Risk of primary intracerebral haemorrhage associated with aspirin and non-steroidal anti-inflammatory drugs: case-control study

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Abstract

Objective To examine the association between use of aspirin or other non-steroidal anti-inflammatory drugs and intracerebral haemorrhage.
Design Case-control study.
Setting 13 major city hospitals in the Melbourne and metropolitan area.
Subjects 331 consecutive cases of stroke verified by computed tomography or postmortem examination, and 331 age (± 5 years) and sex matched controls who were community based neighbours.
Interventions Questionnaire administered to all subjects either directly or by proxy with the next of kin. Drug use was validated by reviewing prescribing records held by the participants' doctors.
Main outcome measures Previous use of aspirin or other non-steroidal anti-inflammatory drugs.
Results Univariate analysis showed no increased risk of intracerebral haemorrhage with low dose aspirin use in the preceding 2 weeks. Using multiple logistic regression to control for possible confounding factors, the odds ratio associated with the use of aspirin was 1.00 (95% confidence interval 0.60 to 1.66, P = 0.998) and the odds ratio associated with the use of other non-steroidal anti-inflammatory drugs was 0.85 (0.45 to 1.61, P = 0.611) compared with respective non-users in the preceding fortnight. Moderate to high doses of aspirin (> 1225 mg/week spread over at least three doses) yielded an odds ratio of 3.05 (1.02 to 9.14, P = 0.047). There was no evidence of an increased risk among subgroups defined by age, sex, blood pressure status, alcohol intake, smoking, and the presence or absence of previous cardiovascular disease.
Conclusions No increase in risk of intracerebral haemorrhage was found among aspirin users overall or among those who took low doses of the drug or other non-steroidal anti-inflammatory drugs. These data provide evidence that doses of aspirin usually used for prophylaxis against vascular disease produce no substantial increase in risk of intracerebral haemorrhage.

Introduction

An increased risk of intracerebral haemorrhage has been observed in several of the major primary and secondary prevention trials using aspirin.[1–12] Because of the poor outcome in patients developing intracerebral haemorrhage,[13–15] there has been concern that intracerebral haemorrhage might offset the benefits of aspirin treatment, particularly when used in low risk settings such as for the primary prevention of coronary heart disease.[2 16]

Despite the large number of clinical trials of aspirin treatment there remains considerable uncertainty about the nature and extent of this risk.[2 4 5 8 11 12 17 18] Firstly, in each of the published trials the absolute numbers of cases of intracerebral haemorrhage have been small, leading to wide confidence intervals about the risk estimates.[4–8 17 19] The uncertainty is compounded by diagnostic inaccuracy, as in most trials only a minority of patients with stroke underwent computed tomography.[2 4–7 12 17–19] Secondly, there is little information about whether the relative risk, if any, is confined to identifiable subgroups such as elderly people or those with hypertension. Finally, it has not been clear whether any increased risk associated with aspirin treatment also affects those taking non-steroidal anti-inflammatory drugs, which share many of the antiplatelet properties of aspirin.[20 21]

To address these issues we established a case-control study to explore the use of aspirin and non-steroidal anti-inflammatory drugs among cases of intracerebral haemorrhage (verified by computed tomography and postmortem examination) and age and sex matched controls. A principal hypothesis of our study was that each of these drug groups would be associated with an increased risk of intracerebral haemorrhage.

Methods

The patients and methods have been described in detail elsewhere.[22] Briefly, from 1990 to 1992 consecutive cases of primary intracerebral haemorrhage in Melbourne were identified by surveillance of discharge records of 13 major city hospitals and by a periodic inspection of coroner's records. The participating hospitals manage most of the cases of primary intracerebral haemorrhage in the metropolitan area, except for minor strokes and strokes occurring in elderly nursing home residents.

