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Clinical and Demographic Characteristics Associated with Sub-optimal Primary Stroke and TIA Prevention: Retrospective Analysis

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Abstract

Background and purpose

Primary prevention of stroke and transient ischaemic attack (TIA) is important to reduce the burden of these conditions; however, prescribing of prevention drugs is sub-optimal. We aimed to identify individual clinical and demographic characteristics associated with potential missed opportunities for prevention therapy with lipid-lowering, anticoagulant or antihypertensive drugs prior to stroke/TIA.

Methods

We analysed anonymised electronic primary care records from a United Kingdom (UK) primary care database that covers 561 family practices. Patients with first-ever stroke/TIA, ≥18 years, with diagnosis between 1 January 2009 and 31 December 2013, were included.

Missed opportunities for prevention were defined as people with clinical indications for lipid-lowering, anticoagulant, or antihypertensive drugs but not prescribed these drugs prior to their stroke/TIA. Mixed-effect logistic regression models evaluated the relationship between missed opportunities and individual clinical/demographic characteristics.

Results

29,043 people with stroke/TIA met the inclusion criteria. Patients with Coronary Heart Disease, Chronic Kidney Disease, Peripheral Arterial Disease or diabetes were at less risk of a missed opportunity for prescription of lipid-lowering and antihypertensive drugs. However, patients with a 10-year CVD risk ≥20% but without these diagnoses had increased risk of having a missed opportunity for prescription of lipid-lowering drugs or antihypertensive drugs. Females were less likely to be prescribed anticoagulants but more likely to be prescribed antihypertensive drugs. The very elderly (≥85 years) were less likely to be prescribed all three prevention drugs, compared to people aged 75-79 years.

Conclusion

Knowing the patient characteristics predictive of missed opportunities for stroke prevention may help primary care identify and appropriately manage these patients. Improving the management of these groups may reduce their risk and potentially prevent large numbers of future strokes and TIAs in the population.

Introduction

Stroke is a leading cause of death and disability worldwide; the Global Burden of Disease Study found stroke is the second leading cause of death[1] and disability.[2] Furthermore stroke incidence, in terms of absolute numbers, and age-adjusted prevalence rates have increased.[3] Therefore, primary prevention of stroke and transient ischaemic attack (TIA), a risk factor for stroke, is essential more than ever to reduce the burden of these conditions.

Dyslipidaemia, atrial fibrillation (AF) and hypertension are modifiable risk factors for stroke which can be targeted through pharmacotherapy to reduce stroke risk.[4-6] However, despite evidence-based guidelines, prescribing of lipid-lowering, anticoagulant and antihypertensive drugs for primary stroke/TIA prevention is suboptimal in primary care. We previously found that over half of people eligible for one or more of these drugs were not prescribed them prior to first stroke/TIA.[7] Approximately 12,000 first-strokes could potentially be prevented annually in the United Kingdom (UK) through optimal prescribing of lipid-lowering, anticoagulant and antihypertensive drugs.[7]

A number of studies suggest variations and inequalities in prescribing of lipid-lowering, anticoagulant and antihypertensive drugs for prevention of cardiovascular disease (CVD).[8-14] There are inconsistent findings regarding the association between deprivation status and prescribing of prevention drugs;[10, 13] a Scottish study found that more deprived people were less likely to be prescribed statins,[11] whereas as a survey of English family practices found higher prescriptions of statins in more deprived areas.[9] Sex differences have also been observed; a survey of hypertension treatment in Europe and North America found women were more likely than men to be prescribed antihypertensive drugs.[14] Conversely, French and Japanese studies reported women were less likely to be prescribed anticoagulant drugs.[8,12] However, these studies did not consider prescribing practice in the context of predicted CVD

and stroke risk and clinical indications for prescribing. This is important because a treatment-risk paradox has been observed whereby there is overprescribing of prevention drugs in people without a clinical indication[13] and sub-optimal prescribing in people at high risk.[15] Understanding what characteristics are associated with sub-optimal prescribing of prevention drugs in eligible patients is important to improve primary prevention of stroke/TIA.

Our objective was to determine the relationship between clinical and demographic characteristics and prescription of lipid-lowering, anticoagulant or antihypertensive drugs in patients with clinical indications prior to stroke/TIA.

