Long term survival after a first transient ischaemic attack in England: A retrospective matched cohort study

Padma Chutoo,[a] Elena Kulinskaya,[a] Ilyas Bakbergenuly,[a] Nicholas Steel,[b] Dmitri Pchejetski,[b] and Bradley Brown,[a]

Objective: Transient ischaemic attacks (TIA) serve as warning signs for future stroke, and the impact of TIA on long term survival is uncertain. We assessed the long-term hazards of all-cause mortality following a first episode of a transient ischaemic attack (TIA). *Design:* Retrospective matched cohort study. *Methods:* Cohort study using electronic primary health care records from The Health Improvement Network (THIN) database in the United Kingdom. Cases born in or before 1960, resident in England, with a first diagnosis of TIA between January 1986 and January 2017 were matched to three controls on age, sex and general practice. The primary outcome was all-cause mortality. The hazards of all-cause mortality were estimated using a time-varying Double-Cox Weibull survival model with a random frailty effect of general practice, while adjusting for different socio-demographic factors, medical therapies, and comorbidities. *Results:* 20,633 cases and 58,634 controls were included. During the study period, 24,176 participants died comprising of 7,745 (37.5%) cases and 16,431(28.0%) controls. In terms of hazards of mortality, cases aged 39 to 60 years at the first TIA event had the highest hazard ratio (HR) of mortality compared to their 39-60 years matched controls (HR = 3.04 (2.91 - 3.18)). The HR for cases aged 61-70 years, 71-76 years and 77+ years were 1.98 (1.55 - 2.30), 1.79 (1.20 - 2.07) and 1.52 (1.15 - 1.97) compared to their same-aged matched controls. Cases aged 39-60 at TIA onset who were prescribed aspirin were associated with reduced HR of 0.93 (0.84 - 1.01), 0.90 (0.82 - 0.98) and 0.88 (0.80 - 0.96) at 5, 10 and 15 years respectively, compared to the same aged cases who were not prescribed any antiplatelet. Statistically significant reductions in hazard ratios were observed with aspirin at 10 and 15 years in all age groups. Hazard ratio point estimates for other antiplatelets (dipyridamole or clopidogrel) and dual antiplatelet therapy were very similar to aspirin at 5, 10 and 15 years but with wider confidence intervals that included 1. There was no survival benefit associated with antiplatelet prescription in controls. *Conclusions:* The overall risk of death was considerably elevated in all age groups after a first-ever TIA event. Aspirin prescription was associated with a reduced risk. These findings support the use of aspirin in secondary prevention for people with a TIA. The results do not support the use of antiplatelet medication in people without TIA.

Keywords: General practice—Weibull-Cox model—Multiple Imputation—Antiplatelets—The Health Improvement Network (THIN) database

From the [a]School of Computing Science, University of East Anglia, Norwich Research Park, Norwich, United Kingdom; and [b]Norwich Medical School, University of East Anglia, Norwich Research Park, Norwich, United Kingdom.

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Corresponding author. E-mail: P.Chutoo@uea.ac.uk.

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Introduction

Stroke is one of the leading causes of death and disability in the UK[1,2]. Transient ischaemic attack is formally defined as "an episode of transient (less than 24 hours) neurological dysfunction caused by focal brain, spinal cord, or retinal ischaemia, without evidence of acute infarction"[2]. A TIA is caused by temporary ischaemia and it resolves completely[4]. While TIA does not cause permanent disability[5], cases are at significantly increased risk of repeated TIAs (crescendo TIAs) or stroke[6,7]. These recurrent strokes are usually more devastating than the first events[8].

According to UK guidelines[3], stroke survivors without major complications are typically managed using cardiovascular secondary prevention medications and antiplatelet therapy is one of the gold standard treatments. Aspirin, clopidogrel, dipyridamole and their combinations are commonly prescribed. However, these medications confer the risk of haemorrhage and gastrointestinal bleeds. Previous trials such as CAPRIE, FASTER, MATCH, ESPRIT, CHANCE, CHARISMA, CAST, Dutch-TIA[9] and meta-analyses[10-11] examined the comparative efficacy and safety of different antiplatelet options. Dual therapy of aspirin and clopidogrel has been shown to reduce stroke recurrence but also to increase the risk of bleeding[9,11-12]. With regards to mortality, the results are inconclusive.

Current guidelines[3] endorse the initiation of antiplatelets for cases for secondary prevention, preferably clopidogrel, modified-released dipyridamole with aspirin as the next option and if both are contraindicated or cannot be tolerated, aspirin is prescribed. Despite major advances in stroke care, the long-term impact of TIA events on all-cause mortality is relatively unexplored. Previous studies found that the risk of mortality for cases is 2 to 3 times higher compared to matched controls[8,14-16]. A case-control study in Canada[8] reported HR=2.1 of composite death outcomes for cases relative to matched controls, and a PRISM study in Australia[16] reported a relative risk of death of 1.42. Some previous studies were often limited by small sample sizes[17-18] or short follow-up periods[19]. Furthermore, comparison of their results was limited due to methodological differences: prospective[16-17] versus retrospective follow-up[8,20], the source of participants: hospital based[8,16] versus community based[15,18,21], by stroke etiology, recruitment period and non-adjustment of confounding factors.

