

Association between Antiplatelet Therapy and Changes in Intraplaque Hemorrhage in Patients with Mild to Moderate Symptomatic Carotid Stenosis: A Longitudinal MRI Study

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Keywords

Stroke · Carotid artery diseases · Hemorrhage · Magnetic resonance imaging

Abstract

Introduction: Carotid atherosclerotic intraplaque hemorrhage (IPH) predicts stroke. Patients with a history of stroke are treated with antiplatelet agents to prevent secondary

cardiovascular events. A positive association between previous antiplatelet use and IPH was reported in a cross-sectional analysis. We investigated the changes in IPH over 2 years in patients who recently started versus those with continued antiplatelet use. **Methods:** In the Plaque at Risk (PARISK) study, symptomatic patients with <70% ipsilateral carotid stenosis underwent carotid plaque magnetic resonance imaging (MRI) at the baseline and after 2 years to determine IPH presence and volume. Participants were

categorized into new users (starting antiplatelet therapy following the index event) and continued users (previous use of antiplatelet therapy before the index event). The association between previous antiplatelet therapy and the presence of IPH at baseline MRI was investigated using multivariable logistic regression analysis. The IPH volume change over a period of 2 years, defined as the difference in volume between follow-up and baseline, was investigated in each group with a Wilcoxon signed-rank test. The IPH volume change was categorized as progression, regression, or no change. Using multivariable logistic regression, we investigated the association between new antiplatelet use and (1) newly developed ipsilateral or contralateral IPH and (2) IPH volume progression. **Results:** A total of 108 patients underwent carotid MRI at the baseline and follow-up. At the baseline, previous antiplatelet therapy was associated with any IPH (OR = 5.6, 95% CI: 1.3–23.1; $p = 0.02$). Ipsilateral IPH volume did not change significantly during the 2 years in patients who continued receiving antiplatelet agents (86.4 mm³ [18.2–235.9] vs. 59.3 mm³ [11.4–260.3]; $p = 0.6$) nor in the new antiplatelet users ($n = 31$) (61.5 mm³ [0.0–166.9] vs. 27.7 mm³ [9.5–106.4]; $p = 0.4$). Similar results of a nonsignificant change in contralateral IPH volume during those 2 years were observed in both groups ($p > 0.05$). No significant associations were found between new antiplatelet use and newly developed IPH at 2 years (odds ratio [OR] = 1.0, 95% CI: 0.1–7.4) or the progression of IPH (ipsilateral: OR = 2.4, 95% CI: 0.3–19.1; contralateral: OR = 0.3, 95% CI: 0.01–8.5). **Conclusion:** Although the baseline association between IPH and previous antiplatelet therapy was confirmed in this larger cohort, the new onset of antiplatelet therapy after transient ischemic attack/stroke was not associated with the newly developed IPH or progression of IPH volume over the subsequent 2 years.

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Plain Language Summary

Carotid artery narrowing due to an atherosclerotic plaque is responsible for around 20% of stroke. Intraplaque hemorrhage (IPH) predicts stroke. Antiplatelet agents are often given to patients who have had a stroke to prevent further cardiovascular events. A previous study found an association between previous antiplatelet use and IPH at a specific point in time. In this study, researchers investigated whether starting antiplatelet therapy after a stroke or continuing to use antiplatelets had any effect on IPH over a 2-year period. The study included patients with <70% carotid narrowing who had a carotid plaque MRI at the baseline and after

2 years to determine the presence and volume of IPH. Patients were categorized into new users (starting antiplatelet therapy following the stroke) and continued users (already using antiplatelet therapy before the stroke). The presence and the volume change of IPH over 2 years were investigated in each group. The study found that IPH was more present at the baseline when patients used antiplatelet agents before the stroke. However, new antiplatelet use after the stroke did not lead to new IPH or an increase in IPH volume over the subsequent 2 years. There were no significant associations between the new antiplatelet use and newly developed IPH or IPH volume progression. Therefore, while the baseline association between IPH and previous antiplatelet therapy was confirmed in this larger cohort, starting antiplatelet therapy after a stroke did not increase the risk of new IPH or progression of IPH volume over the subsequent 2 years.