Methods

The full protocol for this study has been published elsewhere,[16] methods are summarised in brief below. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study design and data source

We conducted a retrospective analysis of electronic medical records from 561 family practices in the UK. Anonymised data were obtained from The Health Improvement Network (THIN),[17] a large primary care database which covers approximately 6% of the UK population and is broadly generalisable in terms of age, sex and morbidity.[18] Recording of stroke and TIA in THIN have a high validity.[19] Furthermore, prescribing data are comprehensive and accurate because this data is automatically retained in patients' electronic medical records from software used to print prescriptions.[20]

Analysis of THIN data has ethical approval from the National Health Service South-East Multicentre Research Ethics Committee, subject to independent scientific review.[21] This

study had approval by a scientific review committee administered by IMS Health Real-World Evidence Solutions (reference: 13-023).

Population

We defined primary stroke prevention as prevention of stroke in individuals with no prior history of stroke; therefore, the study population comprised patients with a diagnosis of first stroke (with or without previous TIA) and first TIA (if no prior stroke). Patients were included who had a stroke/TIA diagnosis between 1 January 2009 and 31 December 2013 and were aged ≥18 years at their diagnosis. The date of first-ever stroke or TIA was taken as the index date.

Definitions of missed opportunities for primary stroke/TIA prevention

A potential missed opportunity for stroke/TIA prevention was defined as a person in whom a prevention drug was clinically indicated at the time of their stroke or TIA, but who was not receiving treatment. This meant no prescription of a lipid-lowering or antihypertensive drug within the previous 90 days (the usual maximum prescription length in the UK) or for an anticoagulant drug within 120 days (to allow for referral to an anticoagulation clinic). Patients with a clinical code for anticoagulation monitoring were also considered to be on anticoagulant drugs.

The most recent risk factor data prior to the stroke/TIA were used to determine if stroke prevention drugs were clinically indicated. Clinical indications for lipid-lowering, anticoagulant, and antihypertensive drugs were based on UK national guidelines used during the study period (Online supplement).[5,22,23]

Analysis

All analysis was conducted using STATA version 12 (StataCorp). The relationship between clinical/demographic characteristics (Online supplement) and missed prescribing

opportunities was evaluated using mixed-effects logistic regression, with family practice as a random effect and odds ratios (OR) reported. Age and sex were forced into the models because they were pre-identified as important predictors of under-treatment.[24-26] Year of stroke/TIA was included as a covariate in the regression models. Backwards elimination with a p-to-eliminate value of >0.05 was used to select variables to be included in the final models. Exploratory analyses are detailed in the online supplement. No attempt was made to impute missing data, but a "missing" category was created for categorical variables.

Results

29,043 people with stroke/TIA met the inclusion criteria (Table 1). The median age was 74 years (IQR 64,82) and 51% were female. 17,680 patients had a clinical indication for one or more stroke prevention drugs, of which, 9,579 were not prescribed these drugs at the time of their stroke or TIA. Missed opportunities for prescribing of prevention drugs was found in 49% (7,836/16,028) of patients with a clinical indication for lipid-lowering drugs, 52% (1,647/3,194) for anticoagulant drugs and 25% (1,740/7,008) for antihypertensive drugs.[7]

Predictors of missed opportunities for prescription of prevention drugs

The adjusted ORs for each prevention drug are presented below and reported in eTables I-III.

Sex

Females had increased odds of having a missed opportunity for prescribing anticoagulant drugs (OR 1.37; 95% CI 1.18,1.58); however, the opposite was true for antihypertensive drugs (OR 0.85; 95% 0.74,0.97) and there was no sex effect for lipid-lowering drugs.

Age

The very elderly (≥85 years) had increased odds of not being prescribed lipid-lowering, anticoagulant and antihypertensive drugs when clinically indicated (eTables I-III). For lipid-lowering and antihypertensive drugs, there was a J-shaped relationship between age and missed prescribing opportunities where younger age categories (50-69 years) also had increased odds of missed opportunities (reference category 75-79 years; eTables I and III). However, for anticoagulant drugs, patients between 55 to 59 years had reduced odds of having a missed opportunity (eTable II).

Comorbidities

The odds of missed opportunities for lipid-lowering drug prescribing were less than a third in stroke/TIA patients with a diagnosis of coronary heart disease (CHD) (OR 0.21; 95% CI 0.19,0.22) or diabetes (OR 0.31; 95% CI 0.28,0.33) and significantly reduced in patients with a diagnosis of peripheral arterial disease (PAD) (OR 0.52; 95% CI 0.45,0.60), hypertension (OR 0.69; 95% CI 0.64,0.75) or chronic kidney disease (CKD) (OR 0.86; 95% CI 0.79,0.94).