Aims

The current study aims to answer two important questions in routine clinical practice, using longitudinal long-term data from a large UK representative database[22]: what is the long-term impact of TIA on survival and what are the benefits or harms of antiplatelet prescription.

Methods

Data extraction

The Health Improvement Network (THIN) is a database of longitudinal anonymised patient primary care records on demographics, diagnoses, referrals and prescriptions from general practices (GP). THIN includes 3.6 million current patients, about 6% of the UK population and is broadly representative and generalizable to the UK population[22,23]. We selected a subset of participants born in or before year 1960 (Fig. S1). Data was extracted using clinical Read codes which involved querying the THIN database and relational files. Any Read Codes for monitoring, "history of", "referral" and "rehabilitation" were excluded to ensure that the initial electronically recorded TIA events were considered (Table S1). TIA/stroke mimic cases, ischaemic and hemorrhagic strokes cases were filtered out using relevant Read codes.

Selection criteria

Eligible participants were patients who were actively registered with a GP for at least 12 months prior to being selected for the study to ensure data quality and to allow adequate time for risk factor data to be recorded. Participants with prior life-limiting conditions at study entry, such as major cancers, dementia (vascular dementia and Alzheimer's disease), chronic kidney disease stages 4-5 (CKD), and haemorrhagic stroke diagnosed were excluded (Table S2).

Cases were individuals aged 18 years and above experiencing a first incident of TIA between 1st January 1986 and 31st January 2017. These were matched to at most 3 controls (who had no incidence of stroke at baseline) by age, gender and GP practice. All patients were followed from study entry date until the earliest of death, censored (transferred to other practice) or end of study.

Study variables

Selected variables were based on literature review and NICE guidance for treatment and management of TIA[1,3]. Further details about levels and coding of covariates are provided in Table S3. Diagnoses of the medical conditions were based on the standard list of clinical READ codes used to identify chronic diseases in the UK. Drug prescriptions corresponding to British National Formulary (BNF).

The covariates used in the model were gender, year of birth, case-control status, age at diagnosis, prior comorbidities such as asthma, CKD 1-3, chronic obstructive pulmonary disease (COPD), heart failure (HF), hypothyroidism, myocardial infarction (MI), peripheral arterial disease (PAD), hypertension, hypercholesterolemia, atrial fibrillation (AF), diabetes type II (T2DM), prior prescription of anticoagulants, antihypertensive, antidiabetic and antiplatelet drugs. Antiplatelet (APL) prescriptions were

classified as aspirin monotherapy, dual therapy consisting of aspirin with other antiplatelets options (DAPT) and other antiplatelets (dipyridamole or clopidogrel).

Other covariates included lifestyle factors such as BMI category, smoking status (ex-consumers, current consumers and non-consumers) and alcohol status (consumers and abstainers) and socio-economic status measured by the quintile of the English index of deprivation (IMD); IMD quintile 1 associated with most deprived areas and IMD quintile 5 with the least deprived areas. Possible dependencies of the survival outcomes within a general practice were modelled by the inclusion of a random frailty term.

Model building

The hazards of all-cause mortality were first studied using Cox regression. However, non-proportionality of hazards was detected. The Double-Cox Weibull model[24] was then used for survival modelling after ascertaining that the baseline hazards followed a Weibull distribution. The Double-Cox Weibull model which is an extension of the Cox model, resolves the problem of non-proportional hazards by modelling both the scale and the shape parameters of the distribution(S3). The model included a Gamma-distributed random effect of general practice to adjust for the correlation between participants from the same practice.

For a particular covariate, the scale parameter represents a constant hazard ratio when there is no significant shape parameter. However, for covariates with significant shape effects, hazards change over time. All statistical analyses were performed using R version 4.0.3.

Missing values for BMI (38%), smoking status (24%) and alcohol consumption (47%) were dealt with by multiple imputation using the *jomo* package. The distributions of known and imputed values were similar (Table S4). Using 10 imputed datasets, significant regression estimates were pooled using Rubin's rules and the resulting multiple imputed model had a good substantially good measure of discrimination with a high concordance C −index of 0.79 (SE error 0.002). Backward elimination with $p < 0.05$ for fixed effects and $p < 0.01$ for interaction effects was used to obtain a parsimonious model.

