihypertensive treatments	86 (40.0)	33.4–46.6	76 (46.1)	38.4–53.7	0.236

**Table 4** Temporal changes in the prevalence of ICH risk factors and pre-stroke treatments in patients aged  $\geq 75$  years by ICH location

Risk factors and treatments	1985–92		1993–2000		2001–08		OR <sup>a</sup> (95% CI)	P
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI		
Lobar								
Hypertension	11 (55.0)	31.1–78.9	24 (53.3)	38.2–68.5	39 (70.9)	58.5–83.3	1.05 (0.99–1.11)	0.115
Diabetes	3 (15.0)	0–32.1	6 (13.3)	3.0–23.7	10 (18.2)	7.7–28.7	1.03 (0.95–1.11)	0.508
Hypercholesterolaemia	0		7 (15.6)	4.5–26.6	13 (23.6)	12.0–35.2	1.16 (1.04–1.29)	0.005
Atrial fibrillation	3 (15.0)	0–32.1	12 (26.7)	13.2–40.1	14 (25.5)	13.6–37.3	1.01 (0.95–1.08)	0.723
Myocardial infarction	2 (10.0)	0–24.4	9 (20.0)	7.8–32.2	5 (9.1)	1.2–16.9	1.00 (0.92–1.09)	0.918
Transient ischaemic attack	3 (15.0)	0–32.1	2 (4.4)	0.0–10.7	6 (10.9)	2.4–19.4	0.98 (0.89–1.08)	0.708
Premorbid treatments								
Antiplatelet agents	2 (10.0)	0–24.4	9 (20.0)	7.8–32.2	14 (25.5)	13.6–37.3	1.09 (1.00–1.18)	0.042
Anticoagulants	1 (5.0)	0–15.5	5 (11.1)	1.6–20.7	11 (20.0)	9.1–30.9	1.12 (1.01–1.24)	0.033
Any antithrombotic treatment	3 (15.0)	0–32.1	14 (31.1)	17.0–45.2	24 (43.6)	30.1–57.2	1.12 (1.04–1.21)	0.002
Antihypertensive treatments	8 (40.0)	16.5–63.5	18 (40.0)	25.1–54.9	28 (50.9)	37.3–64.5	1.03 (0.97–1.09)	0.370
Deep								
Hypertension	15 (83.3)	64.3–100	21 (70.0)	52.6–87.4	24 (63.2)	47.1–79.2	0.96 (0.90–1.04)	0.340
Diabetes	2 (11.1)	0–27.2	7 (23.3)	7.3–39.4	3 (7.9)	0.0–16.9	0.98 (0.89–1.07)	0.622
Hypercholesterolaemia	1 (5.6)	0–17.3	5 (16.7)	2.5–30.8	9 (23.7)	9.5–37.8	1.08 (0.98–1.19)	0.119
Atrial fibrillation	4 (22.2)	0.9–43.5	7 (23.3)	7.3–39.4	13 (34.2)	18.4–50.0	1.08 (1.00–1.18)	0.053
Myocardial infarction	3 (16.7)	0–35.7	3 (10.0)	0.0–21.4	3 (7.9)	0.0–16.9	0.95 (0.86–1.06)	0.361
Transient ischaemic attack	3 (16.7)	0–35.7	5 (16.7)	2.5–30.8	1 (2.6)	0.0–8.0	0.91 (0.82–1.02)	0.093
Premorbid treatments								
Antiplatelet agents	1 (5.6)	0–17.3	10 (33.3)	15.4–51.2	9 (23.7)	9.5–37.8	1.03 (0.95–1.12)	0.407
Anticoagulants	0 (0)		4 (13.3)	0.4–26.2	10 (26.3)	11.6–41.0	1.22 (1.06–1.40)	0.006
Any antithrombotic treatment	1 (5.6)	0–17.3	14 (46.7)	27.7–65.6	19 (50.0)	33.3–66.7	1.12 (1.04–1.22)	0.004
Antihypertensive treatments	14 (77.8)	56.5–99.1	17 (56.7)	37.8–75.5	15 (39.5)	23.2–55.8	0.91 (0.85–0.98)	0.015

<sup>a</sup>Odds ratio (OR) per 1-year increase in time.

people, probably reflecting better control of arterial hypertension, has been outweighed by an increase in lobar ICH associated with the use of antithrombotics in the elderly. This highlights the fact that ICH is not a homogenous entity but encompasses different underlying vasculopathies with different contributing factors, such as antithrombotic treatments, and may suggest the need for personalized medicine in the future to tailor primary prevention to each individual. Hence, the better identification of patients

with severe cerebral amyloid angiopathy, whose risk of lobar ICH is high, could be a valuable opportunity to adapt the use of antithrombotic agents in older people and reduce the risk of ICH. MRI biomarkers such as brain microbleeds might be useful in this perspective (Cordonnier *et al.*, 2007).

Finally, as illustrated by the high prevalence of vascular risk factors, patients with ICH are also affected by vaso-occlusive disease, such as ischaemic heart disease, transient ischaemic

attack or atrial fibrillation. There are no robust recommendations to guide clinicians in the management of patients with ICH under antithrombotic agents (Steiner *et al.*, 2006). Regarding the management of acute ICH in patients with antiplatelets, clinical trials such as the Platelet Transfusion in Cerebral Haemorrhage (PATCH) trial are on underway (de Gans *et al.*, 2010). Regarding secondary prevention, it is unclear whether antithrombotic treatments, especially antiplatelets, modify the risks of recurrent ICH and thrombotic events after ICH (Flynn *et al.*, 2010). In the face of this increase in the incidence of ICH among elderly people under antithrombotic agents, future research should focus on the impact of antithrombotic agents, which may differ according to the underlying vessel disease.

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## Supplementary material

Supplementary material is available at *Brain* online.

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