For antihypertensive drugs, odds of having a missed opportunity were substantially lower in patients with a diagnosis of hypertension (OR 0.09; 95% CI 0.07,0.11), CHD (OR 0.26; 95% CI 0.21,0.33), AF (OR 0.35; 95% CI 0.27,0.47), diabetes (OR 0.43; 95% CI 0.35,0.52), heart failure (OR 0.49; 95% CI 0.33,0.73) and CKD (OR 0.50; 95% CI 0.41,0.60). In addition, significantly reduced odds of having a missed opportunity for a prescription for antihypertensive drugs was found for patients with a diagnosis of PAD (OR 0.62; 95% CI 0.47,0.81), cancer (OR 0.78; 95% CI 0.62,0.98), hypothyroidism (OR 0.79; 95% CI 0.63,1.00) or asthma (OR 0.79; 95% CI 0.62,1.00). For anticoagulant drugs, a diagnosis of heart failure (OR 0.53; 95% CI 0.44,0.63) or diabetes (OR 0.82; 95% CI 0.69,0.98) was associated with reduced odds of having a missed opportunity for prescribing of these drugs.

Increased odds of having a missed opportunity was associated with a diagnosis of dementia for anticoagulant (OR 1.51; 95% CI 1.11,2.06) and antihypertensive drugs (OR 1.78; 95% CI 1.26,2.51); palliative care (OR 2.48; 95% CI 1.83,3.34) for lipid-lowering drugs; and number of comorbidities (OR 1.28 per unit increase; 95% CI 1.16,1.42) for antihypertensive drugs. There was no association between number of comorbidities and prescribing of lipid-lowering or anticoagulant drugs.

CVD risk

Exploratory analyses (Online supplement) found that people with a 10-year CVD risk ≥20% but without 'high risk comorbidities' (CHD, CKD, PAD, diabetes or familial hypercholesterolaemia) had a 3-fold increased odds having a missed opportunity for lipid-lowering drug prescribing (OR 2.81; 95% CI 2.47,3.21). There were 2,780 patients with a clinical indication for lipid-lowering drugs who had a 10-year CVD risk ≥20% but no high risk comorbidities; 81% (2,238/2,780) of these were not prescribed these drugs. Similarly, patients with a clinical indication for antihypertensive drugs who had a 10-year CVD risk ≥20% but no 'high risk comorbidities' had increased odds of having a missed opportunity for these drugs (OR 1.43; 95% CI 1.17,1.75). There were 1,076 of these patients eligible for antihypertensive drugs due to a 10-year CVD risk ≥20% but no 'high risk comorbidities'; 45% (479/1,076) were not prescribed these drugs.

Behavioural and other demographic characteristics

After adjustment for clinical and other patient factors, current smokers and people with a missing smoking status were more likely to have a missed opportunity for prescription of lipid-lowering and anticoagulant drugs, compared to non-smokers (eTable I and II). Stroke/TIA patients who were underweight (body mass index [BMI] <18.5 kg/m^2) or missing BMI had increased odds of not being prescribed lipid-lowering and anticoagulant drugs, compared to people with a healthy BMI (18.5-25.9 kg/m^2) (eTable I and II). Being

overweight (BMI 26.0-30.0 kg/m^2) or obese (BMI >30.0 kg/m^2) was associated with increased odds of having a missed opportunity for anticoagulant drugs, but reduced odds for lipid-lowering drugs (eTable I and II). There was no association between BMI or smoking and antihypertensive prescribing.

Provision of lifestyle advice was associated with reduced odds of missed opportunities for prescribing lipid-lowering drugs (advice on smoking and weight) and antihypertensive drugs (advice on weight; eTables I and III). There were statistically significant regional differences for prescribing of lipid-lowering drugs with stroke/TIA patients in Wales (OR 0.72; 95% CI 0.59,0.89) and Northern Ireland (OR 0.72; 95% CI 0.59,0.88) more likely to be prescribed these drugs (West Midlands region of England as reference).

Deprivation and rurality (urban/rural) status had no effect on missed prescribing opportunities for any of the three prevention drugs.

