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Discontinuation of Antiplatelet Treatment and Risk of Recurrent Stroke and All-Cause Death: A Cohort Study

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Key Words
Antiplatelet therapy · Compliance · Death · Recurrent stroke · Stroke

Abstract
Background: We wished to examine the impact of antiplatelet drug discontinuation on recurrent stroke and all-cause mortality. ***Methods:*** We identified a cohort of incident ischaemic stroke patients in a Danish stroke registry, 2007–2011. Using population-based registries we assessed subjects' drug use and followed them up for stroke recurrence, or all-cause death. Person-time was classified by antiplatelet drug use into current use, recent use (≤150 days after last use), and non-use (>150 days after last use). Lipid-lowering drug (LLD) use was classified by the same rules. We used Cox proportional hazard models to calculate the adjusted hazard ratio (HR) and corresponding 95% confidence intervals (CIs) for the risk of recurrent stroke or death associated with discontinuation of antiplatelet or LLD drugs. ***Results:*** Among 4,670 stroke patients followed up for up a median of 1.5 years, 237 experienced a second stroke and 600 died. Compared with current antiplatelet drug use, both recent use (1.3 (0.8–2.0)), and non-use (1.3 (0.8–1.9)) were associated with increased recurrent stroke risk. The corresponding HRs of death were 1.9 (1.4–2.5) for recent and 1.8 (1.4–2.3) for non-use of antiplatelet drugs. Recent statin use was associated with markedly increased risk of death (2.1 (1.7–2.6)), and only marginally with recurrent stroke (1.2 (0.9–1.6)). ***Conclusions:*** Antiplatelet drug discontinuation may be associated with an increased recurrent stroke risk. Our results on death risk indicate that non-pharmacological biases, such as 'sick stopper', may threaten the validity of this risk estimate.

Introduction

Survivors of a stroke are at an increased risk of having another stroke. While the risk of recurrent stroke has been reported to be highest within the first years of the event (8–15%) [1, 2] and then to decline to around 4% per year [1], the long-term risk of death remains high with a 5-year cumulative risk of 41–72% with proportions of

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deaths caused by acute coronary disease and stroke being similar [3]. The use of antiplatelet drugs in this high-risk group has been documented to reduce the relative risk of stroke, myocardial infarction, or death by about 22% [4]. Therefore, lifelong use of antiplatelet drugs is recommended in both Danish and international guidelines on stroke treatment [5, 6]. However, long-term, nonpersistence and non-adherence to antiplatelet drugs in patients with cerebrovascular disease is a frequent problem [7–9], and undermines the beneficial effects of these drugs [10, 11]. We designed the present study to determine the relative risk of recurrent stroke or death associated with the discontinuation of antiplatelet drugs in a cohort of stroke patients in Denmark.

Methods

We established an inception stroke cohort based on data from the Danish National Indicator Project (DNIP) [12] and linked it to prescription data from Odense University Pharmacoepidemiological Register (OPED) [13]. Linkage between the registries was possible using the civil registration number assigned to all Danish residents [14].

Data Sources

The DNIP database functioned in Denmark in the period 1999 to 2011 with nationwide coverage. It was initiated to monitor and evaluate the quality of care for specific diseases including stroke [12]. It was mandatory for all hospital departments in Denmark that treated patients with stroke to provide data in a standardized format to DNIP on all adult patients (≥18 years) admitted with acute stroke, including information on known stroke risk factors, stroke severity on admittance, and information on procedures performed during the admission, for example, neuroimaging.

The Prescription Registry, OPED, has since January 1st 2007 provided complete coverage of all prescriptions for reimbursed medication presented at community pharmacies in the Region of Southern Denmark (RSD). For each prescription, OPED records the date and a full description of the dispensed product, including the anatomical therapeutic code (ATC) and the total number of defined daily doses (DDD). A DDD, established by a group of experts, represents the typical daily dose required by an adult when the drug is used for its main indication [15]. OPED also includes demographic data on residency and vital status retrieved from the Danish Civil Registration System [14].

