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Long-term Incidence of Ischemic Stroke Following Transient Ischemic Attack: a Nationwide Study During 2014-2020

Running title: *Vinding et al.; Long-term stroke incidence after TIA*

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Abstract

Background: The short-term incidence of ischemic stroke after a transient ischemic attack (TIA) is high. However, data on the long-term incidence are not well known but are needed to guide preventive strategies.
Methods: Patients with first-time TIA (index date) in the Danish Stroke Registry (January 2014-December 2020) were included and matched 1:4 with individuals from the background population and 1:1 with patients with a first-time ischemic stroke based on age, sex, and calendar year. The incidences of ischemic stroke and mortality from index date were estimated by Aalen-Johansen and Kaplan-Meier estimators, respectively, and compared between groups using multivariable Cox regression.
Results: We included 21,500 patients with TIA, 86,000 patients from the background population, and 21,500 patients with ischemic stroke (median age 70.8 years [25th-75th percentile 60.8-78.7]:53% men). Patients with TIA had more comorbidities than the background population, yet less than the control stroke population. The five-year incidence of ischemic stroke following TIA (6.1% [95% CI 5.7-6.5]) was higher than the background population (1.5% [95%CI 1.4-1.6], hazard ratio (HR) 5.14 [95%CI 4.65-5.69]), but lower than the control stroke population (8.9% [95%CI 8.4-9.4], HR 0.58 [95%CI 0.53-0.64]). The five-year mortality for patients with TIA (18.6% [95%CI 17.9-19.3]) was higher than the background population (14.8% [95%CI 14.5-15.1], HR 1.26 [95%CI 1.20-1.32]), but lower than the control stroke population (30.1% [95%CI 29.3-30.9), HR 0.41 [95%CI 0.39-0.44]).
Conclusions: Patients with first-time TIA had an ischemic stroke incidence of 6.1% during the 5-year follow-up period. Following adjustment for relevant comorbidities, this incidence was approximately five-fold higher than what was found for controls in the background population, and 40% lower than for patients with recurrent ischemic stroke.

Keywords: Transient ischemic attach, ischemic stroke, stroke, epidemiology, long-term outcome

Non-standard Abbreviations and Acronyms

ABCD^2 score: age ≥60 years, blood pressure ≥140/90 mmHg, clinical features, duration of TIA symptoms, and presence of diabetes
ADPi: Adenosine diphosphate inhibitor
AF: Atrial fibrillation
ASA: Acetylsalicylic acid
CT scan: computed tomography scan
MR scan: Magnetic resonance scan
OAC: Oral anticoagulation
PDEi: phosphodiesterase inhibitor
PPV: Positive predictive value
SSS: Scandinavian Stroke Scale
TIA: Transient ischemic attack

Clinical Perspective

What is new?

- This is the first study to report long-term risk of ischemic stroke in patients with first-time TIA in a contemporary nationwide real-world setting.
- Patients with TIA were associated with a noteworthy five-year incidence of ischemic stroke of 6.1% compared to 1.5% in the matched background population, corresponding to a five-fold higher relative risk.
- Compared to patients with first-time ischemic stroke, the relative risk of recurrent stroke among patients with TIA was 40% lower.
- Importantly, this elevated risk following TIA persisted beyond the initial high-risk period and was evident regardless of whether the patients were defined as low-risk or high-risk patients with TIA.

What are the clinical implications?

- Our study indicates a potential role for extending the follow-up of patients with TIA beyond the initial high-risk period, highlighting the necessity for future trials to investigate the potential benefits of long-term antithrombotic strategies.
- These findings suggest that all patients with TIA should undergo a full diagnostic workup and should be treated similarly.

Introduction

Transient ischemic attack (TIA) may represent an opportunity to prevent a future ischemic stroke, an event associated with substantial morbidity and mortality. The risk of ischemic stroke within the first three months after TIA is not negligible, with a reported incidence ranging from 3% to 20%.[1] Yet, the long-term incidence of ischemic stroke after TIA is unknown[2–4] and warranted, as it guides risk stratification, preventive strategies, and future trials.

Identification and appropriate management of patients with TIA have been shown to mitigate ischemic stroke risk among high-risk patients with TIA.[5] A prerequisite for future trials on the long-term effects of antithrombotic treatment[6–8] is to know the magnitude of the long-term risk of stroke in patients with TIA.

Two recent studies based on the TIAregistry[3] and the Framingham cohort[2] found a five-year incidence of stroke associated with TIA of 9.6% (2009-2011) and 16.1% (latest epoch 2000-2017), respectively. The TIAregistry included patients with minor strokes, and the primary stroke outcome was a composite of ischemic and hemorrhagic strokes in both studies. The organized study setups may limit generalization to the general public.

A clinical Danish Stroke Registry encompassing all patients with TIA and stroke admitted to Danish hospitals gives a unique possibility for a population-based study.[9] We aimed to investigate the five-year incidence of ischemic stroke and mortality after TIA in a nationwide Danish cohort.

Methods

Data sharing

There is no additional raw data accessible because of data protection rules at Statistics Denmark. For further information regarding the analysis of the study, please contact the corresponding author and request more details.