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Inclusion criteria—Intracerebral haemorrhage was defined as a sudden onset of an acute focal neurological deficit with evidence of intraparenchymal haemorrhage provided by computed tomography (94.9%; 314/331), postmortem examination (4.8%; 16), or magnetic resonance imaging (0.3%; 1). Patients were aged between 18 and 80 years, and the intracerebral haemorrhage was their first episode of stroke (although patients with previous transient ischaemic attacks were not excluded). We excluded patients with intracerebral haemorrhages secondary to arteriovenous malformations, tumours, clotting abnormalities, blood discrasias, or anticoagulant (heparin, warfarin) or thrombolytic use, or after the ingestion of sympathomimetic drugs, and patients with haemorrhagic infarction. Haemorrhagic infarction was defined as a patchy or diffuse haemorrhage within a definite cerebral infarction.

Controls—Controls were individually matched by age (± 5 years) and sex. They were identified by visiting houses in the same street in which the case lived at the time of the stroke (in a strict protocol) until a household with a matching individual free of previous cerebrovascular disease was identified. This method of neighbourhood selection allows for matching by socioeconomic status. To avoid ascertainment bias toward unemployed or housebound individuals, repeat visits were made up to three times during the evening and weekends if no one was home during the day. The nurses conducting the visits were required to verify that no potential control lived at each house before moving on to the next house.

Questionnaire survey

Trained nurse interviewers administered structured questionnaires to all participants eliciting information about potential risk factors. All questions related to the time period immediately preceding the stroke (cases) or interview (controls). Interview of controls was undertaken by the same research nurse who interviewed the corresponding case. Patients who had died or were unable to answer for themselves were included by interview of next of kin. These proxy interviews occurred in 43% of cases (142). To avoid information bias, individuals acting as controls by proxy were asked to nominate an equivalent relative to ensure a similar manner of interview to the corresponding case and similar information sources used. Proxy interviewing occurred for 31% of controls (101). When a proxy control was either not available or refused to participate the index control was interviewed instead. This occurred in 41 instances.

The section of the questionnaire on aspirin and other non-steroidal anti-inflammatory drugs sought information on daily doses of non-steroidal anti-inflammatory drugs taken in the fortnight before the stroke (cases) or interview (controls). Prompt cards displaying samples and names of each pharmaceutical preparation were shown to subjects. There were two prompt cards, one each for aspirin and other non-steroidal anti-inflammatory drugs. A history of ingestion (dose, frequency, and duration) of any of these products over the 14 days preceding the time of stroke (cases) or interview (controls) was obtained. Doctors' prescription records for drug use for the relevant 12 month period were also reviewed in 69% of cases (230) and 74% of controls (245).

Any drugs containing aspirin or other non-steroidal anti-inflammatory drugs taken in the fortnight period were categorised according to dose and regularity of ingestion. Subjects taking >1225 mg/week over at least 3 days in each of the fortnights before the stroke (cases) or interview (controls) were considered to have taken a moderate to high dose. Individuals taking ≥ 200 mg/day were included in this category. The low dose category included those taking 100-175 mg/day, which is the dose range widely used for vascular prophylaxis. These doses were specified before any analysis was undertaken.

Information on other medical conditions was obtained at interview. Hypertension, previous cardiovascular disease, and high serum cholesterol concentrations were considered present when patients reported that one or other of these conditions had been diagnosed by their doctor.

Self reported height and weight data were used to calculate body mass index. A never smoker was a person who had not smoked at least one cigarette, cigar, or pipe per day for at least 3 months at some period in his or her lifetime. A current smoker had smoked at least one cigar, cigarette, or pipe per day for the preceding 3 months. The current smoker category was further divided into those who smoked <20 cigarettes/day on average and those who smoked ≥ 20 cigarettes/day. A former smoker did not meet the criteria for never or current smoking. Alcohol intake was categorised into never drinker, previous drinker, and three levels of current alcohol intake (acceptable, harmful, or hazardous drinking). For men acceptable, hazardous, or harmful drinking was consumption of 1-40 g of alcohol per day, >40-60 g/day, and >60 g/day respectively, whereas for women it was 1-20 g/day, >20-40 g/day, and >40 g/day respectively. Ten grams of alcohol was considered to be equivalent to one standard drink.

