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UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database

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Abstract

Objectives

Stroke is a major cause of morbidity and mortality. This study aimed to investigate secular trends in stroke across the UK.

Design

This study aimed to investigate recent trends in the epidemiology of stroke in the UK. The study was a time-trend analysis from 1999 to 2008 within the UK General Practice Research Database. Outcome measures were incidence and prevalence of stroke, stroke mortality, rate of secondary cardiovascular events, and prescribing of pharmacological therapy for primary and secondary prevention of cardiovascular disease.

Results

The study cohort included 32 151 patients with a first stroke. Stroke incidence fell by 30%, from 1.48/1000 person-years in 1999 to 1.04/1000 person-years in 2008 (P<0.001). Stroke prevalence increased by 12.5%, from 6.40/1000 in 1999 to 7.20/1000 in 2008 (P<0.001). Fifty-six-day mortality after first stroke reduced from 21% in 1999 to 12% in 2008 (P<0.0001). Prescribing of drugs to control cardiovascular risk factors increased consistently over the study period, particularly for lipid lowering agents and antihypertensive agents. In patients with atrial fibrillation, use of anticoagulants prior to first stroke did not increase with increasing stroke risk.

Conclusion

Stroke incidence in the UK has decreased and survival after stroke has improved in the past 10 years. Improved drug treatment in primary care is likely to be a major contributor to this, with better control of risk factors both before and after incident stroke. There is however scope for further improvement in risk factor reduction in high-risk patients with atrial fibrillation.

ARTICLE FOCUS

Regional UK data have suggested a decline in stroke incidence, in association with increased use of preventive treatments and reduction in cardiovascular risk factors

This is the first national study to examine recent trends in stroke incidence and mortality

KEY MESSAGES

In the UK, stroke incidence and stroke mortality fell consistently between 1999 and 2008

This change coincided with marked increase in primary care prescription of primary and secondary cardiovascular prevention therapies

Despite these positive findings, there appears to be a need for better risk stratification. The data suggest underutilisation of anticoagulation in patients with atrial fibrillation at high risk of stroke. There is also evidence of lower use of all preventive treatments in women than in men.

STRENGTHS AND LIMITATIONS

The General Practice Research Database (GPRD) is the largest primary care database in the world, containing the longitudinal records of over 3 million patients.

We are reliant on the quality of GP coding in the GPRD dataset. There may be some coding error and misreporting of cardiovascular events and risk factors.

The GPRD contains secondary care data but this is limited to diagnoses; data on secondary care prescribing is not available.

BACKGROUND

Stroke is a major cause of morbidity and mortality in the United Kingdom. Around 110 000 strokes occur in England each year,[1] with recent studies reporting an incidence of between 1.36/1000/year[2] and 1.62/1000/year in 2002-4.[3] A study in the Scottish Borders reported a higher crude incidence rate of 2.8/1000/year, which was attributed to the higher proportion of elderly in the population.[4] Although deaths from stroke have fallen in the UK over the past 40 years,[5-7] stroke accounted for around 46 500 deaths in England and Wales in 2008 (9% of all deaths).[8]

Current UK health policy places great emphasis on reducing stroke.[9-11] Key to this is the need for better management of vascular risk factors, including hypertension, obesity, high cholesterol, atrial fibrillation and diabetes.[6,11] In 2008, NHS Health Check (formerly called the Vascular Check Programme) was introduced to identify and manage vascular risk.[12] More recently, NHS Improvement has identified atrial fibrillation in primary care as a priority area for the health service for 2010/11.[13] From a public health perspective it is important to know whether national policies and preventive strategies are having an effect on stroke epidemiology. Perhaps the best data on trends in stroke comes from the Oxfordshire region where data from two studies — the Oxford Community Stroke Project (1981-4) and the Oxford Vascular Study (2002-4) — were compared.[3] The results suggested a decline in incidence of stroke (P=0.0002), in association with increased use of preventive treatments and reduction in risk factors.

There has been no study looking at trends in stroke across the UK. We report an analysis of the General Practice Research Database (GPRD), used to investigate trends in the burden of stroke between 1999 and 2008.

DESIGN

Objectives

The objectives of this study were 1) to investigate recent trends in the epidemiology of stroke in the UK, including risk factors associated with first and second strokes, and pharmacological therapies prescribed before and following first stroke, and 2) to examine the trend in stroke fatality and the occurrence of second stroke following survival of a first stroke.

Data source

The GPRD is a database of longitudinal patient primary care records, containing anonymised data on demographics, diagnoses, referrals, prescribing and health outcomes for patients from almost 500 GP practices in the UK (over 3 million patients). The database contains approximately 6% of UK patients, and the geographical distribution is representative of the UK population.[16] Validation studies have confirmed the high data quality and completeness of clinical records within the GPRD.[15-17] A recent systematic literature review of studies using the GPRD reported that the median proportion of diagnoses correctly coded was 89%.[17]

Population

We identified patients aged 18 years and older who had a first stroke between 1999 and 2008. Stroke events were identified by a diagnosis for stroke within the patient record. The Read codes used by GPs to enter a stroke into a patient record do not necessarily specify the type of stroke, so we were not able to distinguish between ischaemic and haemorrhagic strokes. The codes used are shown in Additional Material 1.

We excluded patients if they had any coded cardiovascular disease event (including coronary heart disease or peripheral vascular disease) recorded prior to stroke, except patients with a record of transient ischaemic attack (TIA).

Analysis

Data were extracted using GPRD GOLD online version and analysed using SAS® Software version 9.02. Incidence and prevalence of stroke were calculated based on our stroke cohort and the total study population extracted from GPRD.

Co-morbidities were identified using 'Read' codes (Additional Material 1). In addition to coded diagnosis, a blood pressure result above 160/100mm Hg was defined as hypertension and a cholesterol level above 5mmol/L (193mg/dL) was defined as hypercholesterolemia. Pharmacological therapies prescribed in the year before the first stroke were recorded. We assumed that patients were treated with a medication if they received at least two prescriptions for that medication in the year prior to first stroke.

For follow-up, patient data were available from the time of first stroke until the end of the study period or when the patient transferred out of the practice or died. Stroke events were considered fatal if patients had a death coded in their GP record within 56 days of the stroke. This timescale was used to allow for any delay between the death occurring and the GP receiving notification of the death and entering it into their coding system.

Second cardiovascular disease events were defined as a second stroke or other cardiovascular disease event (coronary heart disease or peripheral vascular disease event) occurring more than 56 days after a first stroke. A life table survival analysis was carried out, with an event defined as either a second cardiovascular event or death. Patients were censored if they transferred out of the practice or reached the end of the study period.

We examined trends in the proportion of patients treated with different classes of pharmacological agents in the year before and after first stroke between 1999 and 2008. For patients with GP-coded atrial fibrillation (AF) prior to first stroke, we calculated $CHADS_2$ scores[9] and recorded use of anticoagulants and antiplatelet drugs for patients by $CHADS_2$ score in the year prior to and after first stroke.

RESULTS

Between 1999 and 2008 first strokes were recorded in 32 151 patients with no previous recorded cardiovascular event. Over this period, stroke incidence fell by 30%, from 1.48/1000 person-years in 1999 to 1.04/1000 person-years in 2008 ($P<0.001$). In patients aged 80 years and over (the group at highest risk) incidence fell

by 42% from 18.97 to 10.97/1000 person-years (P <0.001). Prevalence of stroke increased by 12.5% over the same period from 6.4/1000 persons to 7.2/1000 persons (P<0.001) (Figure 1).

Table 1 shows baseline characteristics of the cohort. The average age at first stroke was 77 years in women and 71 years in men. The most commonly coded stroke risk factor was hypertension, recorded in 65% of patients. Twelve per cent of patients were coded as diabetic, and 11% had coded AF.