Discussion

Principal findings

We identified population subgroups where there are potential missed opportunities for prevention of stroke/TIA. Females were less likely to be prescribed anticoagulants but more likely to be prescribed antihypertensive drugs; however, there was no sex effect for lipid-lowering drugs. Compared to patients aged 75-79 years, the very elderly (≥85 years) and patients aged 50-69 years were less likely to be prescribed preventative drugs. Patients on a disease register for CHD, CKD, PAD or diabetes were markedly more likely to be prescribed lipid-lowering and antihypertensive drugs. In contrast, patients at high risk (i.e. with a 10 year

CVD risk ≥20%) but not on these disease registers were much less likely to be prescribed these drugs. Deprivation and urban/rural status had no effect on prescribing.

Strengths and weaknesses of the study

The strengths of this study are that the data source is generalisable to UK family practices and reflects routine clinical practice. Prescribing data are accurate and comprehensively recorded[27] and the sample size is very large. Stroke and the main comorbidities are likely to be accurately recorded as they are clinically significant; diagnoses have been validated within THIN;[19] and, in the UK, GPs are incentivised through QOF to keep a register of patients with these conditions.

This was an epidemiological, descriptive study; therefore, an important limitation is that the reasons for non-prescribing are unclear. There may be legitimate reasons why patients were not prescribed preventative medication which are not routinely coded in electronic patient records, such as patients' preference, limited life expectancy or increased bleeding risk (when prescribing anticoagulant drugs). Clinical judgment should be used in combination with patient preference when considering prescribing preventative medication. Therefore, non-prescribing of these drugs should not be considered a missed opportunity if the doctor and patient have engaged in a shared decision making process incorporating the best available evidence. Patients with clinical codes indicating prevention drugs were declined, contraindicated or an adverse reaction were not excluded from the analysis because it is unclear if these were relevant at the time of index stroke/TIA. The number of patients in our sample with these codes was small (5%, 7% and 0.7% for lipid lowering, anticoagulant and antihypertensive drugs, respectively), suggesting that this information would not have altered our conclusions. Lastly, prevention of stroke/TIA is complex and our definition of missed prescribing opportunities does not address patients' adherence to medication, appropriate prescribing of drug combinations or medication targets, such as blood pressure levels.

Implications for clinical practice

The relationship we identified between sex and prescribing of preventative drugs has important clinical implications, particularly for anticoagulant drugs. Female sex is an independent risk factor for stroke in AF patients and strokes in women with AF are associated with increased mortality and disability compared to males.[28,29] Therefore, sub-optimal prescribing of anticoagulants in females is likely to have a large impact on the burden of stroke. Bleeding risk has been cited as the most common reason for physicians not prescribing anticoagulants[30] and some evidence suggests that bleeding risk is greater in women.[31] However, a recent systematic review found no difference in risk of bleeding between men and women.[32] Anticoagulation in AF patients with the highest stroke risk is likely to provide the greatest benefit; therefore, raising clinicians' awareness of sub-optimal prescribing of anticoagulants in females and the associated burden has potential to improve stroke prevention in these high-risk patients.

Missed opportunities for stroke prevention in patients with a high 10-year CVD risk may suggest that absolute risk is not considered. This is supported by our finding that patients with a diagnosis of CHD, CKD, PAD or diabetes were more likely to be prescribed lipid-lowering and antihypertensive drugs while those without these diagnoses but with a high 10-year CVD risk were less likely to be prescribed these drugs. Our study calculated patients' CVD risk scores post-hoc; however, many of the patients may not have had their CVD risk calculated by GPs. A survey of physicians from six European countries found that only 38% used risk scores to estimate CVD risk.[33] This has important implications because evidence suggests that both patients[34] and clinicians[35,36] underestimate CVD risk. This is particularly relevant following the most recent guideline recommendations for lipid-lowering drug prescribing which decrease the 10-year CVD risk cut off from ≥20% to ≥10%.[4] Furthermore, perception of risk is influenced by social context, such as the media.[37] A study of UK primary care found

that a period of intense media coverage on statins was associated with a decrease in recording of CVD risk scores and increase in the number of people who stopped taking statins.[38] The responsibility of GPs to accurately assess absolute CVD risk and effectively communicate this risk is essential to inform the shared decision making process and prevent patients missing out on preventative medication that they may benefit from and wish to take.[39]