Adherence to study procedures was monitored at weekly quality control meetings. During these meetings procedures for recently obtained interviews were discussed and response rates were carefully scrutinised.

Our study with 331 matched pairs was designed to achieve a power of 0.8, using a P value of 0.05 and with an estimated 15% of controls (50) being aspirin users, to detect an odds ratio of 1.75.

Statistical analysis—We used conditional logistic regression for matched data (using EGRET[23]) to compute odds ratios approximating the relative risks of intracerebral haemorrhage for various exposures. Initially, we calculated univariate odds ratios for aspirin, other non-steroidal anti-inflammatory drugs, and potentially confounding variables. We included all plausible potential confounding factors in the multivariate analyses (hypertension, serum cholesterol concentration, diabetes, previous cardiovascular disease, body mass index, exercise, alcohol intake, and smoking). We did not include age, sex, and socioeconomic status because the cases were matched on these variables. Interactions between aspirin use and potential confounding variables (age, hypertension, smoking, alcohol intake, serum cholesterol concentration, exercise, diabetes, sex, and previous cardiovascular disease) were assessed by the likelihood ratio

Table 1 Baseline characteristics of patients and controls

Variable	No (%) of cases (n=331)	No (%) of controls (n=331)
Sex:		
Male	200 (60)	200 (60)
Female	131 (40)	131 (40)
Ethnic group:		
White	289 (87)	307 (93)
Disease status:		
Hypertension	176 (54)	121 (37)
Previous cardiovascular disease	35 (11)	52 (16)
High cholesterol concentration	47 (14)	77 (23)
Diabetes	26 (8)	30 (9)
Smoking status:		
Never smoker	139 (42)	142 (43)
Current smoker (<20 cigarettes/day)	31 (9)	34 (11)
Current smoker (≥20 cigarettes/day)	53 (16)	34 (11)
Former smoker	107 (32)	121 (37)
Lifetime sedentary disposition	136 (41)	104 (31)
Alcohol intake:		
Never regular drinker	73 (22)	67 (20)
Current drinker (acceptable)	159 (49)	212 (64)
Current drinker (hazardous)	17 (5)	14 (4)
Current drinker (harmful)	45 (14)	13 (4)
Former drinker	33 (10)	25 (8)
Mean body mass index (kg/m^2) (SD)	25.5 (4.8)	25.7 (4.0)
Mean age (SD)	63.4 (12.4)	63.4 (12.4)

statistic.[24] Confidence intervals for odds ratios were based on large sample theory for conditional maximum likelihood estimators.[24] Two sided significance levels were used throughout.

Ethics—Our study was approved by the responsible ethics committees at Monash University and each of the participating hospitals.

Results

We identified a total of 370 consecutive patients who were eligible for the study. Ten cases could not be contacted and 29 refused to participate, leaving a case series of 331 patients. To obtain the same number of controls, we identified 342 people matched for age, sex, and geography; 11 refused to participate. The mean age was 63.4 years (SD 12.4), and 60% (200) were men (table 1). Over 90% of the participants were white.

Overall, 17% of cases (55) and 18% of controls (58) reported taking aspirin in the fortnight before onset of stroke or interview (table 2). Using multiple logistic regression to control for possible confounding factors, the odds ratio for aspirin use was 1.00 (95% confidence interval 0.60 to 1.66, P = 0.998). Similarly, 13% of cases (42) and 14% of controls (47) reported taking non-steroidal anti-inflammatory drugs in the previous fortnight producing an adjusted odds ratio of 0.85 (0.45 to 1.61, P = 0.611). A similar pattern was evident in individuals who took aspirin or non-steroidal anti-inflammatory drugs in the previous 3 days.