Fifteen per cent (4926/32 151) of first strokes were fatal (death coded within 56 days). Mortality was 18.6% (3301 of 17 792) in women, and 11.3% (1625 of 14 359) in men. Age-adjusted to the 2008 UK population[10] the mortality difference was smaller but remained higher in women (6.8%) than men (5.5%) (P<0.001 for difference between genders). Crude mortality after incident stroke decreased from 21% in 1999 to 12% in 2008 (P<0.0001). This trend was seen in both men and women (Figure 2).

Five-year survival was 82% (11 774/14 359) in men and 81% (14 411/17 792) in women. Life table survival analysis showed that survival free of a second cardiovascular event (recurrent stroke or first CHD event) at five years was 74% (23 766/32 151) and similar in men and women. After first stroke, patients were at high risk of a recurrent event. Of patients followed up for five years, 24% (3316 of 13599) had a second cardiovascular event; 75% of second events (2475) were strokes and 16% of these (385) were fatal within 56 days.

Stroke Risk Factors and Management

Sixty-five per cent of patients (n=20 959) had hypertension. Of these, 67% were treated with antihypertensives in the year prior to stroke: 69% of female and 64% of male patients.

Prescription of treatment for cardiovascular risk reduction in the year prior to a first stroke increased over time (Figure 3A). A similar trend was seen in prescriptions after the first stroke (Figure 3B). By 2008, 96.6% of women and 97.4% of men with coded hypertension in the year after stroke were receiving antihypertensive therapy.

Before first stroke, 38.7% of patients (n=12 440) had hypercholesterolemia; 8.7% were treated with lipid lowering drugs in 1999, rising to 37.6% in 2008. Prescriptions for lipid lowering drugs after a first stroke also increased rapidly over the last 10 years (Figure 3).

Eleven per cent of patients (n=3483) had coded AF before their first stroke: 10% of male patients and 12% of female patients (Table 1). These patients were older than the general stroke cohort. The average age in the AF group at the time of first stroke was 82 years for women and 77 years for men. Stroke mortality was higher in patients with coded AF than for the overall cohort: 27% of women and 19% of men with AF died within 56 days of their first stroke. For those over the age of 70 years, 56-day mortality after first stroke was 32% in men with coded AF compared with 23% in men without coded AF ($p<0.001$), and 36% in women with coded AF compared with 28% in women without coded AF ($p<0.001$).

Women were at higher risk, with 59% having a $CHADS_2$ score of 2 or above prior to first stroke compared with 42% of men. When we excluded age from the $CHADS_2$ calculation, women still scored higher than men: 67% of women and 59% of men had a score of 1 or above, and 18% of women and 16% of men had a score of 2 or above.

Of patients with coded AF, 25% (876) were prescribed anticoagulants before their stroke: 22% of women and 29% of men. Anticoagulant prescribing did not increase with increasing $CHADS_2$ score prior to stroke (Figure 4). Antiplatelet therapy was prescribed to 52% of patients with coded AF (1796/3483) (54% of women and 47% of men) and prescribing increased steeply with increasing $CHADS_2$ score.

For patients with coded AF at time of first stroke, anticoagulant prescribing increased from 22% prior to stroke to 35% after stroke for women, and from 29% to 48% for men (Table 2). In patients aged 80 and older, anticoagulant prescribing increased from 18% to 23% in women and from 24% to 34% in men.

CONCLUSION

Summary of main findings

Our study shows that the incidence of stroke in the UK fell by 29% between 1999 and 2008. The 56-day mortality after a first stroke fell by 43% between 1999 and 2008. Primary care management of cardiovascular risk has improved, with the majority of recorded hypertension being controlled prior to stroke, and a rapid increase in prescriptions for lipid lowering drugs to patients with diagnosed hypercholesterolemia. However there is a clear suggestion that risk stratification is not yet optimal, particularly in relation to patients with AF.

Comparison with existing literature

A fall in stroke incidence similar to that shown in our study has previously been reported in Oxfordshire[3] and South London.[18] Our findings are also in line with data from some other high-income countries, with Feigin reporting a 42% decrease in age-adjusted stroke incidence rates over four decades to 2008.[19]

The observed reduction in stroke incidence is likely to be related to better control of vascular risk factors both prior to and following a stroke. By the end of the study period, GPs were treating cardiovascular risk factors much more aggressively than in 1999. A previous study[3] reported a trend to reduced incidence of stroke in association with increased use of preventive treatments and reduction in risk factors. Our data show improvement compared with a previous analysis of GPRD data (1997-2006) in which only 75% of patients with diagnosed hypertension were receiving antihypertensive therapy 90 days after incident stroke.[20] In our study, 97% of patients with hypertension after stroke were receiving antihypertensive therapy.

Improved primary care management of risk factors presumably reflects national initiatives to reduce cardiovascular disease. These include the Quality and Outcomes Framework whereby GPs in England are incentivised to improve intervention on cardiovascular risk factors. The increased level of prescribing seen in our study is in line with national increase in use of statins[21] and improved treatment of hypertension.[22]

AF is an important risk factor for stroke but recent reports have highlighted that it is both under-recognised and under-treated.[21,23] Our study confirms that such individuals have a higher mortality risk after first stroke than patients in sinus rhythm.

The $CHADS_2$ scoring system[24] is commonly used to assess stroke risk in patients with AF and help guide thromboprophylaxis. In our study, anticoagulant prescribing before stroke in patients with AF increased only slightly between 1999 and 2008. Use of anticoagulants appeared to be unrelated to the patient's $CHADS_2$ score, as has been reported previously.[25] There was a relatively high, and possibly inappropriate, level of anticoagulant prescribing in lower risk patients (those with a $CHADS_2$ score of 0) and no increase in use of anticoagulants with increasing stroke risk. The finding of high use of anticoagulants in AF patients at low risk of stroke has been reported previously in primary care in the UK.[25]

Contrary to data from a previous study using GPRD,[25] we found that antiplatelet prescribing increased significantly with increasing $CHADS_2$ score, indicating that GPs might be responding to increasing thromboembolic risk by prescribing an antiplatelet agent rather than an anticoagulant. Use of anticoagulants was lower in women than men despite women's higher $CHADS_2$ scores. Women were older than men in the AF patient population and lower use of anticoagulants might reflect prescriber concerns that anticoagulants are more dangerous in the elderly. However, there has been shown to be no significant difference in bleeding risk between warfarin and aspirin in patients aged over 75 years.[26] The lower use of anticoagulants in women might also reflect findings from other areas of cardiovascular disease that women are treated less aggressively with drug therapy than men.[27,28]

Limitations of study

We are reliant on the quality of GP coding in the GPRD dataset. There may be some coding error and misreporting of cardiovascular events and risk factors. The GPRD has quality criteria for practices involved in the data collection and we used data only from such "up-to-standard" practices. A recent systematic review of the validity of diagnostic coding within GPRD reported high positive predictive values (>80%) for events such as myocardial infarction or stroke, but a lower value for AF (64.4%).[16]

Despite an observed difference in risk factors between men and women in our cohort, we are not able to evaluate gender difference in the risk of secondary stroke, due to the potential confounding factor of age; female patients were older than male patients. As the objectives of this study were purely descriptive we did not make any adjustment for confounding factors. Further studies are needed to examine gender differences in stroke risk and prevention.

Implications for clinical practice

This is the first UK-wide study to investigate recent trends in stroke and it shows encouraging reduction in incidence of first stroke and improving survival. This is likely to be due (at least partially) to much better identification of vascular risk and prescription of preventive therapies prior to, and after, stroke. Despite these positive findings there are some areas where management appears to remain suboptimal. Women are less well treated than men, perhaps due to an age bias. Patients with AF, who do particularly poorly after stroke, do not appear to be appropriately risk

stratified for anticoagulation therapy. Improved detection of AF and thromboprophylaxis in such patients should be a priority for healthcare systems.