Presence of a single comorbidity was associated with with reduced odds of having a missed opportunity for prescribing antihypertensives; however, an increased number of comorbidities increased the odds of having a missed opportunity for these drugs (eTable III). Prescribing of antihypertensives in patients with a single comorbidity may be higher because in UK primary care general practices are incentivised to include these patients on a disease register and regularly follow them up. This increases the opportunities for detection and treatment of hypertesnsion. The reseaon for underprescribing of antihypertensive drugs in people with multimorbidity is unclear; however, it could be reflective of documented barriers to antihypertensive drug, which include: hypertension not considered a clinical priority,[40] compteting medical problems,[41] polypharmacy[25] and physicians lack of belief of the benefit of these drugs.[25] Inadequate blood pressure control in people with multi morbidity has been observed in the literature.[42]

Missed opportunities to prescribing prevention drugs to the very elderly has important implications because age is one of the most important risk factors for stroke/TIA and the population is ageing.[43] In particular, this is relevant for anticoagulant prescribing where 39% (1,240/3,194) of stroke/TIA patients with these drugs clinically indicated were aged ≥85 years, compared to 21% (3,368/16,028) and 22% (1,538/7,008) for lipid-lowering and antihypertensive drugs respectively. There is a lot of potential gain in this elderly patient group; the net benefit of anticoagulation is greatest in the elderly and the benefits of anticoagulation in the elderly have been shown to outweigh the risk.[44]

Current lipid-lowering guidelines recommend all patients aged ≥85 years are considered high risk[4] and hypertension guidelines recommend people aged >80 years are prescribed the same antihypertensives as patients aged 55-80 years.[5] However, the guidelines acknowledge that there is a lack of evidence to support these recommendations,[4,5] particularly for stroke prevention. Furthermore, there are greater risks for prescribing prevention drugs to the very elderly in the context of multimorbidity and polypharmacy. The benefit of preventative medication may be redundant if a patient has reduced life expectancy, frailty or the treatment burden is greater than the added length or quality of life.[45] Multimorbidity guidelines recommend that prescribing of preventative medication should take a personalised approach and include patients' preferences and health priorities.[45] Therefore, age alone should not preclude prescribing of prevention drugs, but prescribing of these drugs should be undertaken using shared decision making in consideration of the best available evidence, treatment burden and patients' preference.

Conclusions

Stroke can be preventable; however, opportunities for prevention may be missed. We identified characteristics that are associated with missed prescribing opportunities for lipid-lowering, anticoagulant and antihypertensive drugs. Patients with a high calculated CVD risk but who did not have high risk comorbidities were markedly less likely to be prescribed lipid-lowering and antihypertensive drugs. In addition, female patients with AF were less likely to be prescribed anticoagulant drugs and people aged ≥85 years were less likely to be prescribed all three prevention drugs. Despite evidence-based guidelines, prevention of stroke and TIA with pharmacotherapy remains suboptimal in primary care. Knowledge of patient characteristics associated with missed opportunities for prescribing of prevention drugs

provides an opportunity to raise awareness amongst clinicians and improve primary prevention of stroke/TIA.

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References

1. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: A systematic analysis for the global burden of disease study 2015. *Lancet*. 2016;388:1459-1544

2. Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the global burden of disease study 2015. *Lancet*. 2016;388:1545-1602

3. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990–2010: Findings from the global burden of disease study 2010. *Lancet*. 2014;383:245-254

4. National Institute for Health and Care Excellence. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE; July 2014. Clinical guideline-181. ISBN:978-1-4731-0638-3

5. National Institute for Health and Clinical Excellence. Hypertension: The clinical management of primary hypertension in adults. NICE: August 2011. Clinical guideline-127. ISBN:978-1-4731-2195-9

6. National Institute for Health and Clinical Excellence. Atrial fibrillation: The management of atrial fibrillation. NICE; June 2014 Clinical guideline 180. ISBN:978-1-4731-0603-1

7. Turner GM, Calvert M, Feltham MG, Ryan R, Fitzmaurice D, Cheng KK, et al. Under-prescribing of prevention drugs and primary prevention of stroke and transient ischaemic attack in uk general practice: A retrospective analysis. *PLOS Medicine*. 2016;13:e1002169

8. Akao M, Chun YH, Esato M, Abe M, Tsuji H, Wada H, et al. Inappropriate use of oral anticoagulants for patients with atrial fibrillation. *Circulation Journal*. 2014;78:2166-2172