When aspirin users were grouped according to their regular dosage regimen, regular low dose (≤1225 mg/week) intakes were reported by 5% of cases (16) and 6% of controls (21) producing an adjusted odds ratio of 0.86 (0.38 to 1.96, P = 0.724). Moderate to high doses (>1225 mg/week) were reported by 6% of cases (19) and 3% of controls (9) producing an adjusted odds ratio of 3.05 (1.02 to 9.14, P = 0.047). The ratio of these two odds ratios was 3.53 (0.95 to 13.1, P = 0.060). A similar pattern was observed when these analyses were confined to those using either drug within the previous 3 days. These analyses were specified as part of the original hypothesis of our study.

A further prespecified subgroup analysis was undertaken to determine whether the relative risk was increased selectively among members of an identified subgroup of aspirin users. Odds ratios for aspirin use (in the previous fortnight) were examined in subgroups defined by sex, blood pressure, history of cardiovascular disease, smoking, high serum cholesterol concentration, alcohol intake, or age (table 3).

Table 2 Crude and adjusted odds ratios of primary intracerebral haemorrhage for use of aspirin and other non-steroidal anti-inflammatory drugs estimated by multiple logistic regression

Drug use	Cases (n=331)	Controls (n=331)	Crude odds ratio*	Adjusted odds ratio (95% CI)†	P value‡
Aspirin in previous fortnight:					
No	245 (74)	264 (80)	1.00	1.00	
Yes	55 (17)	58 (18)	0.93	1.00 (0.60 to 1.66)	0.998
Aspirin dose in previous fortnight:					
None	245 (74)	264 (80)	1.00	1.00	
Casual: used less than alternate daily	19 (6)	28 (8)	0.66	0.65 (0.31 to 1.36)	0.253
≤1225 mg/week at least alternate daily	16 (5)	21 (6)	0.84	0.86 (0.38 to 1.96)	0.724
>1225 mg/week at least alternate daily	19 (6)	9 (3)	2.34	3.05 (1.02 to 9.14)	0.047
test for heterogeneity: χ^2 (2 df) = 5.73, P=0.057					
Non-steroidal anti-inflammatory drugs in previous fortnight:					
No	258 (78)	277 (84)	1.00	1.00	
Yes	42 (13)	47 (14)	0.93	0.85 (0.45 to 1.61)	0.611
Aspirin in previous 3 days:					
None	252 (76)	284 (86)	1.00	1.00	
Low dose	17 (5)	21 (6)	0.89	0.94 (0.42 to 2.07)	0.871
Moderate-high dose	30 (9)	20 (6)	1.54	1.60 (0.76 to 3.37)	0.215
All aspirin doses	50 (15)	41 (12)	1.30	1.42 (0.81 to 2.48)	0.217
Non-steroidal anti-inflammatory drugs in previous 3 days:					
No	267 (81)	288 (87)	1.00	1.00	
Yes	31 (9)	35 (11)	1.00	1.03 (0.52 to 2.03)	0.942

*Univariate conditional logistic regressions not adjusting for confounding variables.
†Adjusted odds ratio = odds ratio obtained from multivariate analyses adjusted for hypertension, serum cholesterol concentration, diabetes, previous cardiovascular disease, body mass index, exercise, alcohol intake, and smoking. ‡For adjusted odds ratios.