Contributors

AS and SL performed the data extraction and data analyses, and helped write the manuscript. MC advised regarding the study design and data analyses, and wrote the manuscript. He is the guarantor for the study.

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Ethical Approval

The protocol for the study has been approved by the Independent Scientific Advisory Committee at the Medicines and Healthcare products Regulatory Agency.

Competing interests

MRC provides consultancy advice to a number of pharmaceutical companies, including Boehringer Ingelheim. He holds no stocks or shares in any such company. SL and AS are employees of Boehringer Ingelheim Ltd.

Data Sharing Statement

No additional data available.

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Figures

Figure 1 - Incidence (A) and prevalence (B) of stroke in the UK adult population by age group

Figure 2 - Stroke mortality within 56 days of first stroke by age group

Figure 3 - Pharmaceutical therapies prior to first stroke (A) and in the year following first stroke (B)

Figure 4 - Percentage of GP-coded AF patients treated with anticoagulant and antiplatelet therapy prior to stroke by $CHADS_2$ score

Tables

TABLE 1. Baseline characteristics of GPRD stroke cohort

	Male (n=14 359)	%	99% CI	Female (n=17 792)	%	99% CI	Total (n=32 151)	%	99% CI
Demographic characteristics									
Mean (SD) age	71.06 (12.7)		(70.8 to 71.3)	77.02 (13.0)		(76.8 to 77.3)	74.4 (13.2)		(74.2 to 74.6)
Mean (SD) body mass index (n=23,856)	26.52 (4.6)		(26.4 to 26.6)	26.16 (5.6)		(26.1 to 26.3)	26.3 (5.13)		(26.2 to 26.4)
Risk factors prior to initial stroke									
Hypertension (GP diagnosed or >160/100mm Hg)	8851	61.6	(60.6 to 62.7)	12108	68.1	(67.2 to 69.0)	20959	65.2	(64.5 to 65.9)
Hypercholesterolaemia (GP diagnosed or cholesterol > 5 mmol/L (193 mg/dL))	5730	39.9	(38.9 to 41.0)	6710	37.7	(36.8 to 38.7)	12440	38.7	(38.0 to 39.4)
GP-coded Diabetes mellitus	1875	13.1	(12.3 to 13.8)	1909	10.7	(10.1 to 11.3)	3784	11.8	(11.3 to 12.2)
Smoking (ever)	8015	55.8	(54.7 to 56.9)	6210	34.9	(34.0 to 35.8)	14225	44.2	(43.5 to 45.0)
GP-coded Atrial fibrillation	1411	9.8	(9.2 to10.5)	2072	11.6	(11.0 to 12.3)	3483	10.8	(10.4 to 11.3)
GP-coded Transient ischaemic attack	897	6.2	(5.7 to 6.8)	1111	6.2	(5.8 to 6.7)	2008	6.2	(5.9 to 6.6)
Treatments in year prior to initial stroke (at least 2 prescriptions)									
Antihypertensives	6453	44.9	(43.9 to 46.0)	9649	54.2	(53.3 to 55.2)	16102	50.1	(49.4 to 50.8)
ACE inhibitors and angiotensin receptor antagonists	3226	22.5	(21.6 to 23.4)	3845	21.6	(20.8 to 22.4)	7071	22	(21.4 to 22.6)
Beta-blockers	2252	15.7	(14.9 to16.5)	3581	20.1	(19.4 to 20.9)	5833	18.1	(17.6 to 18.7)
Calcium channel blockers	2349	16.4	(15.6 to 17.2)	2988	16.8	(16.1 to 17.5)	5337	16.6	(16.1 to 17.1)
Diuretics	3362	23.4	(22.5 to 24.3)	6142	34.5	(33.6 to 35.4)	9504	29.6	(28.9 to 30.2)
Anticoagulants	703	4.9	(4.4 to 5.4)	787	4.4	(4.0 to 4.8)	1490	4.6	(4.3 to 4.9)
Antiplatelet drugs	4029	28.1	(27.1 to 29.0)	5471	30.7	(29.9 to 31.6)	9500	29.5	(28.9 to 30.2)
Lipid regulating drugs	2004	14	(13.2 to14.7)	2221	12.5	(11.8 to 13.1)	4225	13.1	(12.7 to 13.6)
Diabetes treatment									
Oral antidiabetic agents	1193	8.3	(7.7 to 8.9)	1180	6.6	(6.2 to 7.1)	2373	7.4	(7.0 to 7.8)
Insulin	340	2.4	(2.0 to 2.7)	417	2.3	(2.1 to 2.6)	757	2.4	(2.1 to 2.6)

TABLE 2. Patients with GP-coded atrial fibrillation prior to first stroke

GP-coded atrial fibrillation	Male	%	95% CI	Female	%	95% CI	Total	%	95% CI
Number of patients (% of cohort)	1411	9.8		2072	11.6		3483	10.8	
Baseline characteristics									
Mean (SD) age	77.3 (9.8)		(76.8 to 77.8)	82.4 (8.7)		(82.0 to 82.8)	80.3 (9.5)		(80.0,80.6)
$CHADS_2$ Score prior to initial stroke (% of AF patients)									
0	217	15.4	(13.5 to 17.3)	127	6.1	(5.1 to 7.2)	344	9.9	(8.9 to 10.9)
1	601	42.6	(40.0 to 45.2)	730	35.2	(33.2 to 37.3)	1,331	38.2	(36.6 to 39.8)
2	430	30.5	(28.1 to 32.9)	877	42.3	(40.2 to 44.5)	1,307	37.5	(35.9 to 39.1)
3	108	7.7	(6.3 to 9.0)	213	10.3	(9.0 to 11.6)	321	9.2	(8.3 to 10.2)
4	49	3.5	(2.5 to 4.4)	111	5.4	(4.4 to 6.3)	160	4.6	(3.9 to 5.3)
5	6	0.4	(0.1 to 0.8)	14	0.7	(0.3 to 1.0)	20	0.6	(0.3 to 0.8)
Treatments in year prior to initial stroke (at least 2 prescriptions) (% of AF patients)									
Anticoagulants	415	29.4	(27.0 to 31.8)	461	22.2	(20.5 to 24.0)	876	25.2	(23.7 to 26.6)
Antiplatelet drugs	668	47.3	(44.7 to 49.9)	1128	54.4	(52.3 to 56.6)	1,796	51.6	(49.9 to 53.2)
Follow-up									
Died within 56 days of initial stroke (% of AF patients)	264	18.7	(16.7 to 20.7)	554	26.7	(24.8 to 28.6)	818	23.5	(22.1 to 24.9)
Survived at least 56 days following initial stroke (% of AF patients)	1147	81.3	(79.3 to 83.3)	1518	73.3	(71.4 to 75.2)	2665	76.5	(75.1 to 77.9)
Treatments in year following initial stroke (at least 2 prescriptions) (% of patients who survived at least 56 days)									
Anticoagulants	545	47.50%	(44.9 to 50.1)	529	34.80%	(32.8 to 36.9)	1,074	40.30%	(38.7 to 41.9)
Antiplatelet drugs	566	49.30%	(46.7 to 52)	806	53.10%	(50.9 to 55.2)	1,372	51.50%	(49.8 to 53.1)