Stroke Cohort and Inclusion Criteria

The catchment area for this study was the geographically well-defined RSD with a population of approximately 1.2 million in 2011. Through the DNIP, we identified all individuals discharged with a stroke diagnosis from hospitals in RSD for a 4½-year period (01.01.2007–30.6.2011). The first recorded stroke episode within the study period was identified for each subject – the index episode. Only subjects with diagnoses of ischaemic stroke were included, that is, we excluded patients whose index episode carried a diagnosis of haemorrhagic stroke, or 'uncertain type' stroke. As ischaemic and haemorrhagic stroke can be distinguished only through neuroimaging, we excluded subjects who had not undergone neuroimaging according to DNIP data. Based on demographic data from OPED we excluded subjects who had resided in RSD for less than 6 months prior to their index episode. Furthermore, as subjects already on anticoagulants are ordinarily not prescribed antiplatelet treatment as part of a stroke admission, we excluded those with recorded anticoagulant use (ATC codes B01AA03/04, B01AE07, B01AF01/02) in the 6 months prior to follow-up. Finally, we excluded subjects with stroke episodes prior to the index episode according to information from DNIP or OPED (previous use of dipyridamole). Thus, our sample comprised the first ever ischaemic stroke cases followed-up for recurrent stroke.

Follow-Up and Outcome

High short-term risk of death may influence the use of preventive medication. We therefore excluded subjects who died in the first 30 days after discharge from the inception of the stroke episode. Follow-up began 30 days after discharge and continued until one of the following events, whichever came first: stroke recurrence, death, migration, prescription of an anticoagulant, or end of the study period (30.06.2011).

We regarded the following events during follow-up as outcomes: (i) stroke recurrence (ischaemic, intracerebral haemorrhage, or unspecified), defined as a second stroke episode according to DNIP data; (ii) death by any cause according to demographic data from OPED; and (iii) a combined end-point of stroke recurrence or death.

Exposure

All filled prescriptions on subjects from the stroke cohort were retrieved from OPED. All prescriptions for acetylsalicylic acid (ASA) [ATC code B01AC06, or N02BA01 (≤150 mg), dipyridamole (B01AC07), ASA combined with dipyridamole (B01AC30) and clopidogrel (B01AC04)] were classified as antiplatelet drug. For these drugs, one DDD corresponds to 75, 100 or 150 mg of ASA, 400 mg of dipyridamole and 75 mg of clopidogrel. As DDD values are not defined for the combination tablet of ASA and dipyridamole (B01AC30), we assigned 1 DDD to correspond to 50 mg ASA and 400 mg dipyridamole.

A subject was considered to be using antiplatelet drugs from the day the prescription was dispensed and for the duration of the prescription, calculated as the sum of dispensed DDDs and a *grace period* corresponding to 25% of the dispensed DDDs. The grace period was introduced to allow for some degree of noncompliance. An episode of antiplatelet drug use was defined to last for as long as prescriptions were presented with no gap, that is, each prescription was presented within the time-window defined by the duration of its preceding prescription.

For each subject person-time was classified by use of antiplatelet drugs into:

- *Current use*: person-time within antiplatelet episodes.
- *Recent discontinued use*: person-time 1–150 days after last antiplatelet treatment episode.
- *Non-use*: person-time >150 days after last antiplatelet treatment episode, or >150 days until the filling of the first antiplatelet prescription.

To minimize misclassification of drug use prior to follow-up, we also included the last prescription for antiplatelet drugs pre-

sented prior to the date that follow-up began. Use of any antiplatelet, in mono- or polytherapy, and any pattern of switching between antiplatelets was accepted. The only exception was the use of dipyridamole, which was considered only as antiplatelet use in subjects who also used ASA or clopidogrel. In contrast, ASA in monotherapy was accepted, since this treatment may have represented an acceptable compromise in patients with side effects to the combined ASA and dipyridamole regimen. In practical terms, this meant that exposure in subjects using dipyridamole was calculated according to their use of ASA or clopidogrel.

Potential Confounders

We classified subjects based on DNIP data from the inception stroke admission with regard to sex, age, smoking habits (current, former, never, missing), high weekly alcohol intake (men: >21 units men; women: >14 units), body mass index (weight in kg/height in m^2, BMI: <20, 20–24, 25–29, 30+, missing), cohabitation status on admission (lives alone, cohabits, other, missing), history of atrial fibrillation, or myocardial infarction, and Scandinavian Stroke Scale (SSS) score [16] on admission (quartiles). Furthermore, we used a combination of DNIP and OPED data (ATC codes in parenthesis) to classify the history of diabetes (A10), hypertension (C03A, C07, C08, C09 (excluding verapamile)), hyperkolesterolemia (C10A), or previous use of antiplatelet drugs.