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Introduction

Approximately 20% of ischemic strokes are caused by a vulnerable atherosclerotic carotid plaque rupture [1]. The term “vulnerable plaque” refers to rupture-prone plaques. Intraplaque hemorrhage (IPH) is an important feature of plaque vulnerability. A large meta-analysis showed that IPH is a strong and independent predictor for ipsilateral stroke [2–4]. Magnetic resonance imaging (MRI) is the optimal noninvasive imaging modality to determine the presence and volume of IPH [5].

As a part of routine treatment, platelet aggregation inhibitors are prescribed to prevent further ischemic events in symptomatic patients [6]. However, although antiplatelet agents have a favorable effect in reducing thrombus formation, they also increase the risk of bleeding complications [7]. Previously, in a cross-sectional study, we reported an association between antiplatelet use before the index event and the presence of IPH in transient ischemic attack (TIA) and stroke patients with <70% symptomatic carotid stenosis [8]. We suggested that the use of antiplatelet medication might contribute to the formation of IPH, but since this was a cross-sectional study, causality could not be demonstrated. In the current longitudinal study, we hypothesize that patients who started antiplatelet therapy after the index event (new antiplatelet users) are at higher risk of developing new IPH and IPH progression over a 2-year period than patients who already used antiplatelet agents before the index event.

Materials and Methods

Study Population

The baseline and follow-up MRI and clinical data from patients included in the PARISK study were analyzed (clinicaltrials.gov NCT1208025) [9]. Patients were eligible for inclusion when they had a recent (<3 months) cerebral or monocular TIA or minor ischemic stroke (modified Rankin scale ≤ 3) in the anterior circulation as diagnosed by a neurologist through a comprehensive evaluation involving medical history, physical examination, and neuroimaging (CT or MRI), and an ipsilateral carotid plaque of at least 2–3 mm thick with <70% carotid artery stenosis (NASCET) and were not scheduled for carotid revascularization. Individuals suspected of having embolic origins from cardiac sources or patients with clotting disorders were excluded. Additionally, cases of hemorrhagic stroke were not eligible for inclusion. Approval from the local Institutional Ethical Review Board was obtained, and each patient gave written informed consent.

Clinical Information

At the baseline, information was gathered regarding the index event, history of other symptomatic arterial diseases, and cardiovascular risk factors. Medication prescribed to participants after the index event (baseline) and at 2 years (follow-up) was also collected. Patients who received antiplatelet therapy following the index event were classified as new antiplatelet users, whereas patients who had already used antiplatelet therapy before the index event were classified as continued users. In those patients, the duration of antiplatelet use prior to the index event was recorded.

MRI Acquisition and Analysis

Carotid MRI was scheduled at the baseline and after 2 years in the first 150 patients of the PARISK study using 3.0 T scanners with dedicated carotid coils [9]. Evaluation of the MR images was performed as previously described using dedicated vessel wall analysis software (VesselMass, Leiden University Medical Centre, Leiden, The Netherlands) [10]. IPH, defined as a hyperintense region in the bulk of the plaque compared to the surrounding muscle, was manually delineated on T1-weighted inversion recovery turbo field echo images (three centers), also known as magnetization prepared-rapid gradient echo or on spoiled gradient echo images (one center). Ipsilateral and contralateral IPH at the baseline and after 2 years were delineated by independent, trained observers, who were blinded to the clinical data [11]. The follow-up MR images were delineated blinded to the baseline MRI.

Statistical Analysis

For all statistical analyses, SPSS version 25 (IBM Co., Armonk, NY, United States) was used. Differences in patient characteristics between groups were examined by a χ^2 test for categorical values and a Mann-Whitney U test or unpaired *t* test for continuous values. A potential difference in the prevalence of IPH at the baseline and follow-up was determined using a McNemar test. Any IPH was defined as the presence of IPH in the ipsilateral, contralateral, or both carotid arteries. IPH is categorized as “new” if it is identified on a follow-up carotid MRI in patients who did not display IPH in that particular artery at the baseline. The IPH volume change over a period of 2 years was investigated in each group with a Wilcoxon signed-rank test. A threshold for IPH progression or regression was defined by calculating the mean