Additional files

Web Only file: Appendix 1 – GPRD Codes

STROBE checklist for EARTH study

Cohort Study Checklist

	Item No	Recommendation	Page Number	Section	Additional Information
Title and abstract					
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	Abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract	
Introduction					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Introduction	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	Objectives	
Methods					
Study design	4	Present key elements of study design early in the paper	3	Methods-Study Design	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3	Methods-Data Source	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4	Methods-Population & Follow Up	
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4	Methods-Population & Analysis	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3	Methods-Data Source	
Bias	9	Describe any efforts to address potential sources of bias	9	Limitations	
Study size	10	Explain how the study size was arrived at	NA		This is a descriptive study, and no comparative analysis is being carried out, and therefore a sample size calculation is not appropriate. Our cohort of over 32,000 patients is very large, and allows precise

					estimates of population variables, as shown in the paper by the narrow 99% confidence intervals.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4	Methods-Analysis	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4	Methods-Analysis	
		(*b*) Describe any methods used to examine subgroups and interactions	4 & 5	Methods-Follow Up	
		(*c*) Explain how missing data were addressed	4	Methods-Analysis	
		(*d*) If applicable, explain how loss to follow-up was addressed			This is a GPRD study so the only type of missing data is values which are not recorded for every patients, such as body mass index. This is addressed in the Methods section. Further missing data is unlikely due to the nature of a GP database, All patients are followed up until death or until they transferred out of practice.
		(*e*) Describe any sensitivity analyses	4	Methods-Analysis	
Results			NA		
Participants	13*	(*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	Baseline characteristics	
		(*b*) Give reasons for non-participation at each stage	5	Baseline characteristics	
		(*c*) Consider use of a flow diagram	-	-	
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5	Results- Table 1	
		(*b*) Indicate number of participants with missing data for each variable of interest	5	Results- Table 1	

		(*c*) Summarise follow-up time (eg average and total amount)	5	Results- Baseline characteristics
Outcome data	15*	Report numbers of outcome events or summary measures over time	6	Results- Stroke mortality and Recurrent cardiovascular events
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5 & 6	Results
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses	6 & 7	Results- Atrial fibrillation
Discussion				
Key results	18	Summarise key results with reference to study objectives	7	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8	Discussion- limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7 & 8 & 9	Discussion & Implications
Generalisability	21	Discuss the generalisability (external validity) of the study results	7	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10	Funding

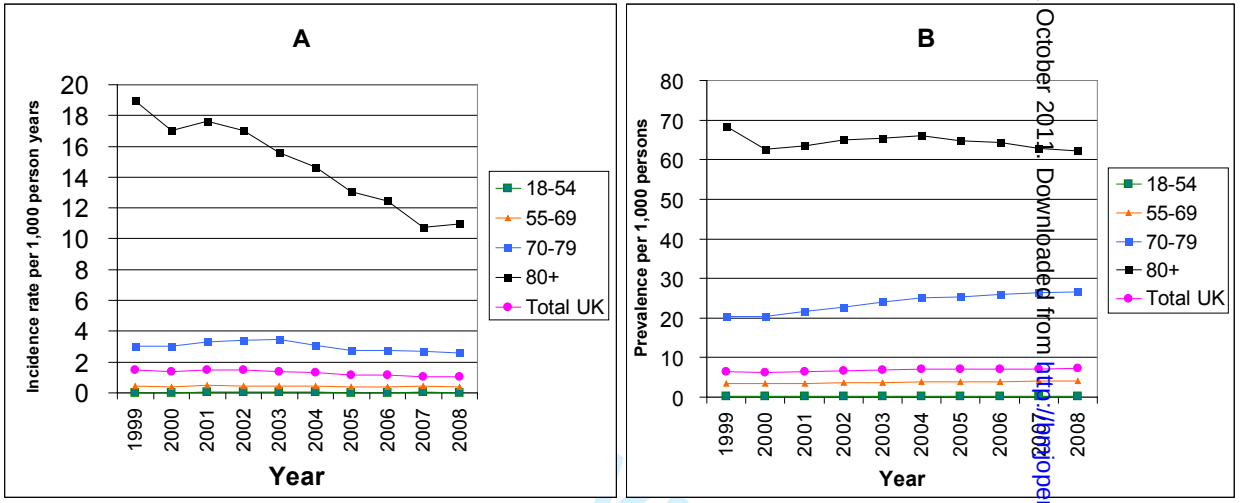

Fig 1

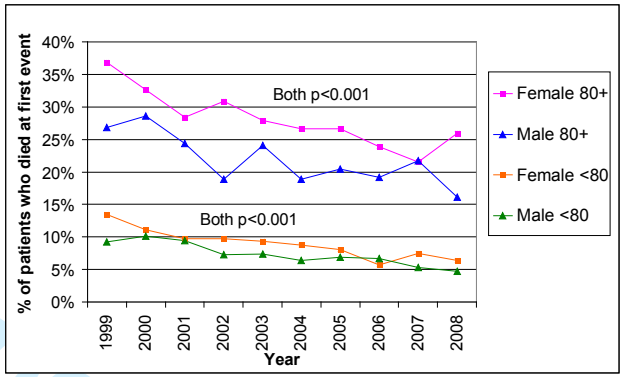

Fig 2

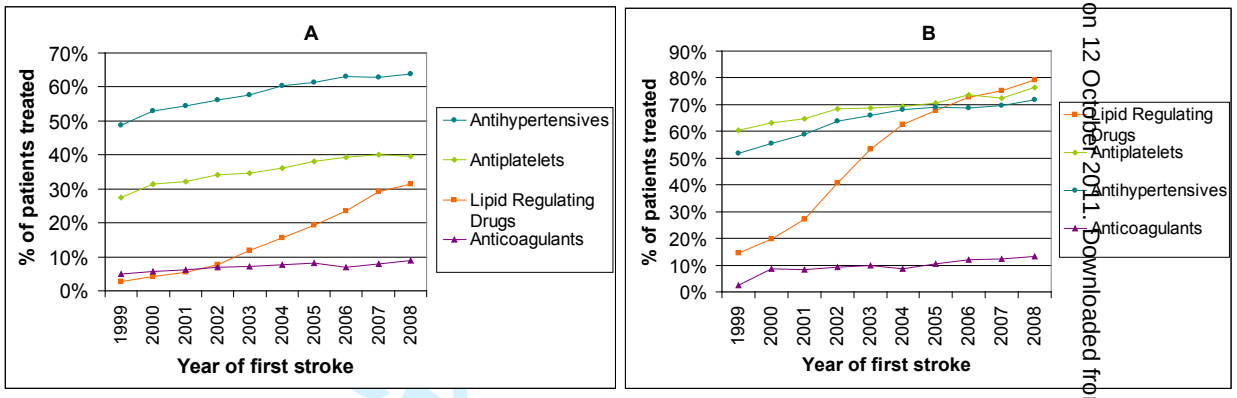

Fig 3

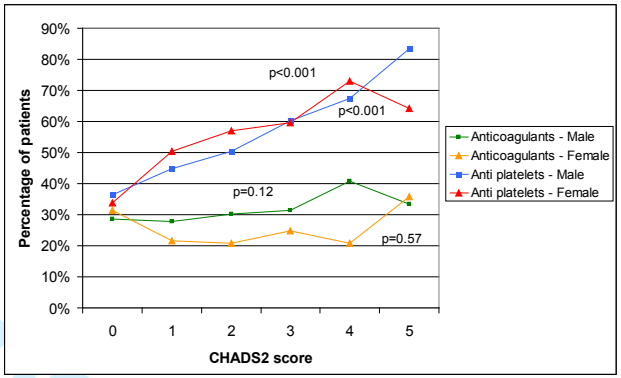

Fig 4

BMJ open

UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database

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Keywords:	CARDIOLOGY, STROKE MEDICINE, EPIDEMIOLOGY

UK stroke incidence, mortality and cardiovascular risk management 1999-2008: time-trend analysis from the General Practice Research Database

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Keywords: Stroke, Cardiovascular diseases, General Practice, Atrial Fibrillation

Word Count: 2,659 (excluding title page, abstract, references, figures and tables)

Abstract

Objectives

Stroke is a major cause of morbidity and mortality. This study aimed to investigate secular trends in stroke across the UK.