Validation Study

Among patients with recurrent stroke episodes identified as described above, we randomly selected 100 patients, retrieved their medical records, and evaluated the diagnosis in accordance with predefined criteria for stroke [17].

Statistical Analyses

We used a Cox proportional hazards model and modelled exposure to antiplatelet drugs as a time-dependent variable to calculate the hazard ratio (HR) and corresponding 95% confidence intervals (CI) for recurrent stroke adjusted for sex and age (Model 1), and for other potential risk factors of stroke measured at the time of the index stroke episode (Model 2; see confounders). In Model 2, we added potential confounders to Model 1 one by one and only kept each added variable in the model if it changed the HR by 5% or more [18]. Time since index episode was also included in Model 2 to account for time-varying risk of stroke. In models studying single outcomes (either recurrent stroke or death) a competing risk analysis was applied. The proportional hazards assumption was verified by the inspection of plots of Schoenfeld residuals.

Supplementary Analyses

We performed a number of supplementary analyses to study the effect of (i) varying the definition of recent discontinued antiplatelet drug use (≤30 days and ≤90 days); (ii) redefining the cohort entry date as discharge date plus 90 days (reduces nonpersistence due to dismal prognosis), and (iii) using a model with adjustment for additional potential confounders (smoking, alcohol use, BMI) regardless of their influence on the HR.

Also, to assess whether non-adherence to antiplatelet treatment was an isolated phenomenon or part of a more general non-adherence to secondary stroke prevention, we also analyzed the risk of recurrent stroke or death stratified by statin use (C10AA). Finally, as an indirect test of our method, we looked at risk of all outcomes with statin as the exposure applying the same time windows for the definition of current, recent and non-use as defined above. We expected to see no risk change in the recent use group since such relatively short discontinuation of statin use should not affect the risk of stroke, or death.

The study was approved by the Danish Data Protection Agency. Review by an ethics board was not required according to Danish law.

Results

We identified a total of 9,711 patients admitted with stroke in the region in 2007 to 2011. We excluded 5,041 subjects, primarily due to history of previous stroke (n = 1,722), inception diagnosis of intracerebral haemorrhage (n = 1,124), and death in hospital or within 30 days of discharge (n = 966) (fig. 1). Thus, a total of 4,670 subjects with ischaemic stroke with a median age of 68.5 (interquartile range 59.7–77.3) were followed for up to 4.5 years (median 1.5 years, interquartile range 0.6–2.6 years). A total of 237 subjects (5.1%) experienced a recurrent stroke, and 600 subjects died during follow-up (12.9%). The characteristics of cohort subjects are presented in table 1.

In the validation study of 100 randomly selected cohort members with recurrent stroke, we could confirm the diagnosis in 94 cases. This corresponds to a positive predictive value of 94% (95% CI: 87.4–97.8) for the recurrent stroke diagnosis. In six cases, the diagnosis could not be confirmed for various reasons: loss of medical record (n = 1), final diagnosis of brain tumour (2), symptomatic epilepsy (1), unspecific confusion (1), and functional disorder (1).

In multivariate analyses, age, sex, and SSS-score quartiles qualified to enter as confounder variables. Compared to current antiplatelet drug use, recent use (HR 1.3, 95% CI: 0.8–2.0), and non-use (HR 1.3, 95% CI: 0.8–1.9) were associated with an increased risk of recurrent stroke. Analyses with death as the end-point produced a similar pattern, that is, recent antiplatelet drug use conferred a risk of death (HR 1.9, 95% CI: 1.4–2.5) that was similar to that associated with non-use (HR 1.8, 95% CI: 1.4–2.3), and this was also the case for the combined end-point stroke or death (table 2).