coefficient of variation (measurement error), defined as 100% * standard deviation (SD)/mean [12]. The coefficient of variation was calculated based on IPH volumes that were calculated by independent delineation of IPH by five trained readers. The measurement error for the IPH volume was 11%. Therefore, progression was considered as a volume increase >11% or new IPH, regression as a volume decrease >11%, or IPH disappearance, and an absolute change $\leq 11\%$ was classified as no change. Multivariable logistic regression analysis was used to evaluate the association between new antiplatelet therapy and the presence of IPH at the baseline or the progression in IPH volume at follow-up (progression vs. regression/no change) after adjusting for potential confounders. Clinical confounders were selected based on biological plausibility [13, 14]. Therefore, based on our sample size and the biological effects, age, sex, smoking, hypercholesterolemia, history of cardiovascular disease (CVD), the type of baseline event (amaurosis fugax, TIA, or stroke) and time from index event to baseline MRI were considered potential confounders. The magnitude of the association was expressed as the odds ratio (OR) with a 95% confidence interval (CI).

Results

Of the 150 patients who were invited to undergo baseline and follow-up carotid MRI, 108 patients were included for further analysis. Forty-two patients were excluded for different reasons, including anticoagulant use ($n = 7$) (online suppl. Fig. 1; for all online suppl. material, see <https://doi.org/10.1159/000535274>). At the baseline, 42 (39%) patients were receiving antiplatelet therapy prior to the index event, and they all continued to use antiplatelet therapy after the index event (referred to as “continued users”), while 66 (61%) patients started antiplatelet treatment immediately following the index event (referred to as “new antiplatelet users”). Twenty-three of the 42 continued patients used antiplatelet therapy for a median period of 6 years (IQR: 3–12 years) before the index event. However, data regarding this period could not be retrieved for 19 patients. All 108 (100%) patients were still on antiplatelet therapy at the 2-year follow-up.

Baseline Analysis

At the baseline, IPH was present on the ipsilateral, contralateral, or bilateral side in 44/108 (41%), 12/108 (11%), or 6/108 (6%) of the patients, respectively. Patients with any IPH (ipsilateral, contralateral, or both) were older, more often male, and more often used antiplatelet agents before the index event (27 [54%] vs. 15 [26%] $p = 0.003$) (Table 1). In the multivariable analysis, after adjusting for covariates, only previous antiplatelet therapy was associated with any IPH at baseline MRI (OR = 5.6, 95% CI: 1.3–23.1; $p = 0.02$) (Table 2).

Table 1. Univariable analyses of clinical variables that are associated with the presence of any IPH at the baseline

Variable	All patients (N = 108)	^a IPH – N = 58 (54%)	^a IPH + N = 50 (46%)	p value
Age, years (mean±SD)	68 (±8)	66 (±9)	70 (±6)	0.02
Sex, male, n (%)	76 (70)	35 (60)	41 (82)	0.01
BMI, kg/m ² median (IQR)	26 (24–28)	26 (23–28)	25 (24–27)	0.5
Currently smoking, n (%)	23 (21)	16 (28)	7 (14)	0.08
Diabetes mellitus, n (%)	25 (23)	12 (21)	13 (26)	0.5
Hypertension, n (%)	61 (56)	31 (53)	30 (60)	0.5
Hypercholesterolemia,* n (%)	54 (50)	24 (41)	30 (60)	0.08
Previous antiplatelet use, n (%)	42 (39)	15 (26)	27 (54)	0.003
Baseline statins use, n (%)	52 (48)	25 (43)	27 (54)	0.3
Baseline antihypertensive medication use, n (%)	60 (55)	29 (50)	31 (62)	0.2
Baseline antidiabetic medication use, n (%)	20 (18)	9 (15)	11 (22)	0.3
History of cardiovascular disease, n (%)	44 (41)	21 (36)	23 (46)	0.2
Type ischemic event, stroke, n (%)	47 (44)	22 (38)	25 (50)	0.2
Time index event to baseline MRI, days; median (IQR)	49 (34–65)	45 (33–62)	52 (35–68)	0.2

IPH, intraplaque hemorrhage; SD, standard deviation; IQR, interquartile range; BMI, body mass index; MRI, magnetic resonance imaging. ^aAny IPH at baseline MRI (ipsilateral, contralateral, or bilateral). *Two missing data.