Design

This study aimed to investigate recent trends in the epidemiology of stroke in the UK. The study was a time-trend analysis from 1999 to 2008 within the UK General Practice Research Database. Outcome measures were incidence and prevalence of stroke, stroke mortality, rate of secondary cardiovascular events, and prescribing of pharmacological therapy for primary and secondary prevention of cardiovascular disease.

Results

The study cohort included 32 151 patients with a first stroke. Stroke incidence fell by 30%, from 1.48/1000 person-years in 1999 to 1.04/1000 person-years in 2008 (P<0.001). Stroke prevalence increased by 12.5%, from 6.40/1000 in 1999 to 7.20/1000 in 2008 (P<0.001). Fifty-six-day mortality after first stroke reduced from 21% in 1999 to 12% in 2008 (P<0.0001). Prescribing of drugs to control cardiovascular risk factors increased consistently over the study period, particularly for lipid lowering agents and antihypertensive agents. In patients with atrial fibrillation, use of anticoagulants prior to first stroke did not increase with increasing stroke risk.

Conclusion

Stroke incidence in the UK has decreased and survival after stroke has improved in the past 10 years. Improved drug treatment in primary care is likely to be a major contributor to this, with better control of risk factors both before and after incident stroke. There is however scope for further improvement in risk factor reduction in high-risk patients with atrial fibrillation.

ARTICLE FOCUS

Regional UK data have suggested a decline in stroke incidence, in association with increased use of preventive treatments and reduction in cardiovascular risk factors

This is the first national study to examine recent trends in stroke incidence and mortality

KEY MESSAGES

In the UK, stroke incidence and stroke mortality fell consistently between 1999 and 2008

This change coincided with marked increase in primary care prescription of primary and secondary cardiovascular prevention therapies

Despite these positive findings, there appears to be a need for better risk stratification. The data suggest underutilisation of anticoagulation in patients with atrial fibrillation at high risk of stroke. There is also evidence of lower use of all preventive treatments in women than in men.

STRENGTHS AND LIMITATIONS

The General Practice Research Database (GPRD) is the largest primary care database in the world, containing the longitudinal records of over 3 million patients.

We are reliant on the quality of GP coding in the GPRD dataset. There may be some coding error and misreporting of cardiovascular events and risk factors.

The GPRD contains secondary care data but this is limited to diagnoses; data on secondary care prescribing is not available.

BACKGROUND

Stroke is a major cause of morbidity and mortality in the United Kingdom. Around 110 000 strokes occur in England each year,[1] with recent studies reporting an incidence of between 1.36/1000/year[2] and 1.62/1000/year in 2002-4.[3] A study in the Scottish Borders reported a higher crude incidence rate of 2.8/1000/year, which was attributed to the higher proportion of elderly in the population.[4] Although deaths from stroke have fallen in the UK over the past 40 years,[5-7] stroke accounted for around 46 500 deaths in England and Wales in 2008 (9% of all deaths).[8]

Current UK health policy places great emphasis on reducing stroke.[9-11] Key to this is the need for better management of vascular risk factors, including hypertension, obesity, high cholesterol, atrial fibrillation and diabetes.[6,11] In 2008, NHS Health Check (formerly called the Vascular Check Programme) was introduced to identify and manage vascular risk.[12] More recently, NHS Improvement has identified atrial fibrillation in primary care as a priority area for the health service for 2010/11.[13] From a public health perspective it is important to know whether national policies and preventive strategies are having an effect on stroke epidemiology. Perhaps the best data on trends in stroke comes from the Oxfordshire region where data from two studies — the Oxford Community Stroke Project (1981-4) and the Oxford Vascular Study (2002-4) — were compared.[3] The results suggested a decline in incidence of stroke (P=0.0002), in association with increased use of preventive treatments and reduction in risk factors.

There has been no study looking at trends in stroke across the UK. We report an analysis of the General Practice Research Database (GPRD), used to investigate trends in the burden of stroke between 1999 and 2008.

DESIGN

Objectives

The objectives of this study were 1) to investigate recent trends in the epidemiology of stroke in the UK, including risk factors associated with first and second strokes, and pharmacological therapies prescribed before and following first stroke, and 2) to examine the trend in stroke fatality and the occurrence of second stroke following survival of a first stroke.

Data source

The GPRD is a database of longitudinal patient primary care records, containing anonymised data on demographics, diagnoses, referrals, prescribing and health outcomes for patients from almost 500 GP practices in the UK (over 3 million patients). The database contains approximately 6% of UK patients, and the geographical distribution is representative of the UK population.[16] Validation studies have confirmed the high data quality and completeness of clinical records within the GPRD.[15-17] A recent systematic literature review of studies using the GPRD reported that the median proportion of diagnoses correctly coded was 89%.[17]

Population

We identified patients aged 18 years and older who had a first stroke between 1999 and 2008. Stroke events were identified by a diagnosis for stroke within the patient record. The Read codes used by GPs to enter a stroke into a patient record do not necessarily specify the type of stroke, so we were not able to distinguish between ischaemic and haemorrhagic strokes. The codes used are shown in Additional Material 1. Stroke codes used were those which described acute stroke events only- any codes for monitoring or stroke rehabilitation were excluded to ensure that we correctly identified the initial stroke event and did not record follow up of the same stroke as a secondary stroke event.

We excluded patients if they had any coded cardiovascular disease event (including coronary heart disease or peripheral vascular disease) recorded prior to stroke, except patients with a record of transient ischaemic attack (TIA).

Analysis

Data were extracted using GPRD GOLD online version and analysed using SAS® Software version 9.02. Incidence and prevalence of stroke were calculated based on our stroke cohort and the total study population extracted from GPRD.

Co-morbidities were identified using 'Read' codes (Additional Material 1). In addition to coded diagnosis, a blood pressure result above 160/100mm Hg was defined as hypertension and a cholesterol level above 5mmol/L (193mg/dL) was defined as hypercholesterolemia. Pharmacological therapies prescribed in the year before the first stroke were recorded. We assumed that patients were treated with a

medication if they received at least two prescriptions for that medication in the year prior to first stroke.

For follow-up, patient data were available from the time of first stroke until the end of the study period or when the patient transferred out of the practice or died. Stroke events were considered fatal if patients had a death coded in their GP record within 56 days of the stroke. This timescale was used to allow for any delay between the death occurring and the GP receiving notification of the death and entering it into their coding system.

Second cardiovascular disease events were defined as a second stroke or other cardiovascular disease event (coronary heart disease or peripheral vascular disease event) occurring more than 56 days after a first stroke. A life table survival analysis was carried out, with an event defined as either a second cardiovascular event or death. Patients were censored if they transferred out of the practice or reached the end of the study period.

We examined trends in the proportion of patients treated with different classes of pharmacological agents in the year before and after first stroke between 1999 and 2008. For patients with GP-coded atrial fibrillation (AF) prior to first stroke, we calculated $CHADS_2$ scores[9] and recorded use of anticoagulants and antiplatelet drugs for patients by $CHADS_2$ score in the year prior to and after first stroke.

RESULTS

Between 1999 and 2008 first strokes were recorded in 32 151 patients with no previous recorded cardiovascular event. Over this period, stroke incidence fell by 30%, from 1.48/1000 person-years in 1999 to 1.04/1000 person-years in 2008 (P<0.001). In patients aged 80 years and over (the group at highest risk) incidence fell by 42% from 18.97 to 10.97/1000 person-years (P <0.001). Prevalence of stroke increased by 12.5% over the same period from 6.4/1000 persons to 7.2/1000 persons (P<0.001) (Figure 1).

Table 1 shows baseline characteristics of the cohort. The average age at first stroke was 77 years in women and 71 years in men. The most commonly coded stroke risk factor was hypertension, recorded in 65% of patients. Twelve per cent of patients were coded as diabetic, and 11% had coded AF.