Among current users of statins, the relative risk associated with the recent use of antiplatelet drugs was higher for stroke (HR 1.3, 95% CI: 0.6–2.6) than for all-cause death (HR 1.1, 95% CI: 0.6–2.2). In patients with recent or past use of statins, the inverse relationship was true, that is, the relative risk associated with the recent use of

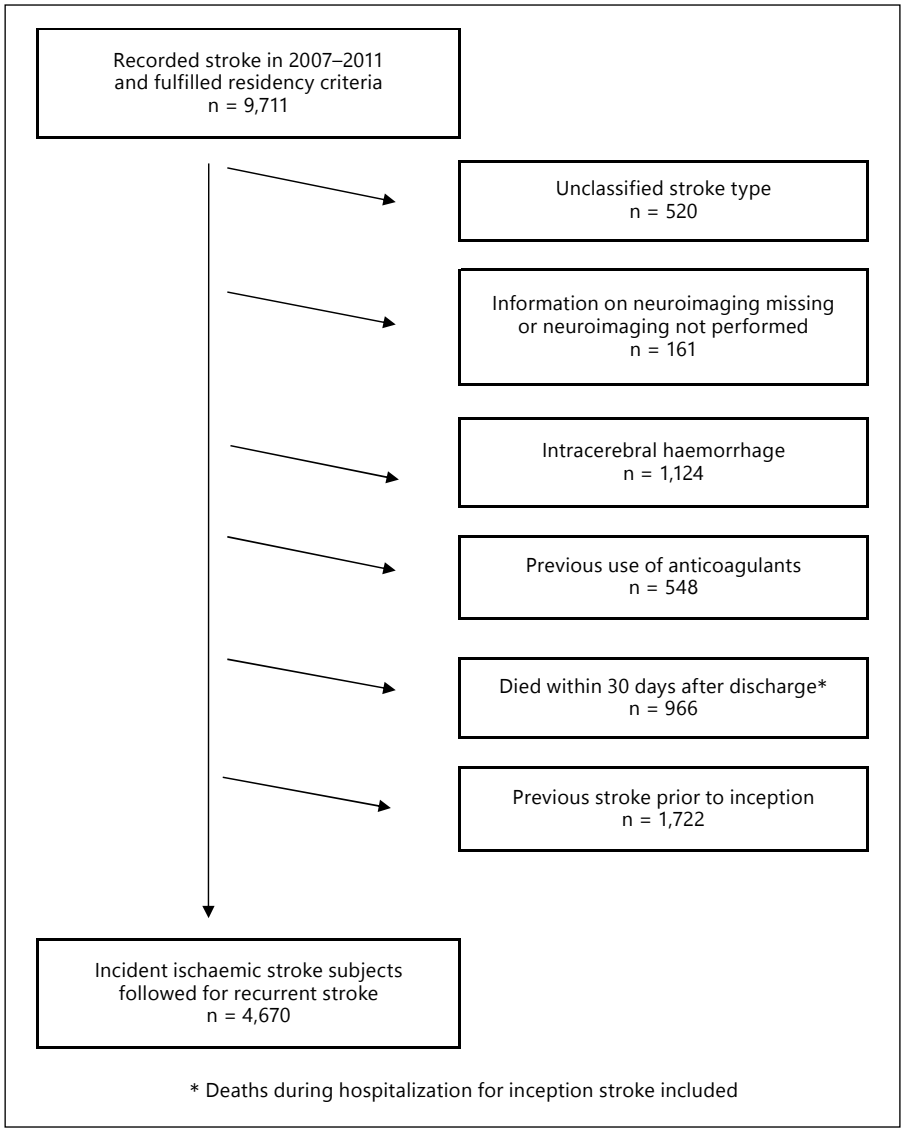

Fig. 1. Inclusion of patients in ischaemic stroke inception cohort in the Region of Southern Denmark.

antiplatelet drugs was higher for overall death (HR 1.8, 95% CI: 1.3–2.4) than for stroke (HR 1.2, 95% CI: 0.7–2.1) (table 3). Also, in a separate analysis where we treated statin use as the exposure of interest with the same definitions for recent use as for antiplatelets, we found that, compared with current use of statins, recent statin use was not associated with stroke risk (HR 1.0, 95% CI: 0.7–1.6), but was associated with death risk (HR 2.9, 95% CI: 2.2–3.7). Likewise, non-use of statins was associated with an increase in the risk of death (HR 2.1, 95% CI: 1.7–2.6), but only a slight increase in the risk of stroke (HR 1.2, 95% CI: 0.9–1.6). The results of all supplementary analyses (see Methods), including varying the definition of recent/past antiplatelet use, redefining the cohort entry date, and using a model with adjustment for other potential confounders, yielded estimates similar to the main analyses (data not presented).