Table 2. Logistic regression analysis of variables associated with any IPH at the baseline

	Univariable, OR (95% CI)	p value	Multivariable, *OR (95% CI)	p value
Age	1.1 (1.0–1.1)	0.03	1.0 (1.0–1.1)	0.3
Sex	3.0 (1.2–7.3)	0.02	2.0 (0.7–5.4)	0.2
Smoking	2.3 (0.9–6.2)	0.09	1.5 (0.4–5.3)	0.5
Hypercholesterolemia	2.0 (0.9–4.3)	0.08	1.5 (0.7–11.1)	0.4
Previous antiplatelet therapy ^a	3.4 (1.5–7.5)	0.003	5.6 (1.3–23.1)	0.02
History of CVD	1.7 (0.8–3.8)	0.2	2.8 (0.7–11.1)	0.1
Time index event to baseline MRI	1.0 (1.0–1.0)	0.3	1.0 (1.0–1.0)	0.8

OR, odds ratio; CI, confidence interval; IPH, intraplaque hemorrhage; CVD, cardiovascular disease; MRI, magnetic resonance imaging; BMI, body mass index; DM, diabetes mellitus. ^aBefore the index event. *Variables in the model: age, sex, current smoking, hypercholesterolemia, antiplatelet agent use, history of CVD, and time index event to baseline MRI.

Association between New Development of IPH during Two Years of Follow-Up and New Antiplatelet Users

The percentage of patients with IPH did not change significantly between baseline and 2-year follow-up in the new antiplatelet users (ipsilateral: 32% vs. 39%; $p = 0.3$, contralateral: 5% vs. 9%; $p = 0.4$, respectively), nor did it change in the continued antiplatelet users (ipsilateral: 55% vs. 57%; $p = 1.0$, contralateral: 21% vs. 29%; $p = 0.4$, respectively). 15% and 8% of new antiplatelet users developed new ipsilateral and contralateral IPH, respectively, while 9% and 9% of patients who were already using antiplatelets prior to the index event developed new

ipsilateral and contralateral IPH, respectively, but these changes were not statistically significantly different (Table 3).

Univariable analysis showed no significant associations between the start of antiplatelet agent use and the formation of newly developed ipsilateral or contralateral IPH at the 2-year follow-up (OR = 2.1, 95% CI: 0.5–8.1; $p = 0.3$). After correcting for potential confounders, the association between new antiplatelet use and newly developed IPH during 2 years of follow-up remained nonsignificant (OR = 1.0, 95% CI: 0.1–7.4; $p = 0.9$). Furthermore, no significant associations were observed between age, sex, current smoking status, hypercholesterolemia, the history of CVDs,

Table 3. Cross table between the status of antiplatelet agent use and changes in prevalence of IPH during 2-year follow-up

	IPH did not change, <i>n</i> (%)	New IPH developed, <i>n</i> (%)	IPH disappeared, <i>n</i> (%)	Total
<i>Presence of ipsilateral IPH during 2-year follow-up</i>				
New antiplatelet user	51 (77)	10 (15)	5 (8)	66
Continued antiplatelet user	35 (83)	4 (9)	3 (7)	42
Total	86 (80)	14 (13)	8 (7)	108
<i>Presence of contralateral IPH during 2-year follow-up</i>				
New antiplatelet user	59 (89)	5 (8)	2 (3)	66
Continued antiplatelet user	37 (88)	4 (9)	1 (2)	42
Total	96 (89)	9 (8)	3 (3)	108

IPH, intraplaque hemorrhage.

the type of baseline event (stroke vs. TIA/amaurosis fugax) and the time from index event to the baseline MRI, and the development of new ipsilateral or contralateral IPH.