Data sources

Nationwide studies in Denmark are possible because of equal access to a tax-funded public health care system along with individual level linkage of data based on the personal identification number.[10] Data on first-time TIA and ischemic stroke were obtained from The Danish Stroke Registry,[9] which is a nationwide clinical quality registry established in 2003 (data on TIA's were prospectively collected from September 1, 2013) with the aim of monitoring and improving quality of care for patients with stroke and TIA. On admission to an outpatient or inpatient clinic, data are registered by the clinical staff treating the patients, and registration of all patients with stroke and TIA is mandatory. If the patient was already admitted to the hospital for another reason, it was the symptom onset time that was set as the time of admission for the TIA or stroke contact. Recurrent TIA was defined by the registration process in The Danish Stroke Registry; as a new contact to an outpatient or inpatient clinic with new symptoms of TIA.

The positive predictive value (PPV) of the stroke diagnosis overall is 90%, the specificity is 90%, and the sensitivity is 97% in the Danish Stroke Registry.[11] Stroke is defined in agreement with the World Health Organization i.e. rapid progression of loss of neurologic function with an assumed vascular etiology lasting more than 24 hours or causing death. TIA is defined as focal neurologic disturbance of cerebral function lasting less than 24 hours with an assumed vascular etiology. As such, in Denmark the time-based definition is still used; however, imaging is a part of the diagnostic work-up for all patients with TIA or

stroke.[12] The Danish Civil Registration System[13] provides data on sex, age, and emigration, and The Danish Registry of Causes of Death holds information on the date of death.[14] The Danish National Patient Registry (since 1978) provides information on comorbidities any time before index as well as prior stroke or TIA.[15] Data on pharmacological therapy were obtained from The National Prescription Registry ≤180 days prior to the index date.[16] The Danish Stroke Registry provided information regarding smoking status, type of residence, cohabitation status, computed tomography (CT) scan and magnetic resonance (MR) scans. Anatomical Therapeutic Chemical (ATC)- and International Classification of Diseases (ICD) classification codes used are displayed in Supplementary Table S1.

Study population

We included patients ≥18 years of age with a first-time TIA between the 1st of January 2014 and the 31st of December 2020. Patients with TIA were excluded if they had a prior ischemic stroke, unspecified stroke, or TIA registered either in the Danish Stroke Registry or The Danish Patient Registry (the latter was included because it contains data on hospital admissions since 1978). The index date was defined as the first day of the TIA event. The discharge date was defined as the last day of admission, including transfers to other hospitals and departments. Patients with TIA were matched with the background population in a 1:4 ratio (four controls to increase power) and with a control stroke population (ischemic stroke or unspecified stroke) in a 1:1 ratio, respectively, by sex, age (up to 2 years difference), and index calendar year by risk-set matching (i.e., individual matching finding the best possible match in every round without replacement). The matched comparators were alive and free of prior ischemic stroke, unspecified stroke, and TIA.

The index date of the background population was defined from a random distribution of index dates from the patients with TIA, as such ensuring comparable follow-up time. The

index date for the control stroke population was the date of admission for first-time ischemic stroke (Figure 1).

In this study an ABCD^2 score for patients with TIA was modified according to data available; (age ≥60 years (1 point), blood pressure ≥140/90 mmHg (1 point) [*replaced with a history of hypertension*], clinical features (speech disturbance without weakness (1 point), unilateral weakness (2 points)[*registered in the SSSJ*), duration of TIA symptoms (10-59 minutes (1 point); ≥ 60 minutes (2 points))[*not available*]), and presence of diabetes (1 point)) (details in supplementary Table S1). Originally an ABCD^2 score of 0-3 points indicates a low risk of stroke and ≥4 points indicates a high-risk of stroke within the first 90 days.[17] In this study a priori, the modified ABCD^2 score was divided into three categories as inclusion or exclusion of 2 points would result in reclassification according to the original dichotomized risk groups i.e. </≥4 points. The modified ABCD^2 risk groups were true low-risk (0-1 points), intermediate-risk (2-3 points), and true high-risk (4-5 points). As such, the true low-risk group and the true high-risk group refer to groups, we know are categorized correctly according to the original dichotomized ABCD^2 risk groups.

Outcomes

Five-year incidence of ischemic stroke and mortality

The primary outcome was the five-year cumulative incidence of ischemic stroke (or unspecified stroke), and the secondary outcome was five-year incidence of all-cause mortality. Patients with TIA and controls were followed from the index until the outcome of interest, emigration, all-cause death, or end of study (31st December 2020), whichever came first. The primary stroke outcome was captured as an admission for stroke during follow-up in the Danish Stroke Registry and all-cause mortality was assessed through the Danish Registry of Causes of Death. For patients with TIA, five-year and 90-day outcomes were subsequently stratified according to the ABCD^2 score.

Stroke severity

The severity of the ischemic stroke outcome among the three groups was assessed by the Scandinavian Stroke Scale (SSS). The SSS score is registered in The Danish Stroke Registry on admission. The score ranges from 0-58 and can be divided into four categories: mild stroke (45-58 points), moderate stroke (30-44 points), severe stroke (15-29 points), and very severe stroke (0-14 points). Patients are scored based on eye movement (4-0 points), facial palsy (2-0 points), level of consciousness (6-0 points), gait (12-0 points), speech (10-0 points), orientation (6-0 points), and hand-, arm-, and leg motor power (6-0 points each).[18]

Post-discharge therapy

Pharmacological therapies initiated at the index event were assessed 3 months after the index (grace period) among those who survived out to 3 months, and did not emigrate or had a stroke in the grace period. Use of post-discharge therapies was defined as redeemed prescriptions of antiplatelet and anticoagulation therapy, antihypertensive drugs, statin treatment, and antidiabetic drugs (Supplementary Table S1 for ATC codes) based on the Danish National Guidelines (which are based on guidelines from the American Heart Association and the European Stroke Organization [ESO]).[8,19]