Discussion

In our long-term, follow-up study of patients with a first-time ever stroke, we found that discontinuation of antiplatelet drugs was associated with an increased risk of recurrent stroke and death. Our supplementary analyses of statin use, although of limited statistical precision, indicate that the association of discontinuation of antiplatelet drugs with recurrent stroke may have biological un-

derpinings, while the association to overall death is probably partly due to non-pharmacological causes, for example, drug discontinuation due to dismal prognosis.

Our results on the risk of stroke recurrence in association with discontinuation of antiplatelet treatment are in line with the results of the previous studies, in spite of the varying definitions of discontinuation of antiplatelet use employed in these studies [10, 11, 19, 20]. We note that our results are also in line with those of the only other study that also analysed the recently discontinued antiplatelet use and reported a relative risk of stroke or transient ischaemic attack for recently discontinued antiplatelet use of 1.40 (95% CI: 1.03–1.92) and for past discontinued use of 1.25 (95% CI: 0.81–1.97) [21].

Our results regarding the link between discontinued antiplatelet use and recurrent stroke risk are at odds with those of a recent Danish study. This study used the same datasource, DNIP, as employed in our study to identify subjects with stroke and stroke recurrence on a national level, and furthermore utilized a highly similar prescription registry to ascertain drug exposure [22]. A hazard ratio of recurrent stroke of 0.99 (95% CI: 0.89–1.10) in association with antiplatelet discontinuation was reported. We note that in the Palnum study, failure to renew an antiplatelet prescription after 90 days was regarded as discontinued use. Low-dose aspirin is mainly sold in packages of 100 tablets. We therefore find it highly likely that the time-window of 90 days employed in the Palnum study may have resulted in considerable misclassification of exposure information and may explain the divergence between their study and the present one.

Although our results regarding the deleterious effect of antiplatelet drug discontinuation on the risk of death are highly similar to those reported in previous studies [20, 23], including the previously mentioned Danish cohort study [22], we find it unlikely that this finding can be entirely ascribed to pharmacological beneficial effects of antiplatelet drugs. We speculate that part of the observed effect is due to patients near death, that is, those with a conceived dismal prognosis, not using antiplatelet drugs, either because of selective non-prescription by physicians or non-adherence by patients. Such a non-pharmacological link between death and drug discontinuation has been proposed for statins [24]. Two findings in our study support this notion. First, the hazard ratio of death in antiplatelet discontinuers was greatly reduced among patients with continued statin use. Second, in analyses with statin use as the main exposure, the recent discontinuation of statin was associated with a risk of death that was

Table 1. Baseline characteristics of ischaemic stroke cohort subjects – overall and by outcome during follow-up

Characteristic	All subjects (n = 4,670)	Subjects with outcome	
		recurrent stroke (n = 237)	death (n = 600)
Sex			
Male	2,528 (54.1)	132 (55.7)	287 (47.8)
Female	2,142 (45.9)	105 (44.3)	313 (52.2)
Age, years			
<45	659 (14.1)	33 (13.9)	56 (9.3)
45–54	408 (8.7)	17 (7.2)	11 (1.8)
55–64	829 (17.8)	47 (19.8)	28 (4.7)
65–74	1,067 (22.9)	47 (19.8)	76 (12.7)
75–84	1,070 (22.9)	451 (21.5)	187 (31.2)
≥85	637 (13.6)	42 (17.7)	242 (40.3)
Stroke severity (SSS-score[a]), tertiles			
1st	1,050 (22.5)	58 (24.5)	262 (43.7)
2nd	1,147 (24.6)	62 (26.2)	177 (29.5)
3rd	1,387 (29.7)	77 (32.5)	93 (15.5)
4th	1,086 (23.3)	40 (16.9)	68 (11.3)
Body mass index[b]			
<25	1,696 (36.3)	94 (39.7)	268 (44.7)
25–29	1,346 (28.8)	67 (28.3)	128 (21.3)
30+	672 (14.4)	27 (11.4)	51 (8.5)
Missing	956 (20.5)	49 (20.7)	153 (25.5)
Smoker			
Current	1,635 (35.0)	91 (38.4)	148 (24.7)
Past	898 (19.2)	43 (18.1)	124 (20.7)
Never	1,497 (32.1)	63 (26.2)	186 (31.0)
Missing	640 (13.7)	41 (17.3)	142 (23.7)
Alcohol intake[c]			
Not high	3,827 (81.9)	194 (81.9)	461 (76.8)
High	369 (7.9)	20 (8.4)	30 (5.0)
Missing	474 (10.1)	23 (9.7)	109 (18.2)
Cohabitation			
Cohabits	2,693 (57.7)	126 (53.2)	222 (37.0)
Alone	1,717 (36.8)	98 (41.4)	299 (49.8)
Other[d]	129 (2.8)	4 (1.7)	50 (8.3)
Missing	131 (2.8)	9 (3.8)	29 (4.8)
History of[e]			
Atrial fibrillation	329 (7.0)	22 (9.3)	107 (17.8)
Myocardial infarction	326 (7.0)	22 (9.3)	59 (9.8)
Diabetes	587 (12.6)	33 (13.9)	109 (17.3)
Hypertension	3,035 (65.0)	90 (38.0)	457 (76.2)
Previous use of			
Cholesterol lowering drugs	1,177 (25.2)	64 (27.0)	127 (21.2)
Antiplatelets	1,437 (30.8)	90 (38.0)	288 (48.0)