Fifteen per cent (4926/32 151) of first strokes were fatal (death coded within 56 days). Mortality was 18.6% (3301 of 17 792) in women, and 11.3% (1625 of 14 359) in men. Age-adjusted to the 2008 UK population[10] the mortality difference was smaller but remained higher in women (6.8%) than men (5.5%) (P<0.001 for difference between genders). Crude mortality after incident stroke decreased from 21% in 1999 to 12% in 2008 (P<0.0001). This trend was seen in both men and women (Figure 2).

Five-year survival was 82% (11 774/14 359) in men and 81% (14 411/17 792) in women. Life table survival analysis showed that survival free of a second cardiovascular event (recurrent stroke or first CHD event) at five years was 74% (23 766/32 151) and similar in men and women. After first stroke, patients were at high

risk of a recurrent event. Of patients followed up for five years, 24% (3316 of 13599) had a second cardiovascular event; 75% of second events (2475) were strokes and 16% of these (385) were fatal within 56 days.

Stroke Risk Factors and Management

Sixty-five per cent of patients (n=20 959) had hypertension. Of these, 67% were treated with antihypertensives in the year prior to stroke: 69% of female and 64% of male patients.

Prescription of treatment for cardiovascular risk reduction in the year prior to a first stroke increased over time (Figure 3A). A similar trend was seen in prescriptions after the first stroke (Figure 3B). By 2008, 96.6% of women and 97.4% of men with coded hypertension in the year after stroke were receiving antihypertensive therapy.

Before first stroke, 38.7% of patients (n=12 440) had hypercholesterolemia; 8.7% were treated with lipid lowering drugs in 1999, rising to 37.6% in 2008. Prescriptions for lipid lowering drugs after a first stroke also increased rapidly over the last 10 years (Figure 3).

Eleven per cent of patients (n=3483) had coded AF before their first stroke: 10% of male patients and 12% of female patients (Table 1). These patients were older than the general stroke cohort. The average age in the AF group at the time of first stroke was 82 years for women and 77 years for men. Stroke mortality was higher in patients with coded AF than for the overall cohort: 27% of women and 19% of men with AF died within 56 days of their first stroke. For those over the age of 70 years, 56-day

mortality after first stroke was 32% in men with coded AF compared with 23% in men without coded AF (p<0.001), and 36% in women with coded AF compared with 28% in women without coded AF (p<0.001).

Women were at higher risk, with 59% having a $CHADS_2$ score of 2 or above prior to first stroke compared with 42% of men. When we excluded age from the $CHADS_2$ calculation, women still scored higher than men: 67% of women and 59% of men had a score of 1 or above, and 18% of women and 16% of men had a score of 2 or above.

Of patients with coded AF, 25% (876) were prescribed anticoagulants before their stroke: 22% of women and 29% of men. Anticoagulant prescribing did not increase with increasing $CHADS_2$ score prior to stroke (Figure 4). Antiplatelet therapy was prescribed to 52% of patients with coded AF (1796/3483) (54% of women and 47% of men) and prescribing increased steeply with increasing $CHADS_2$ score.

For patients with coded AF at time of first stroke, anticoagulant prescribing increased from 22% prior to stroke to 35% after stroke for women, and from 29% to 48% for men (Table 2). In patients aged 80 and older, anticoagulant prescribing increased from 18% to 23% in women and from 24% to 34% in men.

CONCLUSION

Summary of main findings

Our study shows that the incidence of stroke in the UK fell by 29% between 1999 and 2008. The 56-day mortality after a first stroke fell by 43% between 1999 and 2008. Primary care management of cardiovascular risk has improved, with the majority of

recorded hypertension being controlled prior to stroke, and a rapid increase in prescriptions for lipid lowering drugs to patients with diagnosed hypercholesterolemia. However there is a clear suggestion that risk stratification is not yet optimal, particularly in relation to patients with AF.

Comparison with existing literature

A fall in stroke incidence similar to that shown in our study has previously been reported in Oxfordshire[3] and South London.[18] Our findings are also in line with data from some other high-income countries, with Feigin reporting a 42% decrease in age-adjusted stroke incidence rates over four decades to 2008.[19]

The observed reduction in stroke incidence is likely to be related to better control of vascular risk factors both prior to and following a stroke. By the end of the study period, GPs were treating cardiovascular risk factors much more aggressively than in 1999. A previous study[3] reported a trend to reduced incidence of stroke in association with increased use of preventive treatments and reduction in risk factors. Our data show improvement compared with a previous analysis of GPRD data (1997-2006) in which only 75% of patients with diagnosed hypertension were receiving antihypertensive therapy 90 days after incident stroke.[20] In our study, 97% of patients with hypertension after stroke were receiving antihypertensive therapy.

Improved primary care management of risk factors presumably reflects national initiatives to reduce cardiovascular disease. These include the Quality and Outcomes Framework whereby GPs in England are incentivised to improve intervention on

cardiovascular risk factors. The increased level of prescribing seen in our study is in line with national increase in use of statins[21] and improved treatment of hypertension.[22]

AF is an important risk factor for stroke but recent reports have highlighted that it is both under-recognised and under-treated.[21,23] Our study confirms that such individuals have a higher mortality risk after first stroke than patients in sinus rhythm.

The $CHADS_2$ scoring system[24] is commonly used to assess stroke risk in patients with AF and help guide thromboprophylaxis. In our study, anticoagulant prescribing before stroke in patients with AF increased only slightly between 1999 and 2008. Use of anticoagulants appeared to be unrelated to the patient's $CHADS_2$ score, as has been reported previously.[25] There was a relatively high, and possibly inappropriate, level of anticoagulant prescribing in lower risk patients (those with a $CHADS_2$ score of 0) and no increase in use of anticoagulants with increasing stroke risk. The finding of high use of anticoagulants in AF patients at low risk of stroke has been reported previously in primary care in the UK.[25]

Contrary to data from a previous study using GPRD,[25] we found that antiplatelet prescribing increased significantly with increasing $CHADS_2$ score, indicating that GPs might be responding to increasing thromboembolic risk by prescribing an antiplatelet agent rather than an anticoagulant. Use of anticoagulants was lower in women than men despite women's higher $CHADS_2$ scores. Women were older than men in the AF patient population and lower use of anticoagulants might reflect prescriber concerns that anticoagulants are more dangerous in the elderly. However,

there has been shown to be no significant difference in bleeding risk between warfarin and aspirin in patients aged over 75 years.[26] The lower use of anticoagulants in women might also reflect findings from other areas of cardiovascular disease that women are treated less aggressively with drug therapy than men.[27,28]

Limitations of study

We are reliant on the quality of GP coding in the GPRD dataset. There may be some coding error and misreporting of cardiovascular events and risk factors. The GPRD has quality criteria for practices involved in the data collection and we used data only from such "up-to-standard" practices. A recent systematic review of the validity of diagnostic coding within GPRD reported high positive predictive values (>80%) for events such as myocardial infarction or stroke, but a lower value for AF (64.4%).[16]

Despite an observed difference in risk factors between men and women in our cohort, we are not able to evaluate gender difference in the risk of secondary stroke, due to the potential confounding factor of age; female patients were older than male patients. As the objectives of this study were purely descriptive we did not make any adjustment for confounding factors. Further studies are needed to examine gender differences in stroke risk and prevention.

Implications for clinical practice

This is the first UK-wide study to investigate recent trends in stroke and it shows encouraging reduction in incidence of first stroke and improving survival. This is likely to be due (at least partially) to much better identification of vascular risk and prescription of preventive therapies prior to, and after, stroke. Despite these positive

findings there are some areas where management appears to remain suboptimal. Women are less well treated than men, perhaps due to an age bias. Patients with AF, who do particularly poorly after stroke, do not appear to be appropriately risk stratified for anticoagulation therapy. Improved detection of AF and thromboprophylaxis in such patients should be a priority for healthcare systems.