Validation of the TIA diagnosis

The registered TIA episodes were validated by a professor in stroke neurology (rater one) and a neurology trainee (rater two) by going through a random representative sample of 100 patients each from the Danish Stroke Registry; in total 200 cases were evaluated blinded to each other. If any uncertainty regarding the diagnosis of TIA arose among rater one or rater two, a third stroke professor (rater three) reviewed the case and determined the final diagnosis. If the third rater was uncertain of the TIA diagnosis, cases were excluded from the calculation of the PPV. The patients were admitted to either Copenhagen University Hospital, Herlev and Gentofte, or Copenhagen University Hospital, Rigshospitalet and the number of

patients from each unit were equally distributed. Further, the patients were equally dispersed from 2018 through 2020. The neurologists were blinded from the medical charts before and after the TIA admission.

Statistical methods

Baseline characteristics are displayed as frequencies and percentages for categorical variables and as medians with quartiles for continuous variables. The differences between groups were assessed by chi-square test for categorical variables and the Kruskal-Wallis test for continuous data. The cumulative incidence of ischemic and hemorrhagic stroke was estimated by the Aalen-Johansen estimator with death as competing risk, and unadjusted differences between groups determined by Gray's test. The cumulative incidence of mortality was estimated by the Kaplan-Maier estimator and unadjusted differences between groups were assessed by the log-rank test. A stratified Cox proportional hazard model was used to calculate adjusted hazard ratios (HR) with 95% confidence intervals (CI). The models were adjusted for possible confounders: atrial fibrillation (AF), diabetes mellitus, chronic kidney disease, arterial thromboembolism, mitral valve disease, aortic valve disease, ischemic heart disease, prior bleeding, liver disease, chronic obstructive lung disease, cancer, peripheral artery disease, congestive heart failure, hypertension, alcohol abuse, and prior use of statins stratified on the matching (i.e., comparing a case with its matched controls). In the stratified $ABCD^2$ Cox models, diabetes and hypertension were not included in the model as they are part of the $ABCD^2$ criteria. The Cox proportional hazard assumption was found valid for all variables except the exposure variables (TIA versus the background population and TIA versus the control stroke population) on the outcome of stroke and mortality. Because of this, we did a sensitivity analysis splitting the time. No interactions with sex were found. Additionally, outcome estimates underwent adjustments to account for the PPV and sensitivity based on Hall GC. et al. approach and Brenner H. et al. formula: incidence' =

incidence x (sensitivity/PPV), where incidence' denotes the corrected incidence. The estimates were calculated by the app developed by Hall et al..[20,21] The associated odds of very severe stroke were determined by a multivariable logistic regression model adjusted for the same factors as in the Cox model. Continuous variables were tested for linearity (age) and interactions with calendar year, age, and sex were tested. The model assumptions were fulfilled otherwise indicated. The PPV of the TIA diagnosis was calculated by dividing the number of true positive cases by the sum of true positive cases and false positive cases. Uncertain cases beyond rater three were excluded from the calculation. The 95% confidence intervals for the PPV were calculated by the Wilson method.[22] A 95% confidence interval not including 1 and a P value of <0.05 was considered statistically significant. SAS software (version 9.4, SAS Institute, Cary, North Carolina, USA) was used for all analyses.

Sensitivity analysis

1) We made a 90-day landmark analysis depicted by cumulative incidence curves for the outcome of stroke and mortality where time zero was 90 days after the index. Two Cox models were performed. One model adjusting for the same factors as in the main analysis. A second model additionally adjusting for secondary post-discharge antithrombotic treatment groups assessed 3 months after index (no treatment (reference), acetylsalicylic acid (ASA) alone, ASA plus adenosine diphosphate inhibitor (ADPi)/ phosphodiesterase inhibitor (PDEi), ADPI/PDEi alone, and OAC).
2) Because of non-proportionality of the exposure variable (TIA versus the background population and TIA versus the control stroke population) in the Cox model for the outcome of stroke and mortality, we conducted a sensitivity analysis splitting the time from 0 to 90 days, 90 days to 365 days and 365 days to 5 years. The cut-off for this splitting was conducted by examination of Martingale residuals and what was clinically meaningful knowing that the short-term risk is high.

3) As a supplementary analysis, we investigated 90-day landmark and 5-year outcome of hemorrhagic stroke in the study population. The Cox models were adjusted for AF, liver disease, alcohol abuse, cancer, chronic kidney disease, prior bleeding episodes, hypertension, ischemic heart disease, diabetes, peripheral artery disease, left-sided valve disease as well as prior use of ASA, ADP inhibitors, vitamin K antagonists and direct oral anticoagulants.
4) The primary outcome of 5-year stroke was adjusted for the PPV and sensitivity found in the Danish Stroke Registry.[11]
5) Analysis of 5-year ischemic stroke and 5-year mortality risk was conducted on a subpopulation with the possibility of full follow-up time i.e., patients with index events from January 1, 2014, to December 31, 2015.

Ethics

No ethical approval is needed in Denmark for registry-based research where individuals cannot be identified in the data. The Danish Data Protection Agency approved the study (approval number: P-2019-191).