Table 3 Effect of interaction between aspirin and selected risk factors

Factors	Aspirin in previous fortnight: No (%) of cases	Aspirin in previous fortnight: No (%) of controls	Adjusted odds ratios (95% CI)*	P value
Hypertension:†				
Hypertensive	26/160 (16)	26/116 (22)	0.53 (0.25 to 1.14)	0.028
Normotensive	29/135 (21)	32/206 (16)	1.62 (0.83 to 3.14)	
High cholesterol concentration:†				
High cholesterol concentration	10/43 (23)	12/72 (17)	2.62 (0.80 to 8.57)	0.077
Not advised of high cholesterol concentration	44/256 (17)	45/249 (18)	0.81 (0.47 to 1.42)	
Cardiovascular disease history:†				
Yes	11/29 (38)	15/49 (31)	0.98 (0.32 to 3.03)	0.967
No	43/266 (16)	43/271 (16)	1.01 (0.58 to 1.75)	
Smoking status:†				
Current smoker	12/75 (16)	10/68 (15)	1.33 (0.36 to 4.94)	0.896
Never smoker	24/128 (19)	24/135 (18)	0.93 (0.43 to 1.98)	
Former smoker	19/97 (20)	24/119 (20)	1.01 (0.47 to 2.17)	
Alcohol intake:†				
Current drinker	36/205 (18)	45/233 (19)	0.85 (0.47 to 1.51)	0.391
Never drinker	12/65 (18)	8/64 (13)	1.87 (0.52 to 6.67)	
Former drinker	7/30 (23)	5/25 (20)	1.92 (0.40 to 9.38)	
Sex:†				
Female	20/120 (17)	21/123 (17)	1.01 (0.47 to 2.17)	0.981
Male	35/180 (19)	37/199 (19)	1.00 (0.51 to 1.96)	
Age:				
Increases for each year of age	—	—	1.04 (0.997 to 1.09)	0.051

*Multivariate analyses adjusted for hypertension, serum cholesterol concentration, diabetes, previous cardiovascular disease, body mass index, exercise, alcohol intake, and smoking.
†Aspirin use in previous fortnight versus no use in previous fornight for each analysis.

Three of the interactions were of borderline statistical significance at the 5% level (blood pressure, serum cholesterol concentration, and age), but there was no evidence of a substantially increased risk in any of these subgroups.

Discussion

The results of our case-control study show that aspirin treatment in the doses commonly used for cardiovascular protection produces little, if any, increase in the risk of intracerebral haemorrhage. Higher doses were associated with a threefold increase in risk, although this was of borderline statistical significance. The 95% confidence intervals provide evidence to exclude odds ratios in excess of 1.7 among all aspirin users and of 2.0 for users of low dose aspirin. Low doses of aspirin have been shown to effectively inhibit the production of thromboxane A_2 (98% inhibition) in platelets[25] and to be associated with less gastrointestinal toxicity than are high doses.[11 26 27]

A similar result was found among users of non-steroidal anti-inflammatory drugs, where the overall adjusted odds ratio was 0.85. The 95% confidence interval indicates that the true odds ratio is unlikely to be >1.6.

Our findings are in keeping with those recently reported in a large cohort study of 87 678 US nurses.[28] Over a 6 year period, 62 (0.07%) participants developed a haemorrhagic stroke. Among those taking between one and six doses of aspirin per week the relative risk was 0.76 (95% confidence interval 0.27 to 2.13). Those taking 7 to 14 doses per week had a relative risk of 1.65 (0.83 to 3.27). These risk estimates changed little after adjustment for age, smoking, hypertension, and alcohol intake.

Primary and secondary prevention trials

The possibility that aspirin might increase the risk of intracerebral haemorrhage has been raised in two large primary intervention studies and several large secondary prevention trials among patients with a history of stroke or transient ischaemic attack (table 4).[1 2 4–8 11 12 17–19] It has been difficult, however, to draw firm conclusions about the extent and nature of the relative risk owing to the small number of cases observed, the diagnostic imprecision involved in clinically diagnosing intracerebral haemorrhage, and the varying aspirin doses used. Several studies included intracerebral haemorrhage within the category of haemorrhagic stroke and are therefore likely to have included a substantial number of individuals with haemorrhagic transformation after an ischaemic stroke.