Results

20,633 TIA patients and their eligible 58,634 controls were considered and were followed up to a maximum of 30 years. 7,745 (37.5%) cases and 16,431(27.7%) controls died during follow-up. Distributions of basic characteristics and risk factors by case-control status are shown in Table 1. The cases had a mean age of 72.3 years and the controls of 71.6 years at study entry. At baseline, there was a significantly ($p < 0.05$) higher prevalence of cardiovascular comorbidities in cases than in controls;

Table 1. *Study Population (Characteristics of cases and controls).*

	Type of participant		
Variable	Cases (n = 20,633)	Controls (n = 58,634)	**P-value**
Demographical variables			
Age (mean (SD)) (years)	72.3 (10.7)	71.6 (10.7)	
39-60	3209 (15.6%)	9669 (16.5%)	
61-70	5229 (25.3%)	15608 (26.6%)	
71-76	4103 (19.9%)	11975 (20.4%)	
77+	8092 (39.2%)	21382 (36.5%)	
Sex: Males	9582 (46.4 %)	27269 (46.5 %)	
Year of entry			
1986-1992	971 (4.7 %)	2642 (4.5 %)	
1993-1999	5175 (25.1 %)	14530 (24.8 %)	
2000-2006	8474 (41.1 %)	24052 (41.0 %)	
2007-2016	6013 (29.1%)	17410 (29.7 %)	
IMD Quintile[1]			
1 (Most deprived)	2739 (13.3 %)	6988 (11.9%)	
2	3706 (18.0 %)	10312 (17.6 %)	
3	4385 (21.2 %)	12506 (21.4%)	
4	4983 (24.2%)	14468 (24.6%)	
5 (Least Deprived)	4820 (23.4%)	14360 (24.5%)	
Pre-TIA conditions			
Asthma	2116 (10.3%)	5142 (8.8%)	*

(*Continued*)

Table 1 (*Continued*)

Variable	Type of participant		**P-value**
	Cases (n = 20,633)	Controls (n = 58,634)	
Atrial Fibrillation	2000 (9.7%)	2900 (4.9%)	*
Diabetes II			
No Diabetes	18211 (88.3%)	53726 (91.6%)	
Treated Diabetes	1965 (9.5%)	3867 (6.6%)	
Untreated Diabetes	457 (2.2%)	1041 (1.8%)	
COPD	1100 (5.3%)	2293 (3.9%)	*
Heart Failure	1419 (6.9%)	2557 (4.4%)	*
Hypertension	8960 (43.4%)	19282 (32.9%)	*
Hypercholesterolaemia	1447 (7%)	3118 (5.3%)	*
Myocardial Infarction	1632 (7.9%)	2916 (5%)	*
PAD	4936 (23.9%)	11244 (19.2%)	*
Premorbid prescriptions			
Anticoagulant agents	1640 (7.9%)	2965 (5.1%)	*
Lipid lowering agents	5840 (28.3%)	10670 (18.2%)	*
Antihypertensive agents	13772 (66.7%)	29820 (50.9%)	*
Antiplatelet therapy			
None	6373 (31%)	48959 (83.5%)	*
Aspirin monotherapy	9282 (45%)	8924 (15.2%)	*
Combination with aspirin(dual)	2584 (12.5%)	321 (0.5%)	< 0.05
Other antiplatelets agents[2]	2424 (11.7%)	430 (0.7%)	*
Lifestyle factors			
Body Mass Index (BMI)			
Underweight (<= 18.5)	338 (1.6%)	1024 (1.7%)	
Healthy weight (18.5 to 24.9)	4470 (21.7%)	13208 (22.5%)	
Overweight (25 to 29.9)	5048 (24.5%)	14632 (25%)	
Obese (30 to 40)	2956 (14.3%)	7804 (13.3%)	
Missing	7821 (37.9%)	21966 (37.5%)	
Smoking status			
Non-smoker	7936 (38.5%)	24204 (41.3%)	
Ex-Smoker	5394 (26.1%)	13922 (23.7%)	
Current smoker	2363 (11.5%)	6040 (10.3%)	
Missing	4940 (23.9%)	14468 (24.7%)	
Alcohol consumption			
Abstainer	2489 (12.1%)	6479 (11%)	
Ex-consumer	530 (2.6%)	1086 (1.9%)	
Current consumer	7659 (37.1%)	23485 (40.1%)	
Missing	9955 (48.2%)	27584 (47%)	

[1]IMD stands for Index of Multiple Deprivation in England. Quintile 1 is the most deprived group and Quintile 5 is least deprived group.

*$p < .05$. for proportion difference (χ^2 test).

[2]Other antiplatelet (APL) agents included dipyridamole or/& clopidogrel

hypertension (43.4% for cases versus 32.9% for controls), MI (7.9% versus 5%), AF (9.7% versus 4.9%) and PAD (23.9% versus 19.2%). Cases were more medicated than controls; anticoagulant drugs (7.9% for cases versus 5.1% for controls), lipid-lowering drugs (28.3% versus 18.2%) and antihypertensive drugs (66.7% versus 50.9 %). Cases experienced a higher risk of cardio-vascular morbidity (Table S5). 17.5% of cases experienced at least one recurrent TIA event in the first year following the initial event.