Results

Baseline characteristics

We included 21,500 patients with a first-time TIA, 86,000 individuals from the background population, and 21,500 patients in the control stroke population (Figure 1). The overall median age was 70.8 years (25^{th}-75^{th} percentile: 60.8-78.7), and 53.1% of the patients were males. Patients with TIA had more comorbidities compared to the background population, although they had fewer comorbidities compared to the control stroke population. More patients with TIA had prior treatment with ASA, ADP inhibitor, oral anticoagulation therapy, and statins compared to both the background population and the control stroke population in

absolute numbers. In relation to the index event, 99.3% of patients with TIA and 99.1% of the control stroke population underwent CT or MR scans. (Table 1). The median length-of-stay in the hospital (in- and out-hospital contacts) for patients with TIA was 1 day (25^{th}-75^{th} percentile 1-2) and 5 days (25^{th}-75^{th} percentile 2-12) for the control stroke population (p value <0.01). Among patients with TIA, 4,357 (20.3%) were discharged the same day as admitted, 8,866 (41.2%) were discharged the day after admission, and 2,971 (13.8%) were discharged 2 days after admission. 1,078 (5.0%) patients had recurrent TIA, of whom 132 (0.6%) had three or more events prior to the stroke outcome. Data on the time from symptoms to admission and characteristics of symptoms of the patients with TIA are displayed in Supplementary Table S2.

Five-year risk of ischemic stroke

Patients with TIA were associated with a higher five-year risk of ischemic stroke than the background population (6.1% [95% CI 5.7-6.5] versus 1.5% [95%CI 1.4-1.6], adjusted HR 5.14 [95%CI 4.65-5.69]), but a lower risk than the control stroke population (6.1% [95% CI 5.7-6.5] versus 8.9% [95%CI 8.4-9.4], adjusted HR 0.58 [95%CI 0.53-0.64]) (Displayed in Figure 2a and Table 2). The median time from index to ischemic stroke for patients with TIA, the background population, and the control stroke population was 336 days (25^{th}-75^{th} percentile 64.0-880.0), 672.0 days (25^{th}-75^{th} percentile 338.5-1122.5), and 312.0 days (25^{th}-75^{th} percentile 71.0-742.0), respectively. No difference in the incidence of stroke was found when the results were stratified by calendar year. The median followup time was 3.0 years (25^{th}-75^{th} percentile 1.3-4.8) for patients with TIA, 3.2 years (25^{th}-75^{th} percentile 1.5-5.0) for the background population, and 2.5 years (25^{th}-75^{th} percentile 0.8-4.1) for the control stroke population.

Severity of ischemic stroke during follow-up

TIA was associated with a lower proportion of very severe ischemic strokes (4.1%) compared to the background population (7.5%) (P value <0.01) and the control stroke population (6.4%) (P value 0.02) (Supplementary Figure S1). In adjusted analyses, TIA was associated with a lower odds of very severe stroke compared to the background population (OR 0.55 [95%CI 0.36-0.83]) and the control stroke population (OR 0.59 [95%CI 0.40-0.87]).

Five-year mortality

The five-year mortality for patients with TIA was 18.6% [95% CI 17.9-19.3] thus higher than the background population (14.8% [95%CI 14.5-15.1], HR 1.26 [95%CI 1.20-1.32]), but lower than the control stroke population (30.1% [95%CI 29.3-30.9], HR 0.41 [95%CI 0.39-0.44] (displayed in Figure 2b and Table 2).

Outcome according to the modified ABCD^2 score

A total of, 12,570 (58.5%) patients were in the true low-risk group, 7,705 (35.8%) were in the intermediate risk group, and 1,222 (5.7%) were in the true high-risk group (≤3 patients missing) according to the modified ABCD^2 score. The five-year cumulative incidence of ischemic stroke was lowest for the background population, followed by the low-risk patients with TIA, intermediate and high-risk patients with TIA, and highest for the control stroke population (Supplementary Figure S2.B). Low-risk patients with TIA were associated with the lowest incidence of five-year mortality followed by the background population, intermediate risk patients with TIA, high-risk patients with TIA and the control stroke population. However, after one year the curve for high-risk TIA crossed the curve for the control stroke population (supplementary Figure S2.D). The results on 90-day incidence of stroke were consistent with the main analyses, yet the high-risk patients had similar absolute (p value <0.29) and relative risk of stroke compared to the control stroke population (Supplementary Figure S2.A). On the outcome of 90-day mortality, no difference was found

between low-risk patients with TIA and the background population (Supplementary Figure S2.C).

Post-discharge medication

In total, 94.2% of patients with TIA were treated with either an antiplatelet drug or oral anticoagulation therapy within three months after discharge (vs. 28.5% prior). The proportion was 94.2% (vs. 27.4% prior) among the control stroke population. Additionally, more patients were treated with statins after TIA than prior to TIA (69.8% vs. 26.3%); and this was also the case for the control stroke population (73.6% vs. 23.9%). There were no major differences in prior and post-treatments with antihypertensives or antidiabetic drugs (Supplementary Table S3).

Validation of the TIA diagnosis

Out of 200 random selected patients with TIA recorded in the Danish Stroke Registry rater one found 81 confirmed cases (12 were not TIA, 7 were uncertain), rater two confirmed 70 cases (21 were not TIA, 9 were uncertain). The third rater provided a diagnosis in 9 of the uncertain cases; thus, 7 uncertain cases remained. Consequently, the PPV for the 193 cases was 78.8% (95%CI 72.2-84.2).