Volume Change of IPH

The IPH volumes in the 58 ipsilateral and 20 contralateral arteries that showed IPH at the baseline, at follow-up, or both were analyzed. The median ipsilateral IPH volume did not change after 2 years of follow-up in patients who continued receiving antiplatelet therapy ($n = 27$) (86.4 mm^3 [18.2–235.9] vs. 59.3 mm^3 [11.4–260.3]; $p = 0.6$) nor in the new antiplatelet users ($n = 31$) (61.5 mm^3 [0.0–166.9] vs. 27.7 mm^3 [9.5–106.4]; $p = 0.4$). Similar results of a nonsignificant change in contralateral IPH volume during those 2 years were observed in the continued antiplatelet therapy ($n = 12$) (26.6 mm^3 [1.0–111.8] vs. 12.8 mm^3 [6.0–144.4]; $p = 0.8$), as well as in the new antiplatelet users ($n = 8$) (0.0 mm^3 [0.0–8.6] vs. 11.8 mm^3 [1.4–77.0]; $p = 0.2$) (Fig. 1). Nevertheless, even though the overall median volume did not significantly change, 26 out of 58 (45%) ipsilateral carotid arteries and 12 out of 20 (60%) contralateral carotid arteries showed progression of IPH volume (defined as volumetric increase >11% or new IPH) after 2 years (Table 4; Fig. 2), while 29 out of 58 (52%) on the ipsilateral side and 6 out of 20 (30%) on the contralateral side exhibited regression.

No association was found between new antiplatelet use after the index event and the progression of ipsilateral or contralateral IPH volume after 2 years (OR = 1.4, 95% CI: 0.5–3.9; $p = 0.6$ and OR = 1.2, 95% CI: 0.2–7.5; $p = 0.8$, respectively). In the multivariable analysis, there was also no significant association between starting antiplatelet therapy after the index event and IPH volume progres-

sion on the ipsilateral (OR = 2.4, 95% CI: 0.3–19.1; $p = 0.4$) or on the contralateral side after 2 years (OR = 0.3, 95% CI: 0.01–8.5; $p = 0.5$). Furthermore, there was no significant association between age, sex, current smoking status, hypercholesterolemia, the history of CVDs, the type of baseline event (stroke vs. TIA/amaurosis fugax) and the time from index event to the baseline MRI, and the progression of ipsilateral and contralateral IPH after 2 years of follow-up.

Discussion

In the present study, we reported on longitudinal changes in IPH prevalence and volume in relation to continued versus new antiplatelet agent use. Our study confirmed the association between the presence of IPH at the baseline and previous use of antiplatelet therapy in symptomatic patients with ipsilateral nonsignificant (<70%) carotid artery stenosis. However, the frequency and volume of IPH did not increase during the 2 years of follow-up in the new antiplatelet users or in the continued users. Additionally, although we showed a slightly higher prevalence of new IPH in the new antiplatelet users, no significant association was found between new antiplatelet agent use and the formation of new IPH or IPH volume progression during the 2-year follow-up.

Most of the previous studies focused on a cross-sectional analysis on the association between IPH and antiplatelet use. A histopathological study showed a significantly higher amount of multiple carotid IPH in 154 endarterectomy specimens from patients who used antiplatelet therapy (80.1% vs. 19.7%; $p < 0.001$) [15]. Another histopathology study failed to identify an association between antiplatelet use and the prevalence of