9. Ashworth M, Lloyd D, Smith RS, Wagner A, Rowlands G. Social deprivation and statin prescribing: A cross-sectional analysis using data from the new uk general practitioner 'quality and outcomes framework'. *J Public Health*. 2007;29:40-47

10. Marshall IJ, Wang Y, McKevitt C, Rudd AG, Wolfe CD. Trends in risk factor prevalence and management before first stroke: Data from the south london stroke register 1995-2011. *Stroke*. 2013;44:1809-1816

11. Pears E, Hannaford PC, Taylor MW. Gender, age and deprivation differences in the primary care management of hypertension in scotland. *Family Practice*. 2003;20:22-31

12. Sabouret P, Depret-Bixio L, Cotte FE, Marie P, Bedira N, Blin P. Sex differences in stroke prevention in atrial fibrillation in french primary care. *Clinical Research in Cardiology*. 2014;103:887-893

13. Wu J, Zhu S, Yao GL, Mohammed MA, Marshall T. Patient factors influencing the prescribing of lipid lowering drugs for primary prevention of cardiovascular disease in uk general practice: A national retrospective cohort study. *PLoS ONE*. 2013;8:e67611

14. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five european countries, canada, and the united states. *Hypertension (Dallas, Tex.:1979)*. 2004;43:10-17

15. Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: The treatment-risk paradox. *JAMA*. 2004;291:1864-1870

16. Moran GM, Calvert M, Feltham MG, Marshall T. Retrospective case review of missed opportunities for primary prevention of stroke and TIA in primary care: Protocol paper. *BMJ Open*. 2014;4:e006622

17. The Health Improvement Network (THIN). Vision Health. https://www.visionhealth.co.uk/portfolio-items/the-health-improvement-network-thin/ Accessed December 6, 2017

18. Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of the health improvement network (THIN) database: Demographics, chronic disease prevalence and mortality rates. *Informatics in Primary Care*. 2011;19:251-255

19. Ruigomez A, Martin-Merino E, Rodriguez LA. Validation of ischemic cerebrovascular diagnoses in the health improvement network (THIN). *Pharmacoepidemiology & Drug Safety*. 2010;19:579-585

20. Vision Health. https://www.visionhealth.co.uk Accessed December 6, 2017

21. THIN database. University Central London. https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database. Accessed December 6, 2017

22. National Collaborating Centre for Chronic Conditions. Atrial fibrillation: National clinical guideline for management in primary and secondary care. London: Royal College of Physicians (UK);2006. Clinical guideline-36. ISBN-10:1-86016-282-7

23. National Institute for Health and Care Excellence. Lipid modification: Cardiovascular risk assessment and the primary and secondary prevention of cardiovascular disease. NICE; May 2008. Clinical guideline-67.

24. McKinlay JB, Link CL, Freund KM, Marceau LD, O'Donnell AB, Lutfey KL. Sources of variation in physician adherence with clinical guidelines: Results from a factorial experiment. *J Gen Internal Med*. 2007;22:289-296

25. Midlov P, Ekesbo R, Johansson L, Gerward S, Persson K, Nerbrand C, et al. Barriers to adherence to hypertension guidelines among gps in southern sweden: A survey. *Scand J Primary HealthCare*. 2008;26:154-159

26. Ramsay SE, Whincup PH, Wannamethee SG, Papacosta O, Lennon L, Thomas MC, et al. Missed opportunities for secondary prevention of cerebrovascular disease in elderly british men from 1999 to 2005: A population-based study. *J Public Health*. 2007;29:251-257

27. Gnani S and Majeed A. A user's guide to data collected in primary care in England. Imperial College London. https://www1.imperial.ac.uk/resources/579D8B09-C1C1-4026-A7BE-C3E936EE9567/ Accessed Decmber 6, 2017

28. Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke severity in atrial fibrillation. The Framingham study. *Stroke*. 1996;27:1760-1764

29. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham study. *Stroke*. 1991;22:983-988

30. Pugh D, Pugh J, Mead GE. Attitudes of physicians regarding anticoagulation for atrial fibrillation: A systematic review. *Age Ageing*. 2011;40:675-683

31. Humphries KH, Kerr CR, Connolly SJ, Klein G, Boone JA, Green M, et al. New-onset atrial fibrillation: Sex differences in presentation, treatment, and outcome. *Circulation*. 2001;103:2365-2370