The model results of the fitted Double-Cox Weibull model provided in Table 2 include all significant medical risk factors, age, gender, socio-demographic details, and medication profiles. The results consist of two parts: the shape parameters (for the covariates with the time-varying hazards) and

Table 2. *Estimates of parameters with confidence intervals, frailty terms and concordance statistics based on the Weibull-Cox model.*

Variables	Levels	Estimates	CI
Sample Size		79,267	
Number of non-censored		24,176	
Weibull Parameters	*a*	29.19	28.79-29.58
	b	2.39	2.31-2.48
Shape parameters			
Age categories	39-60 years	1	
	61-70 years	0.9	0.82-0.98
	71-76 years	0.77	0.7-0.85
	77+ years	0.59	0.51-0.67
Birth cohort	1900 to 1920	1	
	1921 to 1930	0.84	0.82-0.86
	1931 to 1940	0.66	0.62-0.7
	1941 to 1960	0.48	0.4-0.56
Antiplatelet prescriptions	None	1	
	Aspirin only	0.96	0.94-0.98
	Dual therapy (Aspirin)	0.9	0.84-0.95
	Other Antiplatelets	0.89	0.83-0.95
Heart Failure	Yes	0.79	0.77-0.81
Scale parameters			
Birth cohort	1900 to 1920	1	
	1921 to 1930	0.5	0.44-0.56
	1931 to 1940	0.23	0.15-0.31
	1941 to 1960	0.09	0.03-0.2
Sex	Female	1	
	Male	1.3	1.28-1.33
IMD Quintile	1 (Most Deprived)	1	
	2	0.91	0.87-0.97
	3	0.92	0.88-0.96
	4	0.87	0.81-0.93
	5 (Least Deprived)	0.81	0.75-0.87
Case/Control Status	Controls	1	
	Cases	3.04	2.91-3.18
Age Category	39-60	1	
	61-70	1.77	1.66-1.89
	71-76	2.12	2-2.24
	77+	2.65	2.55-2.76
BMI	Normal + Underweight	1	
	Obese + Overweight	0.87	0.82-0.92
Asthma	Yes	1.16	1.12-1.2
COPD	Yes	1.73	1.67-1.79
CKD	Yes	1.04	0.96-1.11
Myocardial Infarction	Yes	1.2	1.16-1.24
Peripheral Arterial Disease	Yes	1.14	1.1-1.18
Atrial Fibrillation	Yes	1.27	1.21-1.32

(*Continued*)

Table 2 (*Continued*)

Variables	Levels	Estimates	CI
Smoking	Non-smoker	1	
	Current smoker	2.04	1.96-2.11
	Ex-smoker	1.24	1.2-1.29
Alcohol Consumption	Non-current	1	
	Current consumer	0.89	0.85-0.93
Diabetes	No diagnosis/No treatment	1	
	Yes and Treated	1.52	1.48-1.56
	Yes and Untreated	1.12	1.04-1.2
Anticoagulant agents	Yes	1.23	1.17-1.29
Hypertension	Yes	1.41	1.18-1.59
Antiplatelet prescriptions	None	1	
	Aspirin only	1.01	0.95-1.07
	Dual therapy (Aspirin)	1.11	0.9-1.33
	Other Antiplatelets	0.99	0.79-1.18
Interactions (Scale effects)			
	Cases & Hypertension	0.92	0.86-0.97
	Cases & aspirin only	0.88	0.83-0.94
	Cases & Dual therapy	0.75	0.53-0.96
	Cases & Other Antiplatelets	0.86	0.66-1.06
	Cases & Age 61-70	0.65	0.51-0.79
	Cases & Age 71-76	0.54	0.41-0.68
	Cases & Age 77+	0.5	0.36-0.64
σ^2	Frailty	0.08	0.04-0.13
Concordance	C-index	0.79	

the scale parameters. Time-varying hazards were found for antiplatelet therapy, age at diagnosis of TIA, heart failure and birth cohort. It is noteworthy that case-control status (TIA diagnosis) was found to have significant interactions with hypertension, antiplatelet therapy at follow-up, and the age category at entry/diagnosis. This means that the other variables in the model affected equally the survival of both TIA patients and controls. Table 3 shows the HRs of risk factors having interactions with the case-control status. Other HRs can also be calculated using the model (S3).

The survival analysis showed that cases were associated with higher all-cause mortality compared to matched controls (Table 3). The cases experiencing a first TIA at age 39-60 years had at least 3 times higher hazards of death [HR = 3.04 (2.91 - 3.18)] relative to 39-60 controls. The hazard ratio for the 61-70 years, 71-76 years and 77+ cases relative to their controls of same age had HR of 1.98 (1.55 - 2.30), 1.72 (1.20 - 2.07) and 1.52 (1.15 - 1.97) respectively. Hypertensive cases had HR=3.94 (3.66 - 4.27) relative to non-hypertensive controls, implying that the combined effects of hypertension and TIA diagnosis were associated with a significant risk of all-cause mortality.