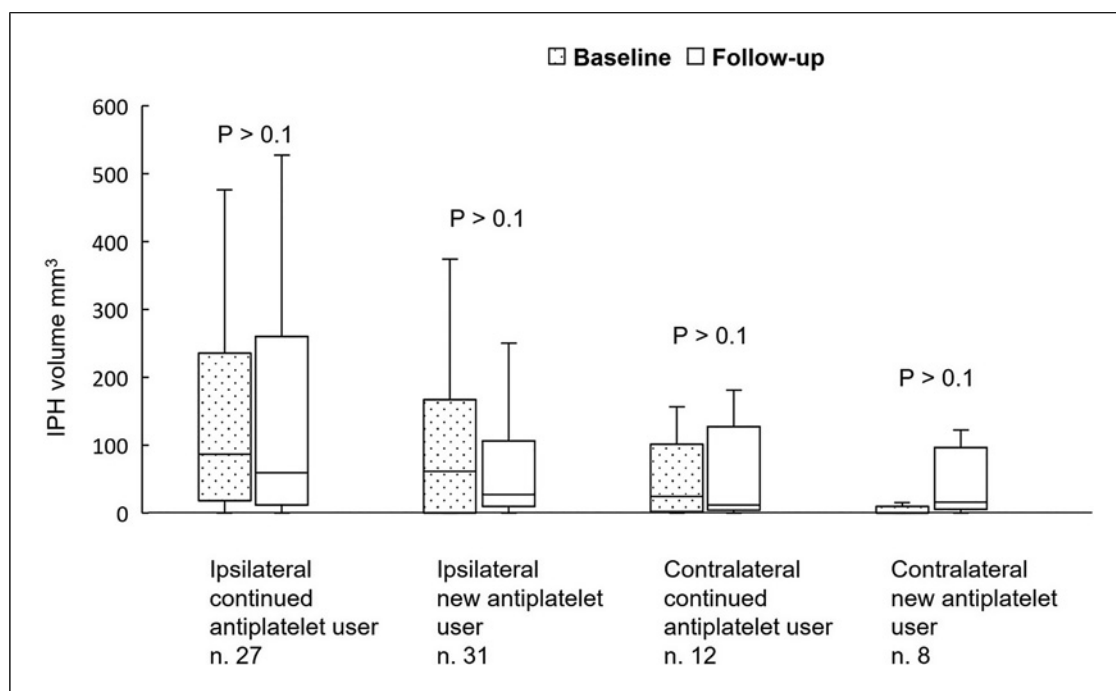


Fig. 1. Volume of IPH at the baseline and after the 2-year follow-up was categorized by using antiplatelet therapy before the index event.

Table 4. The prevalence of IPH progression in relation to antiplatelet therapy after the index event in patients with IPH at the baseline, at follow-up, or at both time points

	Progression, n (%)	Regression, n (%)	No change, n (%)	Total
<i>Ipsilateral IPH during 2-year follow-up</i>				
New antiplatelet user	15 (48)	15 (48)	1 (3)	31
Continued antiplatelet user	11 (41)	15 (56)	1 (4)	27
Total	26 (45)	29 (52)	2 (3)	58
<i>Contralateral IPH during 2-year follow-up</i>				
New antiplatelet user	6 (75)	1 (13)	1 (13)	8
Continued antiplatelet user	6 (50)	5 (42)	1 (8)	12
Total	12 (60)	6 (30)	2 (10)	20

IPH, intraplaque hemorrhage.

IPH in 1,070 patients [16]. Current and past use of antiplatelet agents was (nonsignificantly) associated with a higher prevalence of carotid IPH in a subpopulation of the Rotterdam Study with a carotid plaque larger than 2.5 mm in at least one of the carotid arteries [17]. Furthermore, a recent longitudinal study in 34 symptomatic patients with carotid IPH and at least 6 months of follow-

up showed that atherosclerotic plaques were significantly more likely to be in the progressed IPH group if the patient used antiplatelet therapy at the baseline (86.7 vs. 53.3%, $p = 0.046$) [18]. In that study, the use of antiplatelet therapy at follow-up was not reported. In our study, all patients were on antiplatelet therapy during the follow-up period.