Contributors

AS and SL performed the data extraction and data analyses, and helped write the manuscript. MC advised regarding the study design and data analyses, and wrote the manuscript. He is the guarantor for the study.

Funding

The study was funded by Boehringer Ingelheim Ltd.

Ethical Approval

The protocol for the study has been approved by the Independent Scientific Advisory Committee at the Medicines and Healthcare products Regulatory Agency.

Competing interests

MRC provides consultancy advice to a number of pharmaceutical companies, including Boehringer Ingelheim. He holds no stocks or shares in any such company. SL and AS are employees of Boehringer Ingelheim Ltd. Boehringer Ingelheim Ltd market a number of cardiovascular therapies.

Data Sharing Statement

No additional data available.

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Figures

Figure 1 - Incidence (A) and prevalence (B) of stroke in the UK adult population by age group

Figure 2 - Stroke mortality within 56 days of first stroke by age group

Figure 3 - Pharmaceutical therapies prior to first stroke (A) and in the year following first stroke (B)

Figure 4 - Percentage of GP-coded AF patients treated with anticoagulant and antiplatelet therapy prior to stroke by $CHADS_2$ score

Tables

TABLE 1. Baseline characteristics of GPRD stroke cohort

	Male (n=14 359)	%	99% CI	Female (n=17 792)	%	99% CI	Total (n=32 151)	%	99% CI
Demographic characteristics									
Mean (SD) age	71.06 (12.7)		(70.8 to 71.3)	77.02 (13.0)		(76.8 to 77.3)	74.4 (13.2)		(74.2 to 74.6)
Mean (SD) body mass index (n=23,856)	26.52 (4.6)		(26.4 to 26.6)	26.16 (5.6)		(26.1 to 26.3)	26.3 (5.13)		(26.2 to 26.4)
Risk factors prior to initial stroke									
Hypertension (GP diagnosed or >160/100mm Hg)	8851	61.6	(60.6 to 62.7)	12108	68.1	(67.2 to 69.0)	20959	65.2	(64.5 to 65.9)
Hypercholesterolaemia (GP diagnosed or cholesterol > 5 mmol/L (193 mg/dL))	5730	39.9	(38.9 to 41.0)	6710	37.7	(36.8 to 38.7)	12440	38.7	(38.0 to 39.4)
GP-coded Diabetes mellitus	1875	13.1	(12.3 to 13.8)	1909	10.7	(10.1 to 11.3)	3784	11.8	(11.3 to 12.2)
Smoking (ever)	8015	55.8	(54.7 to 56.9)	6210	34.9	(34.0 to 35.8)	14225	44.2	(43.5 to 45.0)
GP-coded Atrial fibrillation	1411	9.8	(9.2 to10.5)	2072	11.6	(11.0 to 12.3)	3483	10.8	(10.4 to 11.3)
GP-coded Transient ischaemic attack	897	6.2	(5.7 to 6.8)	1111	6.2	(5.8 to 6.7)	2008	6.2	(5.9 to 6.6)
Treatments in year prior to initial stroke (at least 2 prescriptions)									
Antihypertensives	6453	44.9	(43.9 to 46.0)	9649	54.2	(53.3 to 55.2)	16102	50.1	(49.4 to 50.8)
ACE inhibitors and angiotensin receptor antagonists	3226	22.5	(21.6 to 23.4)	3845	21.6	(20.8 to 22.4)	7071	22	(21.4 to 22.6)
Beta-blockers	2252	15.7	(14.9 to16.5)	3581	20.1	(19.4 to 20.9)	5833	18.1	(17.6 to 18.7)
Calcium channel blockers	2349	16.4	(15.6 to 17.2)	2988	16.8	(16.1 to 17.5)	5337	16.6	(16.1 to 17.1)
Diuretics	3362	23.4	(22.5 to 24.3)	6142	34.5	(33.6 to 35.4)	9504	29.6	(28.9 to 30.2)
Anticoagulants	703	4.9	(4.4 to 5.4)	787	4.4	(4.0 to 4.8)	1490	4.6	(4.3 to 4.9)
Antiplatelet drugs	4029	28.1	(27.1 to 29.0)	5471	30.7	(29.9 to 31.6)	9500	29.5	(28.9 to 30.2)
Lipid regulating drugs	2004	14	(13.2 to14.7)	2221	12.5	(11.8 to 13.1)	4225	13.1	(12.7 to 13.6)
Diabetes treatment									
Oral antidiabetic agents	1193	8.3	(7.7 to 8.9)	1180	6.6	(6.2 to 7.1)	2373	7.4	(7.0 to 7.8)
Insulin	340	2.4	(2.0 to 2.7)	417	2.3	(2.1 to 2.6)	757	2.4	(2.1 to 2.6)

TABLE 2. Patients with GP-coded atrial fibrillation prior to first stroke

GP-coded atrial fibrillation	Male	%	95% CI	Female	%	95% CI	Total	%	95% CI
Number of patients (% of cohort)	1411	9.8		2072	11.6		3483	10.8	
Baseline characteristics									
Mean (SD) age	77.3 (9.8)		(76.8 to 77.8)	82.4 (8.7)		(82.0 to 82.8)	80.3 (9.5)		(80.0,80.6)
$CHADS_2$ Score prior to initial stroke (% of AF patients)									
0	217	15.4	(13.5 to 17.3)	127	6.1	(5.1 to 7.2)	344	9.9	(8.9 to 10.9)
1	601	42.6	(40.0 to 45.2)	730	35.2	(33.2 to 37.3)	1,331	38.2	(36.6 to 39.8)
2	430	30.5	(28.1 to 32.9)	877	42.3	(40.2 to 44.5)	1,307	37.5	(35.9 to 39.1)
3	108	7.7	(6.3 to 9.0)	213	10.3	(9.0 to 11.6)	321	9.2	(8.3 to 10.2)
4	49	3.5	(2.5 to 4.4)	111	5.4	(4.4 to 6.3)	160	4.6	(3.9 to 5.3)
5	6	0.4	(0.1 to 0.8)	14	0.7	(0.3 to 1.0)	20	0.6	(0.3 to 0.8)
Treatments in year prior to initial stroke (at least 2 prescriptions) (% of AF patients)									
Anticoagulants	415	29.4	(27.0 to 31.8)	461	22.2	(20.5 to 24.0)	876	25.2	(23.7 to 26.6)
Antiplatelet drugs	668	47.3	(44.7 to 49.9)	1128	54.4	(52.3 to 56.6)	1,796	51.6	(49.9 to 53.2)
Follow-up									
Died within 56 days of initial stroke (% of AF patients)	264	18.7	(16.7 to 20.7)	554	26.7	(24.8 to 28.6)	818	23.5	(22.1 to 24.9)
Survived at least 56 days following initial stroke (% of AF patients)	1147	81.3	(79.3 to 83.3)	1518	73.3	(71.4 to 75.2)	2665	76.5	(75.1 to 77.9)
Treatments in year following initial stroke (at least 2 prescriptions) (% of patients who survived at least 56 days)									
Anticoagulants	545	47.50%	(44.9 to 50.1)	529	34.80%	(32.8 to 36.9)	1,074	40.30%	(38.7 to 41.9)
Antiplatelet drugs	566	49.30%	(46.7 to 52)	806	53.10%	(50.9 to 55.2)	1,372	51.50%	(49.8 to 53.1)