The year of birth category had significant time-varying effect on survival (Fig. S2). Earlier birth cohorts had raised hazards of all-cause mortality for both cases and controls. The improvement in survival prospects in later decades might have been a result of medical advances.

Antiplatelets had time varying effects. The trend over time of their hazard ratios with associated 95% confidence intervals (Table S6) were plotted in Figs. 1 and 2. The hazards of the uptake of the antiplatelets were estimated relative to non-users for both cases and controls.

With regards to cases, at 1 year, aspirin, DAPT and other antiplatelets were not associated to statistically significant reductions in hazards of death with point estimates ranging from 0.98 to 1.29 for the different age groups with confidence intervals including 1. The DAPT and other antiplatelets were associated with long-term positive but statistically not significant effects. Aspirin, however was associated with statistically significant longer-term survival benefits with HRs of 0.93 (0.84 - 1.00), 0.90 (0.82 - 0.98) and 0.88 (0.80 - 0.96) at 5, 10 and 15 years respectively, compared to the cases of the same ages who were not prescribed any APL.

Table 3. *Adjusted estimated hazard ratios of all-cause mortality by age at diagnosis, case-control status and hypertension diagnosis (from the Weibull- Cox model on the imputed data).*

Comparison group	Relative to:	HR	95% CI
Cases aged 39-60 years	Controls aged 39-60 years	3.04	(2.91 - 3.18)
Cases aged 61-70 years	Controls aged 61-70 years	1.98	(1.55 - 2.30)
Cases aged 71-76 years	Controls aged 71-76 years	1.72	(1.20 - 2.07)
Cases aged 77+ years	Controls aged 77+ years	1.52	(1.15 - 1.97)
Hypertensive controls	Non-hypertensive controls	1.41	(1.18 - 1.59)
Non-hypertensive cases	Non-hypertensive controls	3.04	(2.91 - 3.18)
Hypertensive cases	Non-hypertensive controls	3.94	(3.66 - 4.27)

Note: The table is only showing the HRs of the risk factors with interactions with the case-control diagnosis. Other HRs for other risk profiles and comparison groups can be calculated using the model parameters.

The situation for the controls, however, was different. When compared to antiplatelet-free controls, none of the antiplatelets was associated with significant survival improvement; with all HR estimates not statistically significant (Table S7).

Male participants had a HR of 1.31 (1.28 - 1.34) compared to their female counterparts (Fig. 3). Participants from less deprived areas (IMD quintile 5) had lower HR, 0.81 (0.75-0.86), compared to those in most deprived areas (IMD quintile 1). Selected medical conditions increased the mortality hazard in both cases and controls; AF with HR of 1.27 (1.21 - 1.32), COPD, 1.73 (1.67 - 1.78) and treated T2DM 1.52 (1.47 - 1.57).

Discussion

The large study (n = 79,267) with a long follow-up predicted the hazards of all-cause mortality associated with a first TIA diagnosis in GP-registered participants in England. Cases were associated with a higher risk of death compared to their matched controls. In cases, aspirin prescription was associated with improved survival at 10 and 15 years. Hazard ratio point estimates for other antiplatelets (dipyridamole or clopidogrel) and dual antiplatelet therapy were very similar to aspirin at 5, 10 and 15 years but with wider confidence intervals that included 1. Antiplatelets were not associated to survival benefits in controls. Both at baseline and at follow-up, cases had a higher