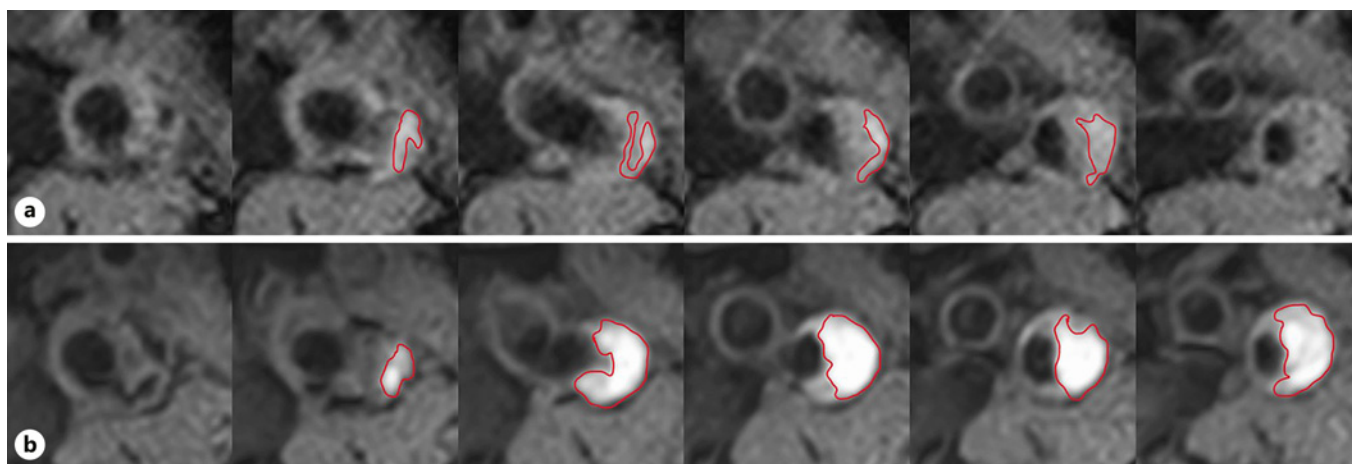


Fig. 2. IPH progression after two 2-year follow-up in a new antiplatelet user. 3D T1-weighted inversion recovery turbo field echo images of carotid atherosclerotic plaque with IPH at the baseline (**a**) and follow-up (**b**). IPH volume (red contours) increased from 121.0 mm³ at the baseline to 250.6 mm³ after 2 years of follow-up (107% increase). IPH, intraplaque hemorrhage.

Although the baseline association between IPH and previous antiplatelet therapy was confirmed in our study, against our hypothesis, the new onset of antiplatelet therapy after TIA/stroke was not associated with the newly developed IPH or progression of IPH volume over the subsequent 2 years. Possibly, the baseline association between IPH and previous antiplatelet therapy is affected by the fact that previous antiplatelet users may have had a more severe disease stage, since usually antiplatelet therapy is prescribed in high risk patients, although we did correct for previous CVD in the multivariable analysis.

Another explanation may be that the present study lacks a control group consisting of patients who did not use antiplatelet agents at follow-up. The current clinical guideline states that the prescription of antiplatelet therapy after stroke has to be continued for a lifetime; therefore, we could not include such a control group. Following a stroke, a significant number of patients previously treated with a single antiplatelet agent often have a transition to dual antiplatelet therapy, typically involving both aspirin and clopidogrel, for a few weeks. Nevertheless, in this current study, we opted not to distinguish between mono- and dual therapy among continued users due to the limited sample size. Moreover, in the present study, the follow-up MRI was performed after 2 years and we cannot exclude that this period may not have been long enough to show an association between the new onset of antiplatelet therapy and new IPH or progression of IPH. In the previous cross-sectional studies that demonstrated an association between antiplatelet use and IPH, the median interval between the initiation of antithrombotic medication and the subse-

quent MRI was 6 years (with a range of 1–28 years) and 72 months (interquartile range: 30–123 months), respectively [8, 17]. One study reported no association between the duration of antiplatelet therapy and IPH ($p = 0.94$) [8], while in the other study, a longer duration of the use for antiplatelet agents showed a positive, but statistically nonsignificant, trend of IPH (OR: 1.21, 95% CI: 0.88–1.67) [17].

Finally, our population was limited to patients with ipsilateral carotid artery stenosis <70% who were not scheduled for revascularization surgery or stenting. Symptomatic patients with severe stenosis (>70%) will be operated on in the Netherlands, which means follow-up of the plaque and IPH is not possible. Future studies could be performed in asymptomatic individuals with and without IPH in the carotid plaque. If that group consists of both subjects using antiplatelet agents and subjects who do not use antiplatelet agents, the relationship between (no) the use of antiplatelet agents and the presence/volume of IPH can be studied.