Data are presented as the number (of subjects), with the percentage given in parenthesis. [a] Scandinavian stroke scale score on admission. [b] Weight in kg/height in m^2. [c] High weekly alcohol intake: men: >21 units, women: >14 units. [d] Majority of subjects lived at retirement homes and other institutions. [e] Based on stroke database information only (stroke, atrial fibrillation, myocardial infarct), combination of stroke database and prescription data (diabetes, hypertension), or prescription data only (previous antiplatelet or cholesterol-lowering drug use).

Table 2. Antiplatelet drug use and risk of recurrent stroke or death in an ischaemic stroke cohort

Outcome type	Antiplatelet use	Person-years	Events	Hazard ratio (95% confidence interval)			p value
				crude	adjusted, model 1[a]	adjusted, model 2[b]	
Recurrent stroke	Current[c]	6,547	191	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
	Recent[d]	572	21	1.3 (0.8–2.0)	1.3 (0.8–2.0)	1.3 (0.8–2.0)	0.32
	Non-use[e]	710	25	1.2 (0.8–1.9)	1.3 (0.8–2.0)	1.3 (0.8–1.9)	0.29
Death	Current[c]	6,547	462	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
	Recent[d]	572	60	1.7 (1.3–2.3)	1.9 (1.4–2.5)	1.9 (1.4–2.5)	<0.01
	Non-use[e]	710	78	1.5 (1.2–2.0)	1.9 (1.5–2.4)	1.8 (1.4–2.3)	<0.01
Stroke or death	Current[c]	6,547	653	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)	
	Recent[d]	572	81	1.7 (1.3–2.1)	1.7 (1.3–2.1)	1.7 (1.3–2.1)	<0.01
	Non-use[e]	710	103	1.5 (1.2–1.8)	1.8 (1.4–2.2)	1.7 (1.3–2.0)	<0.01

[a] Adjusted for sex and age. [b] Adjusted for sex, age, and SSS-score. Time since inception also included in the model. In single outcome models (stroke only or death only), a competing risk analysis was applied; this approach results in an identical amount of follow-up for the various outcomes. [c] No gap in antiplatelet treatment. [d] 1–150 days since after last antiplatelet treatment episode. [e] >150 days since last antiplatelet treatment episode, or >150 days since until the filling of the first antiplatelet prescription.

Table 3. Antiplatelet drug use in a cohort of stroke patients and risk of recurrent stroke or death stratified by statin use

Outcome type	Antiplatelet use	Person-years	Events	Hazard ratio, adjusted[a] (95% confidence interval)	p value
Statin current use[c]					
Recurrent stroke	Current[b]	4,292	113	1.0 (ref.)	
	Recent[c]	244	8	1.3 (0.6–2.6)	0.49
	Non-use[d]	217	7	1.3 (0.6–2.7)	0.55
Death	Current[b]	4,292	164	1.0 (ref.)	
	Recent[c]	244	9	1.1 (0.6–2.2)	0.70
	Non-use[d]	217	11	1.5 (0.8–2.8)	0.17
Statin recent or past use[d]					
Stroke	Current[b]	2,255	78	1.0 (ref.)	
	Recent[c]	328	13	1.2 (0.7–2.1)	0.58
	Non-use[d]	493	18	1.2 (0.7–2.0)	0.54
Death	Current[b]	2,255	376	1.0 (ref.)	
	Recent[c]	328	64	1.8 (1.3–2.4)	<0.01
	Non-use[d]	493	85	1.5 (1.1–1.9)	<0.01