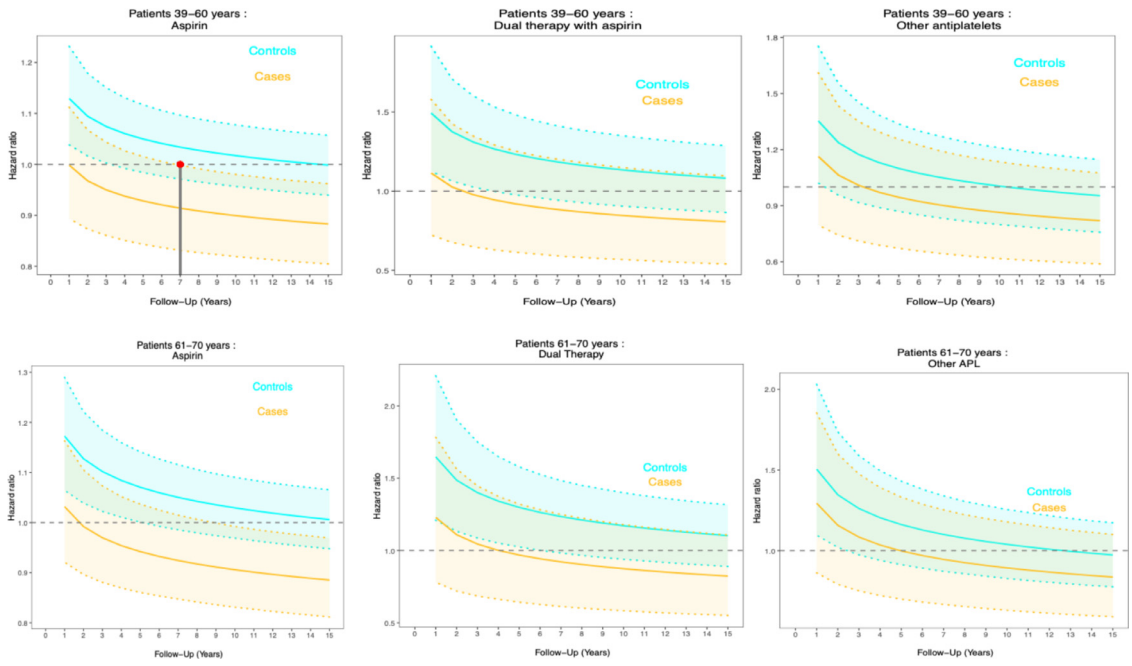

Fig. 1. *Hazard ratio curves with 95% confidence intervals for participants aged 39-60 years (top panel) and 61-70 years (lower panel) at entry on different antiplatelets (left: Aspirin monotherapy, centre: DAPT, right: Other APL). Cases on APL prescriptions were compared to cases who are non-users of APL. The gold solid lines represent the HRs over time and the dotted gold lines represent the 95% limits of the HRs for cases. Controls on APL were compared to controls who are non-users of APL. The blue solid lines represent the HRs over time and the dotted blue lines represent the 95% limits of the HRs for controls. The grey horizontal lines of HR=1 are added as thresholds (above: high mortality risk, below: low mortality risk, across: insignificant effects).*

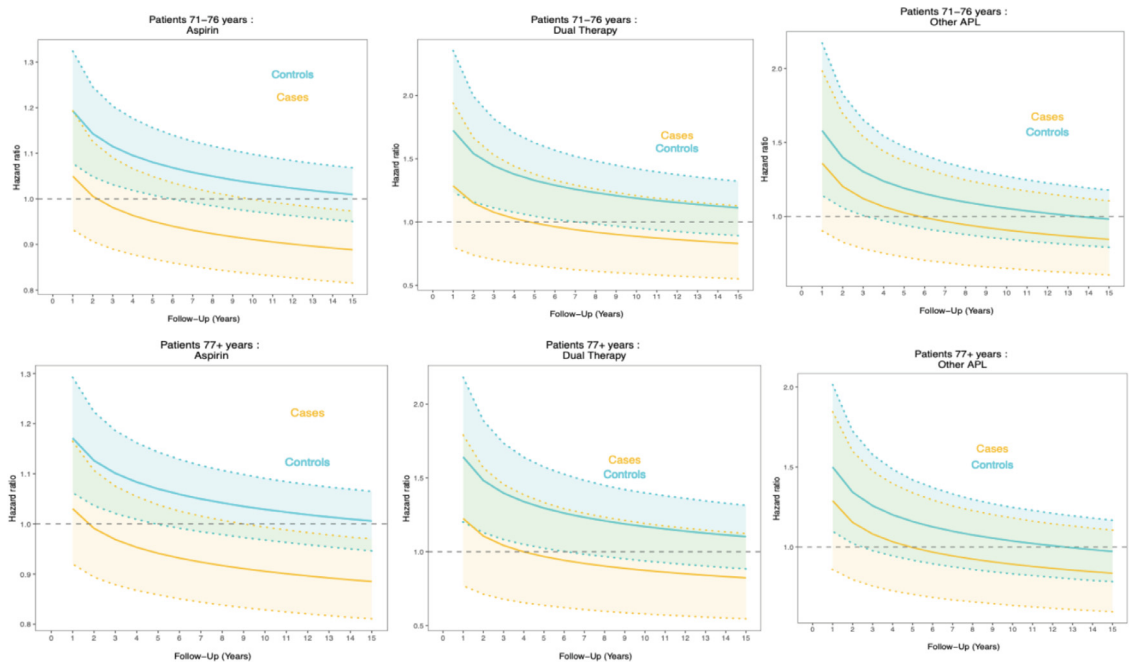

Fig. 2. *Hazard ratio curves with 95% confidence intervals for participants aged 71-76 years (top panel) and 77+ years (lower panel) at entry on different antiplatelets. (Left: Aspirin monotherapy, centre: DAPT, right: Other APL). Cases on APL prescriptions compared to cases who are non-users of APL. The gold solid lines represent the HRs over time and the dotted gold lines represent the 95% limits of the HRs for cases. Controls on APL were compared to controls who are non-users of APL. The blue solid lines represent the HRs over time and the dotted blue lines represent the 95% limits of the HRs for controls. The grey horizontal lines of HR=1 are added as thresholds (above: high mortality risk, below: low mortality risk, across: insignificant effects).*

burden of cardio-vascular disease, and the prevalence of recurrent TIAs or stroke was higher in the first year following the initial event of TIA than in subsequent years.