Sensitivity analysis

1) The results of 90-day landmark analysis of the stroke and mortality outcomes are depicted in Supplementary Figure S4 and showed similar relative differences as in the main analysis. The five-year cumulative incidence of ischemic stroke beyond the 90-day landmark was 4.9% (95%CI 4.6-5.3) for patients with TIA which was higher than the background population (1.4% (95%CI 1.3-1.5) (p value <0.001), HR 3.90 (95%CI 3.48-4.36), and lower than the control stroke population 7.7% (95%CI 7.2-8.2), P value <0.01; HR 0.57 95%CI (0.53-0.60). The five-year cumulative incidence of mortality beyond the 90-day landmark was 17.5% (95%CI 16.9-18.2) for patients with TIA which was higher than the background

population (14.2% (95%CI 13.8-14.5), P value < 0.01), HR 1.22 (95%CI 1.16-1.28), and lower than the control stroke population 24.4% (95%CI 23.6-25.2), P value < 0.01), HR 0.56 (95%CI 0.50-0.62). Adjustment for secondary antithrombotic therapy did not change the results (model 2).

2) Because of non-proportionality of the case variable in the Cox model, we split time into different intervals (supplementary Table S4). The associated risk of stroke for patients with TIA versus the background population were: [0-90 days]: HR 19.75 (95%CI 14.71-26.53),]90-365 days]: HR 5.18 (95%CI 4.20-6.39), and]365-5 years]: HR 3.47 (95%CI 3.03-3.96). No big differences were seen in the rest of the models regarding the outcome of stroke and mortality.

3) The 5-year cumulative incidence of hemorrhagic stroke was lower than the incidence of ischemic stroke for all three groups: background population (0.9% [95%CI 0.8-0.96]), patients with TIA (2.3% [95%CI 2.1-2.6]), and control stroke population (3.23% [95%CI 2.96-3.52], p value <0.01). In adjusted Cox models, patients with TIA had a higher risk of hemorrhagic stroke compared to the background population (HR 2.81 [95%CI 2.43-3.25] and lower compared to the control stroke population (HR 0.56 [95%CI 0.48-0.65] (Supplementary Figure S5). In the 90-day landmark analysis patients with TIA remained in a higher risk of hemorrhagic stroke compared to the background population and had a lower risk compared to the stroke population.

4) The 5-year incidence of stroke adjusted for a PPV of 90% and a sensitivity of 97%, was 5.66% (95%CI 5.29-6.03).

5) Results on a subpopulation from January 1, 2014, to December 31, 2015, with full follow-up time, were not overall different from the main results. 5-year ischemic stroke risk: TIA vs. background population (5.7% (95%CI 5.2-6.3) vs. 1.4% (95%CI 1.3-1.6), HR 4.39 (95%CI 3.74-5.15)) and TIA vs. control stroke population (5.7% (95%CI 5.2-6.3) vs. 8.8% (95%CI

8.1-9.5), HR 0.55 (95%CI 0.47-0.64)). Results on 5-year mortality: TIA vs. background population (18.8% (95%CI 17.8-19.8) vs. 14.8% (95%CI 14.4-15.3), HR 1.25 (95%CI 1.16-1.34)) and TIA vs. control stroke population (18.8% (95%CI 17.8-19.8) vs 29.9% (95%CI 28.8-31.1), HR 0.46 (95%CI 0.42-0.50)).

Discussion

We used nationwide clinical registry data to examine the long-term incidence of ischemic stroke and mortality among all-comer patients presenting to the hospital with TIA, and this was benchmarked against individuals from the background population as well as patients with prior ischemic stroke. Our study results may be summarized by two main findings: First, TIA was associated with a 5-fold higher 5-year relative rate of ischemic stroke compared with the background population, but 40% lower compared with the control stroke population. The elevated risk persisted beyond the first 90-days. Second, patients with TIA were associated with 1.2-fold higher five-year mortality compared with the background population, but 60% lower compared with the control stroke population.

This study is the first to report long-term incidence of ischemic stroke in patients with TIA in an unselected nationwide real-world cohort. TIA and ischemic stroke represent a continuum of disease development[23] differentiated by symptoms duration of less or more than 24 hours (i.e., time-base definition), respectively. Today imaging is a part of the diagnostic workup and is used to exclude differential diagnoses. In the American Heart Association/American Stroke Association guidelines TIA is defined by the absence of acute cerebral infarction i.e. the tissue-based definition.[24] Stroke-risk in patients with TIA is potentially modifiable by careful diagnostic workup and identification of targets for risk factor control and treatment.[19]

TIA is a challenging diagnosis; however, the present study represents the best possible setup for investigating real-world population-based study on the long-term risk of stroke associated with TIA. In Denmark treatment of patients with stroke are centralized to highly specialized stroke units, and most patients are treated by neurologists. We found that above 99% of patients with TIA or stroke had a CT or MR scan within the first 6 hours after arriving at the hospital. The Danish Stroke Registry has a high completeness, and we validated the diagnosis of TIA with a PPV of 78.8%.