Additional files

Web Only file: Appendix 1 – GPRD Codes

STROBE checklist for EARTH study

Cohort Study Checklist

	Item No	Recommendation	Page Number	Section	Additional Information
Title and abstract					
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2	Abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract	
Introduction					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	3	Introduction	
Objectives	3	State specific objectives, including any prespecified hypotheses	3	Objectives	
Methods					
Study design	4	Present key elements of study design early in the paper	3	Methods-Study Design	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3	Methods-Data Source	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4	Methods-Population & Follow Up	
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4	Methods-Population & Analysis	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	3	Methods-Data Source	
Bias	9	Describe any efforts to address potential sources of bias	9	Limitations	
Study size	10	Explain how the study size was arrived at	NA		This is a descriptive study, and no comparative analysis is being carried out, and therefore a sample size calculation is not appropriate. Our cohort of over 32,000 patients is very large, and allows precise

					estimates of population variables, as shown in the paper by the narrow 99% confidence intervals.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4	Methods-Analysis	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4	Methods-Analysis	
		(*b*) Describe any methods used to examine subgroups and interactions	4 & 5	Methods-Follow Up	
		(*c*) Explain how missing data were addressed	4	Methods-Analysis	
		(*d*) If applicable, explain how loss to follow-up was addressed			This is a GPRD study so the only type of missing data is values which are not recorded for every patients, such as body mass index. This is addressed in the Methods section. Further missing data is unlikely due to the nature of a GP database, All patients are followed up until death or until they transferred out of practice.
		(*e*) Describe any sensitivity analyses	4	Methods-Analysis	
Results			NA		
Participants	13*	(*a*) Report numbers of individuals at each stage of study? eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5	Baseline characteristics	
		(*b*) Give reasons for non-participation at each stage	5	Baseline characteristics	
		(*c*) Consider use of a flow diagram	-	-	
Descriptive data	14*	(*a*)Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	5	Results- Table 1	
		(*b*) Indicate number of participants with missing data for each variable of interest	5	Results- Table 1	

		(*c*) Summarise follow-up time (eg average and total amount)	5	Results- Baseline characteristics
Outcome data	15*	Report numbers of outcome events or summary measures over time	6	Results- Stroke mortality and Recurrent cardiovascular events
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	5 & 6	Results
		(*b*) Report category boundaries when continuous variables were categorized	NA	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA	NA
Other analyses	17	Report other analyses done? eg analyses of subgroups and interactions, and sensitivity analyses	6 & 7	Results- Atrial fibrillation
Discussion				
Key results	18	Summarise key results with reference to study objectives	7	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8	Discussion- limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7 & 8 & 9	Discussion & Implications
Generalisability	21	Discuss the generalisability (external validity) of the study results	7	Discussion
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10	Funding

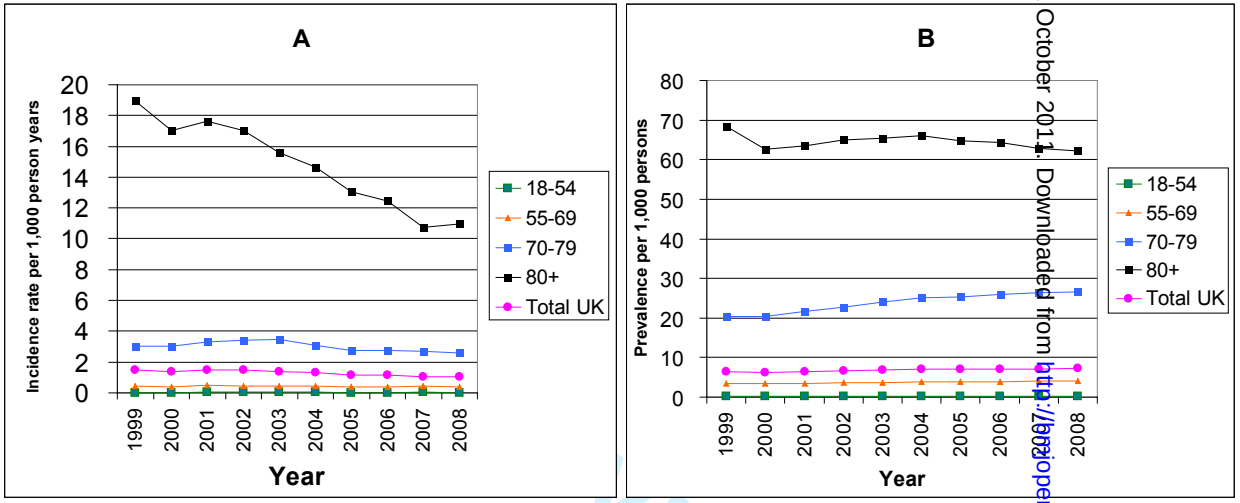

Fig 1

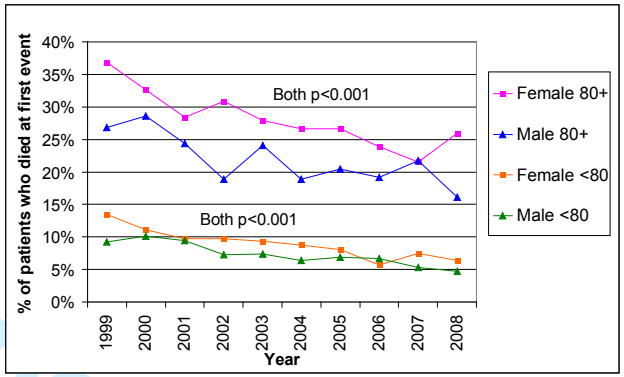

Fig 2

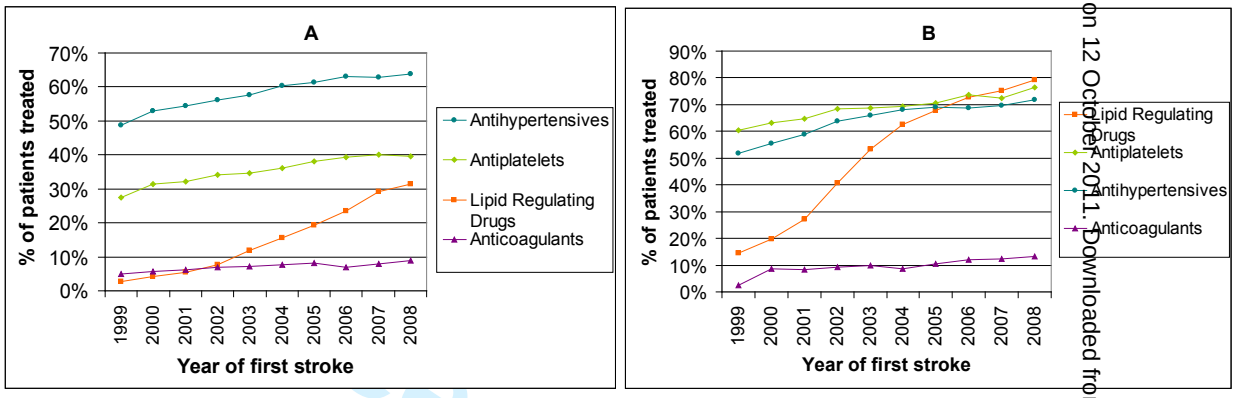

Fig 3

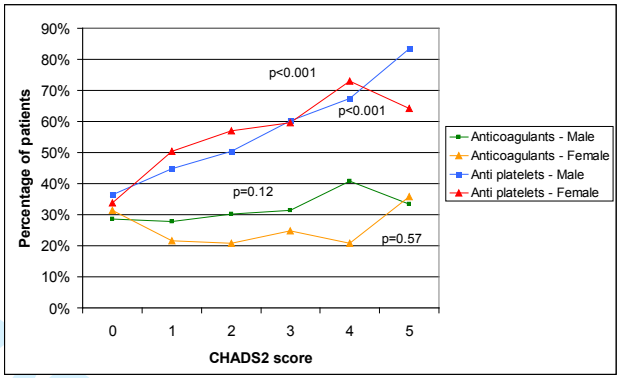

Fig 4