Our findings show that cases had a higher risk of death than controls, with the younger participants, 39-60 years old at diagnosis associated with HR = 3.04 (2.91-3.18) relative to their same-aged controls, whereas the risk was virtually twice for older participants with HR ranging from 1.52-1.98, when compared to their respective age-matched controls. This does not translate to the risk of mortality decreasing for older patients but only implies that the effect of TIA diagnosis is not as pronounced as in younger patients. Older patients already have unfavourable medical conditions related to ageing, so the impact of TIA only increases the risk of mortality by 1.5 -2 times. The younger patients, on the other hand, when diagnosed TIA, have an almost 3 times higher HR compared to their same-aged controls. The results agree with the findings of Rutten-Jacobs (2013) [28] indicating that stroke at a young age continues to contribute increased risk of death even after two decades after the index event. The current study also found that cases had more vascular incidents at follow-up than controls (recurrent TIAs, strokes and myocardial infarctions). The relative hazards of death were a little higher than previously reported[8,16,21]. Hence, our study suggests that TIA should not be considered as a 'minor' neurological condition.

Aspirin is recommended for the initial management of cases according to clinical guidelines[3]. Clopidogrel is recommended for secondary prevention after a TIA, according to the current NICE Clinical Knowledge Summary[1]. NICE based their recommendations of clinical benefit of aspirin early after stroke/TIA on Rothwell et al. (2016)[13], who found participants on aspirin having a lower short-term risk of stroke recurrence when compared to placebo. Clopidogrel (compared to aspirin) lowered the risk of a first ischemic stroke, myocardial infarction, or vascular mortality in the CAPRIE study for secondary care[9]. According to current guidelines[3], all TIA diagnosed patients should be prescribed antiplatelet therapy, yet some TIA patients from the study were not on it. The under-prescription of therapy despite clinical indications of TIA has also been observed by Turner et al. (2016)[27] who explained that the reasons could be linked to the risk of polypharmacy, fear of side effects such as bleeding, risk of overmedicalization, old age, GP related barriers and patients related factors[27].

Our findings found aspirin to be associated with improved long-term survival in individuals diagnosed with TIA, with consistent results across all age groups. The effects of dual aspirin therapy and other antiplatelets on cases' survival were of similar size but not statistically significant. Our research adds to the body of existing evidence supporting the use of aspirin in TIA management. Our findings support the use of aspirin as secondary prevention in persons who have experienced a TIA. Our research suggests that antiplatelets may be doing more harm than benefit in controls which corroborate with