The five-year incidence of ischemic stroke for patients presenting with first-time TIA was 6.1%. The 90-day landmark analysis depicted a substantial residual risk of 4.9% beyond the first high-risk period. These numbers may also indicate that the registration process, which categorizes patients experiencing a stroke during a TIA admission as stroke patients, might lead to an underestimation of the short-term risk. The five-year incidence in this study was lower than the 9.5% (7.7% ischemic strokes) found in the TIAregistry (2009-2011)[3] and the 16.1% found in the Framingham cohort (2000-2017).[2] Yet, the numbers cannot be compared directly as the TIAregistry included patients with minor strokes and the primary stroke outcome was a composite of ischemic and hemorrhagic strokes in both studies. Further, the patients were evaluated in an organized study setup and the study periods differed. In a Norwegian study, the one-year cumulative incidence of ischemic stroke after TIA was 5.4%, which was approximately 2-fold higher than the present study. However, they included patients with prior TIA (18%) or ischemic stroke (15%) between 2012 and 2014 which may explain the higher risk.[4] The absolute risk difference for a recurrent ischemic stroke in the control stroke population was 2.8% compared to patients with TIA; however, the difference was even higher when considering the high risk of mortality among the control stroke population (i.e., lower number at risk). The overall results did not appear to be affected by the disparity in follow-up duration between patients experiencing a first-time TIA and

those experiencing a first-time stroke, despite the higher mortality risk among the control stroke population.

In the present study, the incidence of ischemic stroke was related to the modified ABCD^2 risk score and the five-year incidence of ischemic stroke in the true high-risk and intermediate risk patients with TIA were approaching the incidence of the control stroke population. The rates in this study indicates high long-term risk across all TIA groups and may be in line with recommendations on equal diagnostic work-up and treatment across risk groups.[19,25] The ABCD^2 score were originally designed to predict early stroke risk, however Holzer K et al. have demonstrated the ability of using it for long-term outcomes.[26]

The five-year mortality was higher among patients with TIA (18%) compared with the background population (15%) and substantially lower than the control stroke population (30%). Accordingly, prevention of ischemic stroke after TIA may also save lives. In the TIAregistry they found a five-year mortality of 10.6% among patients with TIA or minor stroke, which is lower compared to our study.[3] The differences may be explained by different study populations in different study setups. In this study the true high-risk patients with TIA, according to the modified ABCD^2 score, had a higher absolute incidence of five-year mortality compared with the control stroke population which underpins that long-term surveillance of these patients with TIA is paramount. The findings on the ABCD^2 groups is also helps verify that we have included true TIA patients.[27]

The elevated ischemic stroke risk in the period shortly after a TIA has been a major focus in the clinical settings and research. In the long term, patients with TIA still have a greater relative risk of ischemic stroke, despite initiation of antithrombotic and lipid-lowering medications, compared to individuals without TIA. Fortunately, preventive strategies for patients with TIA have been more aggressive in the recent years,[19] and we observed a high post-discharge antithrombotic treatment rate of 94% among patients with TIA. Efforts should

be made to decrease this residual risk by identifying non-classical risk factors, along with clinical trials on long-term antiplatelet strategies.

Limitations

The main strength of the study is the contemporary unselected data from the nationwide Danish Stroke Registry encompassing all patients admitted with a TIA or stroke to Danish hospitals (primarily stroke departments), irrespective of sociodemographic factors, insurance status, or health status. Diagnosing TIA is difficult, and we validated the diagnosis in the Danish Stroke Registry with a PPV of 78.8%. TIA is a clinical diagnosis with high-risk of misclassification of TIA mimics (e.g., patients with migraine) and TIA chameleons (a TIA that present like another disease), hence also hard to study. Therefore, the incidences presented in this study are likely to be underestimated. A patient is only registered once per hospitalization in the Danish Stroke Registry; as such any new cerebral event during admission for the index event is not registered. Consequently, the initial short-term risk of stroke after TIA may be underestimated as well as the number of recurrent TIA. Furthermore, as with most other study designs, patients who do not seek medical assistance or who are not referred by a general practitioner are not caught by the registry. However, the median hospitalization time was 1 day and most of the patients with TIA were discharged the day after admission. This study did not account for adherence to secondary prevention regimes, as such we cannot know if the rate of stroke were different according to antithrombotic medication. The Danish Stroke Registry only contains information on symptoms included in the Scandinavian Stroke Scale scoring. Results from imaging are primarily registered on patients going to thrombolysis in the Danish Stroke Registry and not included in the study. The modified $ABCD^2$ score used in this study missed data on duration of symptoms (0-2 points). However, patients in the true low-risk group (0-1 points) and the true high-risk group

(4-5 points) were not affected by this missing variable, as patients originally is categorized into low-risk and high-risk by having 0-3 points and ≥4 points, respectively. We did not have information on blood pressure; however, a single initial blood pressure measurement in patients with TIA is highly variable and using history of hypertension in the $ABCD^2$ score may not alter the performance (C statistics) of the score.[28,29] We did not have information on etiology or Trial of Org 101072 in Acute Stroke Treatment (TOAST) classification of neither TIA nor stroke events.

Conclusion

This nationwide real-world cohort study found a higher five-year incidence of ischemic stroke and mortality among patients with TIA compared with the background population, along with a lower incidence compared with the control stroke population in absolute and relative numbers. As such, a potential exists to reduce residual long-term incidence of ischemic stroke in patients with TIA with a subsequent reduction in disability and mortality.