Table 4 Primary and secondary prevention studies of ischaemic stroke and transcient ischaemic attack: double blind placebo controlled trials of aspirin treatment (includes only studies in which intracerebral haemorrhage is categorised separately from cerebral infarction, and excludes studies with less than 1 month follow up and those not including results for haemorrhagic strokes separately)

Study	Strokes verified by computed tomography (%)*	Aspirin dose (mg/day)	No of haemorrhagic strokes: Treated group	No of haemorrhagic strokes: Placebo group	Odds ratio (95% CI)
Secondary prevention studies:					
Aspirin in transient ischemic attacks study[4 5 17]	No	1300	1	0	7.2 (0.1 to 365)
Accidents ischémiques cérébraux liés à l'athéroslérose study[6 19]	No	990	2 intracerebral haemorrhages	2 intracerebral haemorrhages	1.0 (0.1 to 7.4)
Danish cooperative study[7]	No	1000	1 death from intracerebral haemorrhage	1 death from intracerebral haemorrhage	1.0 (0.1 to 16.3)
Swedish cooperative study[8]	Yes (66)	1500	3	2	1.5 (0.3 to 8.7)
Swedish Aspirin Low-dose Trial Collaborative Group[11]	Yes (98)	75	11	7	1.6 (0.6 to 4.0)
UK Transient Ischaemic Attack Study Group[12 18]	Yes (45)	1200	7 definite	2 definite	2.6 (0.9 to 7.3)
		300	7 definite		
All secondary prevention studies					1.80 (0.99 to 3.25)
Primary prevention studies:					
British doctors[1]	No	500 or 300	13	6	1.1 (0.4 to 2.8)
US physicians'[2]	No	325 alternate daily	23	12	1.9 (0.97 to 3.6)
All primary prevention studies					1.57 (0.91 to 2.70)
All studies					1.67 (1.12 to 2.49)

*No includes those with no mention of computed tomography.

Low dose aspirin treatment was used in two of the large scale trials of this drug.[2 11] In the US physicians' health study (a primary prevention study), where the dose of aspirin was 325 mg on alternate days, 23 out of 11 037 cases (0.21%) of intracerebral haemorrhage were identified among aspirin users and 12 out of 11 034 cases (0.11%) were identified among controls yielding an odds ratio of 2.14 (95% confidence interval 0.96 to 4.77). In the Swedish Aspirin Low-dose Trial (SALT) Collaborative Group study (a secondary prevention study), where the dose of aspirin was 75 mg/day, 11 out of 676 cases (1.6%) of haemorrhagic stroke were observed among those taking aspirin and 7 out of 684 cases (1.0%) were observed among the controls yielding an odds ratio of 1.6 (0.6 to 4.0). The results of both studies were compatible with a 4.0-fold to 4.8-fold increase in risk of intracerebral haemorrhage, which would substantially reduce the net benefit of aspirin treatment in low risk populations.

Key messages

- Low to moderate dose aspirin treatment does not substantially increase the risk of intracerebral haemorrhage
- No increase in risk of intracerebral haemorrhage was observed among users of non-steroidal anti-inflammatory drugs
- Users of high doses of aspirin may have an increased risk of intracerebral haemorrhage, but numbers of cases in the group were small and the finding is therefore tentative

Advantages of study methodology

The case-control methodology used in our study has several advantages over clinical trials or cohort studies. Firstly, the large number of cases allows a substantially more precise estimate of the relative risk than has previously been available. Our study would not exclude a small increase in risk but no study design could achieve this.

Secondly, our study design allows an examination of relative risks in specific subgroups of patients where the risks and benefits of treatment may differ from the average. There was no evidence that the use of aspirin produced a larger excess risk of intracerebral haemorrhage among particular subgroups of patients, such as elderly people or those with a history of hypertension or high serum cholesterol concentrations. Although moderate increases in odds ratios were seen in some subgroups, these were of borderline statistical significance and likely to be attributable to chance.

Another advantage of our study is that all cases of intracerebral haemorrhage were confirmed by computed tomography, magnetic resonance imaging, or postmortem examination. Since cases associated with neoplasms, aneurysms, trauma, and anticoagulant use were excluded, the results of our study apply specifically to spontaneous intracerebral haemorrhage. The validity of our results is supported by the fact that an association between intracerebral haemorrhage and use of aspirin or non-steroidal anti-inflammatory drugs was the principal a priori hypothesis of our study.