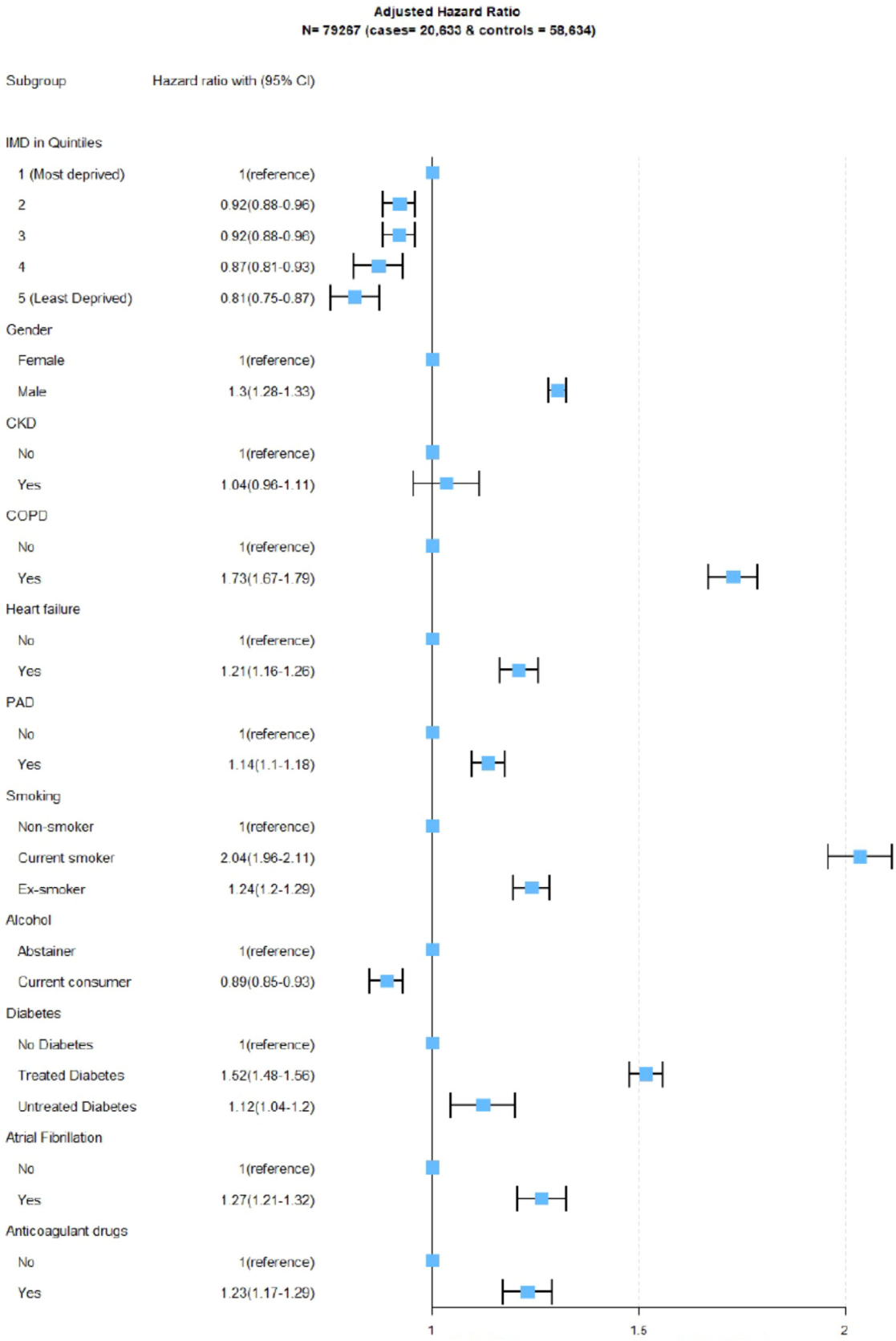

Fig. 3. *Adjusted HRs of all-cause mortality for covariates with significant time-invariant effects.*

McNeil et al. (2018)[25], who reported no benefit associated with aspirin use in 19,114 healthy elderly participants compared to non-users. Our study included participants with multiple comorbidities, and hence gave a better reflection of a general elderly population. Our analysis of all-cause mortality showed that aspirin therapy was associated with long-term survival benefits for cases but further studies are required to identify what patient groups are at risk and what particular outcomes and mechanisms are involved in this overall survival benefit.

Our analysis found a significant interaction of hypertension and TIA diagnoses associated with higher mortality risk. Hypertension is a risk factor that contributes to nearly half of strokes globally[26]. Currently, the most important goal in primary and secondary prevention of stroke is a strict normotensive blood pressure control[3]. Antihypertensive treatment is recommended for both prevention of recurrent stroke and prevention of other vascular events in individuals who have had an ischaemic stroke or TIA.

Strengths and limitations

This study used routinely collected primary care data that were representative of the UK[20,23] and the data is recent, accurate and recorded comprehensively. The study had large sample size which provided high power in evaluating the difference of hazards of all-cause mortality among different groups. The electronic medical records are very rich in information and our model could incorporate a large number of covariates.

This study had a long follow-up of maximum 30 years. Our model included GP practice as a latent term to account for the shared risk component by participants from the same practice. The coefficient of concordance of 0.79 provided a satisfactory goodness of fit.

While many studies have overlooked checking for proportionality assumptions in Cox regression or did not report diagnostic checks for factors that violated the PH assumptions, this study uses a novel parametric model was used to handle the time dependency of any factors that violate the PH assumptions of Cox regression.

However, we were limited by the available information stored in the THIN database. The data did not include psychological factors, familial history of disease, diet, family status and adherence to therapy because these variables were poorly coded and/or were not present. We were also limited by the level of detail with regards to the type of medical centre admissions i.e., whether the patients were admitted to the emergency department or hospital. Information about the severity of the TIA at diagnosis was also not available therefore we could not study the subgroups of TIA according to severity.

We attempted to reduce the effect of confounding by adjusting the regression analyses for known confounders associated with survival prospects of TIA. The nature of observational data means that we cannot assume that aspirin caused the benefits seen.

Conclusion

The research reported the survival prospects associated with a history of a TIA, as well as how medication or medical conditions could affect those chances. The findings showed that cases were worse off than previously estimated, especially for the age group 39-60 years. Cases were not only at a higher risk of death than their matched controls, they were also at a higher risk of long-term sequelae of recurrent stroke(s) and myocardial infarction.

Our pragmatic study design with few exclusion criteria and a large number of participants with TIA found that long term aspirin monotherapy was associated with lower all-cause mortality. While DAPT and other antiplatelets were associated with long-term survival benefits of a similar size, only aspirin was associated with statistically significant long-term benefits. Our study does not support the prescription of aspirin to people with no history of TIA.

Author's contribution

EK and NS designed the study. PC analyzed the data. IB and BB extracted the data. PC wrote the first draft of the study. NS, EK & DP provided input to the interpretation of the data.

All authors contributed to redrafting and approved the final version.

Ethical approval

This study was approved by THIN Scientific Review Committee (SRC) with approval number 16THIN095.

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Declaration of Competing Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2022.106663.

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