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Supplemental Materials

Tables S1-S4

Figure S1-S5

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Table 1. Baseline Characteristics

	Background Population	TIA	Stroke Population
N	86000	21500	21500
Sex (male)	45704 (53.1)	11426 (53.1)	11426 (53.1)
Median age, years (25^{th}-75^{th} percentile)	70.8 [60.8, 78.7]	70.8 [60.8, 78.7]	70.8 [60.8, 78.7]
Comorbidities, n (%)			
Atrial fibrillation	6632 (7.7)	2202 (10.2)	2257 (10.5)
Diabetes	7441 (8.7)	2225 (10.3)	2732 (12.7)
Hypertension	21727 (25.3)	6257 (29.1)	6791 (31.6)
Alcohol abuse	2630 (3.1)	880 (4.1)	1363 (6.3)
Abnormal Liver function	1552 (1.8)	506 (2.4)	603 (2.8)
Prior bleeding	8787 (10.2)	2976 (13.8)	2861 (13.3)
Prior brain hemorrhage	946 (1.1)	426 (2.0)	459 (2.1)
Cancer	10744 (12.5)	2963 (13.8)	3080 (14.3)
Congestive heart failure	3390 (3.9)	1043 (4.9)	1368 (6.4)
Chronic kidney disease	2500 (2.9)	857 (4.0)	1059 (4.9)
Chronic obstructive lung disease	4674 (5.4)	1419 (6.6)	1727 (8.0)
Peripheral artery disease	1525 (1.8)	530 (2.5)	748 (3.5)
Ischemic heart disease	10389 (12.1)	3623 (16.9)	3511 (16.3)
Arterial thromboembolism	227 (0.3)	104 (0.5)	131 (0.6)
Pulmonary embolism	1171 (1.4)	294 (1.4)	366 (1.7)
Deep venous thrombosis	1809 (2.1)	569 (2.6))	684 (3.2)
Native left sided heart valve disorder	2908 (3.4)	1123 (5.2)	1105 (5.1)
Concomitant medicine, n(%)			
Acetylsalicylic acid	11551 (13.4)	3678 (17.1)	3616 (16.8)
ADP inhibitors	2019 (2.3)	1051 (4.9)	1040 (4.8)
Oral anticoagulants	6426 (7.5)	1923 (9.4)	1751 (8.1)
NSAID	8612 (10.0)	2742 (12.8)	2835 (13.2)
Statins	20022 (23.3)	5658 (26.3)	5131 (23.9)
Beta blockers	13232 (15.4)	4310 (20.0)	4789 (22.3)
Calcium channel blockers	13866 (16.1)	3837 (17.8)	4160 (19.3)
RAAS inhibitors	24340 (28.3)	7232 (33.6)	7412 (34.5)
Diuretics*	20992 (24.4)	5764 (26.8)	6226 (29.0)
CT or MR scan at admission †			
Yes	NA	15136 (99.3)	15060 (99.1)
Smoking			
Smoker	NA	421 (22.7)	6376 (33.6)
Former smoker (>0.5 year)	NA	6788 (34.8)	5692 (30.0)
Never	NA	8288 (42.5)	6927 (36.5)
Cohabitation status			
Co-habiting	NA	14105 (67.5)	12602 (59.8)
Alone	NA	6487 (31.0)	8039 (38.1)
Other	NA	320 (1.5)	450 (2.1)
Type of residence			
Own residence	NA	20052 (96.1)	19953 (92.9)
Care home	NA	689 (3.3)	905 (4.3)
Other	NA	122 (0.6)	175 (0.7)
Smoking			
Smoker	NA	421 (22.7)	6376 (33.6)
Former smoker (>0.5 year)	NA	6788 (34.8)	5692 (30.0)

Never	NA	8288 (42.5)	6927 (36.5)

Abbreviations: TIA; Transient ischemic attach, ADP inhibitors; adenosine diphosphate receptor inhibitors, NSAID; Non-Steroidal Anti-Inflammatory Drugs, RAAS inhibitors; renin-angiotensin-aldosterone-inhibitors, CT; Computed tomography scan, MR; magnetic resonance scan. Modified $ABCD^2$ (age ≥60 years, blood pressure ≥140/90 mmHg [*replaced with a history of hypertension*], clinical features (*registered in the SSS)*, duration of TIA symptoms (*not available*), and presence of diabetes) score (missing ≤3). Diuretics*: Thiazides, non-loop diuretics, loop-diuretics, diuretics in combination. †Missing 4 patients with TIA, 48 patients with stroke. Missing on; Smoking (TIA: 2003, stroke: missing 2505), Cohabitation status (TIA 588, Stroke 409), Type of residence (TIA 637, Stroke 67). NA: not applicable as data are form the Danish Stroke Registry.