[a] Adjusted for sex, age, history of atrial fibrillation, and previous use of antiplatelet drugs. Time since inception also included in the model. A competing risk analysis was applied, which results in an identical amount of follow-up for both outcomes. [b] No gap in antiplatelet treatment. [c] 1–150 days since after last antiplatelet/statin treatment episode. [d] >150 days since last antiplatelet/statin treatment episode, or >150 days since until the filling of the first antiplatelet/statin prescription.

almost 3 times that observed among patients with continuous statin use, a finding that seems unlikely to be explained by the lack of statin effects for such a short time-period. Both indicate a considerable non-pharmacological contribution to the association between antiplatelet discontinuation and death. We therefore believe that our results overestimate the preventive effects of antiplatelet drugs on mortality. Although we cannot overrule the effect of a 'sick stopper' bias on the risk of recurrent stroke, we find it likely that the magnitude of this bias is negligible, given the very modest effect of recent statin use on the risk of recurrent stroke.

Our study has a number of strengths. We used a geographically well-defined area to conduct the study where access to health services is free of charge, and cerebrovascular services are provided by stroke units with referral for evaluation strictly based on residency status. During the study period, there were national guidelines on preventive treatment of stroke. Follow-up for subsequent stroke was achieved through register data free of recall bias. As documented by our validation study, the positive predictive value of a recurrent stroke diagnosis identified through the DNIP was high. The prescription register data offered complete coverage on the use of reimbursed drugs by all subjects. ASA is the only antiplatelet that is available over the counter. However, the coverage of OPED for low-dose ASA is in the order of 91% (www.medstat.dk/en). Death and emigration during follow-up were fully covered by the Danish Civil Registration System data included in the OPED data.

Several potential limitations of our study should be considered. First, we have to consider a 'healthy adherer' effect. In a meta-analysis, adherence to placebo was associated with improved mortality compared with poor adherence to placebo, which indicates that adherence may be a surrogate marker for overall healthy behaviour [25]. Although we have attempted to adjust for several potential confounders in our analyses, we cannot exclude the possibility that unmeasured confounders, particularly in the time-period after discharge from the inception stroke, may have influenced patient behaviour with regard to drug adherence. However, we find it unlikely that a 'healthy adherer' behaviour would predict different patterns of adherence for different preventive drug classes, that is, statins versus antiplatelet drugs. We therefore believe that our finding of a largely unchanged risk of recurrent stroke in patients with current use of statins testifies to a minor effect of 'healthy adherer' bias for this outcome. Second, it can be difficult to correctly infer the exact time point of discontinuation of drug use from prescription data alone. This is even more so the case for brief discontinuation, for example, in association with planned surgery, which nonetheless may carry a relatively high risk of stroke [26]. Our approach probably resulted in some misclassification of exposure with regard to the recent use of antiplatelet drug. However, such non-differential misclassification is a conservative bias and would tend to influence hazard ratios towards unity. Third, it can be argued that persistence, which in this study corresponds to current use, is not necessarily indicative of adherence. We have, however, in previous studies documented that persistent users of antiplatelet drugs were also highly adherent [8, 9]. Conversely, in a study of antiplatelet drug use after transient ischaemic attack, nonpersistence was clearly associated with poorer adherence prior to the cessation of antiplatelet use and was also linked to poorer adherence to statins [9]. Fourth, we had no information on the reasons for discontinuation of antiplatelet drugs – whether it was based on the patient's or the prescriber's initiative. A recent study based on UK primary care data, a health system similar to the Danish one, reported that among patients with a stroke who had recently discontinued low-dose aspirin, 77.8% had stopped treatment on their own initiative [21].

We conclude that our study provides important insights on the risks associated with nonpersistence in the use of antiplatelet drugs by stroke patients. Our findings underline the risk of recurrent stroke associated with the discontinuation of antiplatelet drugs. We find the high impact of discontinuation of antiplatelet drugs on overall death more questionable and speculate whether it may partly be explained by a 'sick stopper' effect.

Conflict of Interest

Drs. Kamilla Østergaard, Søren Bak, David Gaist, pharmacist Anton Pottegård, and statistician René dePont Christensen report no disclosures. Jesper Hallas has participated in research projects funded by Takeda with grants paid to the institution where he was employed, and he has personally received fees for teaching and consulting from Takeda.

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