32. Lapner S, Cohen N, Kearon C. Influence of sex on risk of bleeding in anticoagulated patients: A systematic review and meta-analysis. *JTH*. 2014;12:595-605

33. Graham IM, Stewart M, Hertog MG. Factors impeding the implementation of cardiovascular prevention guidelines. *Eur J Cardiovasc Prevent & Rehab*. 2006;13:839-845

34. Samsa GP, Cohen SJ, Goldstein LB, Bonito AJ, Duncan PW, Enarson C, et al. Knowledge of risk among patients at increased risk for stroke. *Stroke*. 1997;28:916-921

35. Heeley EL, Peiris DP, Patel AA, Cass A, Weekes A, Morgan C, et al. Cardiovascular risk perception and evidence--practice gaps in Australian general practice. *Med J Australia*. 2010;192:254-259

36. McManus RJ, Mant J, Meulendijks CF, Salter RA, Pattison HM, Roalfe AK, et al. Comparison of estimates and calculations of risk of coronary heart disease by doctors and nurses using different calculation tools in general practice: Cross sectional study. *BMJ*. 2002;324:459-464

37. Mosca L, Mochari-Greenberger H, Dolor RJ, Newby LK, Robb KJ. Twelve-year follow-up of american women's awareness of cardiovascular disease risk and barriers to heart health. *Circulation: Cardiovascular Quality & Outcomes*. 2010;3:120-127

38. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, et al. Impact of statin related media coverage on use of statins: Interrupted time series analysis with UK primary care data. *BMJ*. 2016;353:839-845

39. Webster R, Heeley E. Perceptions of risk: Understanding cardiovascular disease. *Risk Management & Healthcare Policy*. 2010;3:49-60

40. Lin ND, Martins SB, Chan AS, Coleman RW, Bosworth HB, Oddone EZ et al. Identifying barriers to hypertension guideline adherence using clinician feedback at the point of care. *AMIA Annu Symp Proc.* 2006;2006:494–498

41. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM. Physician-related barriers to the effective management of uncontrolled hypertension. *JAMA Internal Medicine*. 2002;162(4):413-420

42. Li YT, Wang H, Liu K, Lee G, Chan W, Griffiths S et al. Medication adherence and blood pressure control among hypertensive patients with coexisting long-term conditions in primary care settings. *Medicine.* 2016;95(20):e3572.

43. Townsend N, Bhatnagar P, Smolina K, Nichols M, Leal J, Luengo-Fernandez R, Rayner M. Coronary heart disease statistics: A compendium of health statistics. 2012;2017

44. Mant J, Hobbs FDR, Fletcher K, Roalfe A, Fitzmaurice D, Lip GYH, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation: A randomised controlled trial. *Lancet*.370:493-503

45. National Institute for Health and Care Excellence. Multimorbidity: Clinical assessment and management. NICE: September 2016. 1-23. NG56. ISBN:978-1-4731-2065-5

Tables

Table 1: Characteristics of the study population.

Diagnosis (n,%)	Stroke only	16,245 (55.9)
	TIA only	10,446 (36.0)
	Stroke with previous TIA	2,352 (8.1)
Age (Median [IQR])	(years)	74 [64, 82]
Sex (n,%)	Male	14,204 (48.9)
	Female	14,839 (51.1)
Comorbidity (n,%)	Atrial fibrillation	3,544 (12.2)
	Asthma	3,062 (10.5)
	Cancer	3,239 (11.2)
	CHD	5,543 (19.1)
	CKD	5,774 (19.9)
	COPD	2,198 (7.6)
	Dementia	1,270 (4.4)
	Depression	6,174 (21.3)
	Diabetes	4,512 (15.5)
	Epilepsy	614 (2.1)
	Heart failure	1,625 (5.6)
	Hypertension	14,646 (50.4)
	Hypothyroidism	2,890 (10.0)
	Learning disability	130 (0.5)
	Osteoporosis	2,318 (8.0)
	PAD	1,431 (4.9)
	Palliative care	359 (1.2)
	Psychosis	439 (1.5)
	Rheumatoid arthritis	655 (2.3)

CHD: Coronary Heart Disease, CKD: Chronic Kidney Disease, COPD: Chronic Obstructive Pulmonary Disease, PAD: Peripheral Artery Disease, TIA: Transient Ischaemic Attack