Table 2. 5-year Adjusted Relative Outcomes

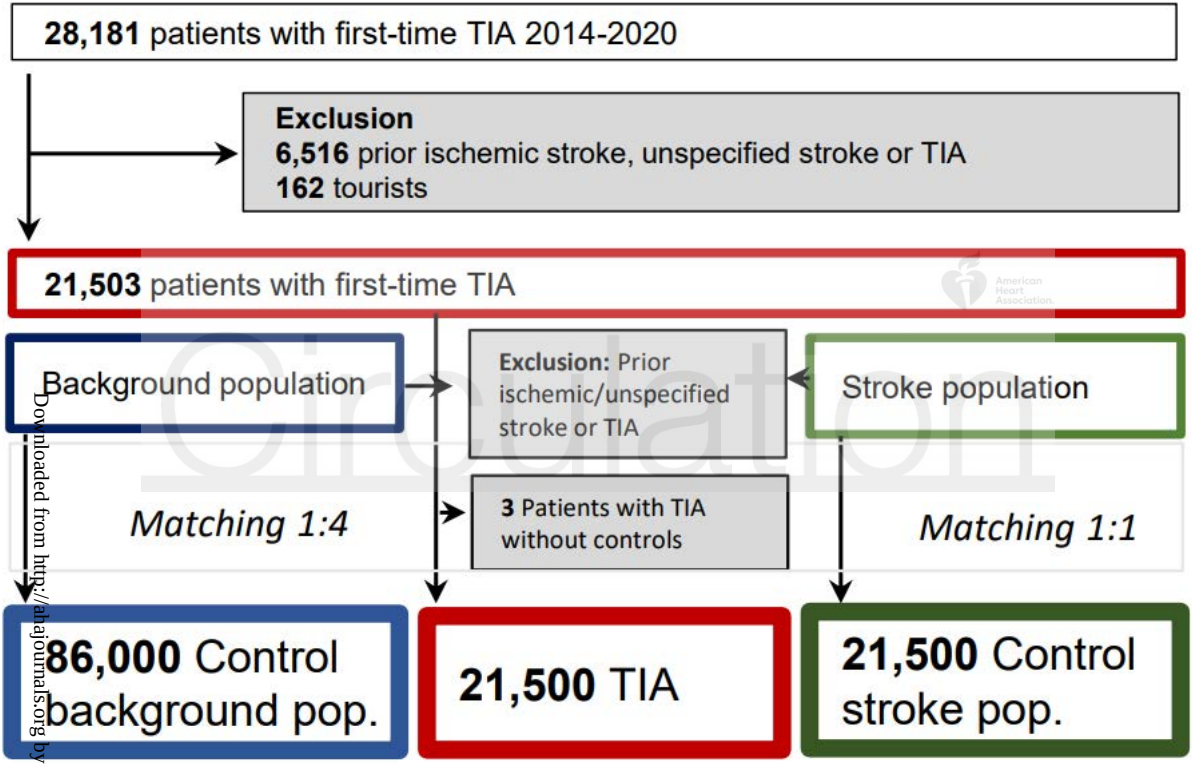
	5-year outcomes	
	Stroke (HR 95%CI)	**Mortality (HR 95%CI)**
TIA vs. background population (ref.)	5.14 (95%CI 4.65-5.69)	1.26 (95%CI 1.20-1.32)
TIA vs. stroke population (ref.)	0.58 (95%CI 0.53-0.64)	0.41 (95%CI 0.39-0.44)

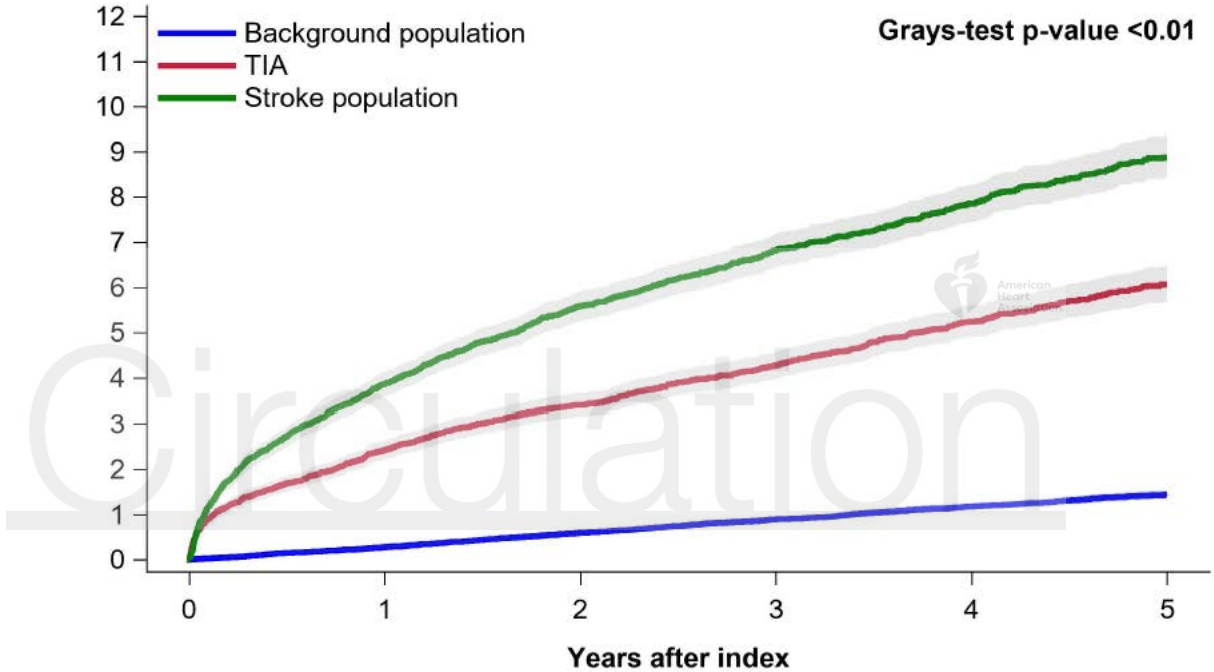
TIA: Transient ischemic attack. The models were adjusted for atrial fibrillation, diabetes mellitus, chronic kidney disease, arterial thromboembolism, valve disease, ischemic heart disease, prior bleeding, liver disease, chronic obstructive lung disease, cancer, peripheral artery disease, heart failure, hypertension, alcohol abuse, and prior use of statins stratified on the matching. Ref.; Reference.

Figure Legends

Figure 1. Selection of the study population

Figure 2. Five-year cumulative incidence of A) ischemic stroke and B) mortality after transient ischemic attach (TIA).





Numbers at risk

Background population	86000	71043	57775	45222	32657	20921
TIA	21500	17193	13796	10675	7618	4804
Stroke population	21500	15467	12126	9190	6448	3956