Potential biases and confounding

As with all case-control studies, the results of our investigation are potentially influenced by both bias and confounding. The most significant of these is recall bias as the results depend largely on subjects providing information about their past. To minimise the differences between cases and controls, the questionnaire focused mainly on retrieving simple information likely to be memorable to both the subjects and their next of kin.

When any significant level of memory impairment was suspected, information was obtained from the closest available next of kin (in such cases information was also sought from the next of kin of the controls). It is possible that the greater number of proxy interviews conducted among cases (142), when compared with controls (101), may have introduced some bias. Respondent-proxy agreement has been shown to be greatest when the proxy lives in the same house as the respondent.[29] In our study, interviews were conducted with either the index participant or with a proxy living in the same household as the index subject in 82% of cases (271) and 91% of controls (300), thus reducing potential for bias introduced by proxy respondents not living in the same household. Exclusion of cases requiring proxy interview would be likely to severely limit the generalisability of the data toward the less severe intracerebral haemorrhages. Studies using this design have been widely employed in stroke research, and where similar questions have been subsequently examined by other research designs (principally cohort studies) the results have generally been similar.[30–32]

Clinical significance

The increased risk of intracerebral haemorrhage among users of moderate to high doses of aspirin (>1225 mg/week) was based on a small number of cases and only just reached statistical significance. This finding should therefore be regarded as tentative and requiring confirmation. It is also notable that the adjusted risk ratio was similar regardless of whether or not a history of hypertension was controlled for in the analysis. This suggests that any risk associated with high doses of aspirin is unlikely to be confounded by interference with blood pressure control.

The significance of our results to preventive medicine can be seen by applying the results to the findings of the US physicians health study.[2] In this trial, for every 10 000 patients treated per year 18 cases of myocardial infarction were prevented and two excess cases of haemorrhagic stroke occurred. However, the 95% confidence interval was compatible with up to eight additional cases of haemorrhagic stroke. Our results indicate a 95% probability that the number of cases of intracerebral haemorrhage in this setting would not exceed two.

Conclusion

Our study did not identify any meaningful increase in risk of intracerebral haemorrhage among aspirin users overall or among low dose aspirin users in particular. Although a statistically significant threefold increase in

risk was observed among users of high dose aspirin, this finding should be regarded as tentative and requiring confirmation. Fear of intracerebral haemorrhage should not therefore discourage the use of low doses of aspirin for vascular prophylaxis when it is otherwise indicated. Despite the reassurance provided by our study, it should be emphasised that a proper assessment of the risks and benefits of treatment with aspirin in low risk settings—for example, for primary prevention—will only be established by large clinical trials.

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Corrections

Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up

Two errors occurred in this paper by Thorsteinn Blondal and colleagues (30 January, pp 285-9). The results section of the abstract should read "Sustained abstinence rates for the patch and nasal spray group and patch only group were 51% *v* 35% after 6 weeks (odds ratio 1.97, 95% confidence interval 1.17 to 3.32; P = 0.011(χ^2)), 37% *v* 25% after 3 months (1.76, 1.01 to 3.08; P = 0.045), 31% *v* 16% after 6 months (2.40, 1.27 to 4.50; P = 0.005), 27% *v* 11% after 12 months (3.03, 1.50 to 6.14; P = 0.001), and 16% *v* 9% after 6 years (2.09, 0.93 to 4.72; P = 0.08)."

The statistical analyses section should read "We based the number of participants required for the efficacy analysis on a significance level of 5% using a one tailed test, a power of 90%, and there being 55% of participants in the patch and nasal spray group and 35% in the patch and placebo group, successful after 3 months; 105 participants were needed in each treatment group."

Assessment of competence to complete advance directives:validation of a patient centred approach

An error occurred in this paper by Seena Fazel and colleagues (20 February, pp 493-7). In the question and answer sheet, the answer to the second question should read "Clear answer (0) [not 1]."