Conclusion

Stroke patients with mild to moderate carotid artery stenosis who previously used antiplatelet therapy show a significantly higher prevalence of IPH at the baseline. However, no association was found between starting antiplatelet agents and either newly developed IPH or progression of IPH volume during 2 years of follow-up. Additional studies are warranted to further investigate the

relationship between antiplatelet agent use and IPH progression in asymptomatic individuals with carotid stenosis.

Acknowledgments

Participating centers: Academic Medical Centers, Amsterdam (P.J. Nederkoorn); Erasmus Medical Center, Rotterdam (A. van der Lugt, P.J. Koudstaal); Flevoziekenhuis, Almere (M. Limburg); Kennemer Gasthuis, Haarlem (M. Weisfelt); Laurentius Ziekenhuis, Roermond (A.G. Kortjen); Maastricht University Medical Center (M.E. Kooi, R.J. van Oostenbrugge, W.H. Mess); Sint Antonius Ziekenhuis, Nieuwegein (S.C. Tromp); Sint Franciscus Gasthuis, Rotterdam (S.L.M. Bakker); Slo-tervaartziekenhuis, Amsterdam (N.D. Kruijff); Tergooi Ziekenhuizen Hilversum/Blaricum (J.R. de Kruijff); University Medical Center Utrecht (J. Hendrikse, G.J. de Borst); Viecuri Medisch Centrum, Venlo (B.J. Meems); Vlietland Ziekenhuis, Schiedam (J.C.B. Verhey); IJsselland Ziekenhuis, Capelle a/d IJssel (A.D. Wijnhoud); Zuyderland, Sittard/Heerlen (N.P. van Orshoven, A.H.C.M.L. Schreuder).

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, Maastricht, The Netherlands (Ethische Toetsingscommissie MUMC+, ref. number METC 09-2-082, December 7, 2009). All subjects gave their written informed consent.

Conflict of Interest Statement

J.E. Wildberger reports institutional grants from AGFA, Bard, Bayer, GE, Optimed, Philips, and Siemens outside the submitted work; and speakers Bureau: Bayer, Siemens outside the submitted work. F.H.B.M. Schreuder reports in-kind support for the conduction of a clinical trial by Swedish Orphan Biovitrum (Sobi). The authors declare that they have no competing interests.

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Funding Sources

This research was performed within the framework of the Center for Translational Molecular Medicine (www.ctmm.nl), project PARISK (grant 01C-202), and supported by the Dutch Heart Foundation. ME Kooi is supported by an Aspasia Grant 2018/SGw/00460457 from NWO. J. Hendrikse has received funding from the European Research Council under the European Union's Horizon 2020 Program (H2020)/ERC grant agreement n°637024. FHBM Schreuder is supported by the Dutch Heart Foundation (2019T060). M. Kassem is supported by an NWO VidW grant (VidW.1154.18.02L7637).

Author Contributions

Mohamed Kassem, Geneviève A.J.C. Crombag, Jens Stegers, and M. Eline Kooi contributed to the conception and design of the study. Mohamed Kassem, Geneviève A.J.C. Crombag, Madieke I. Liem, Eline Koorstra, Floris H.B.M. Schreuder, Dianne H.K. van Dam-Nolen, Carlo Lucci, Rob J. van der Geest, Mat J. Daemen, Anton F.W. van der Steen, Jeroen Hendrikse, Werner H. Mess, Daniel Bos, Joachim E. Wildberger, Robert J. van Oostenbrugge, Paul J. Nederkoorn, and M. Eline Kooi contributed to the acquisition of data and/or critical revision of the manuscript. Mohamed Kassem, Geneviève A.J.C. Crombag, Jens Stegers, Madieke I. Liem, and M. Eline Kooi contributed to the analysis of data, drafting the manuscript, and preparing the figures. Each author has approved the submitted version and has agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated and resolved.

Data Availability Statement

For ethical reasons, the raw data that we collected cannot be made publicly available. The study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, Maastricht, The Netherlands, under the condition that access to the data is granted only to (1) members of the research team, (2) the Medical Ethics Committee members who approved this study, and (3) authorized personnel of the Healthcare Inspectorate. Hence, participants did not consent to publicly archive their data. However, requests for anonymous data can be sent to Prof. Dr. ME Kooi at eline.kooi@mumc.nl.

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