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CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Antithrombotic treatment is associated with intraplaque haemorrhage in the atherosclerotic carotid artery: a cross-sectional analysis of The Rotterdam Study

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Aims Antithrombotic treatment plays a key role in stroke prevention, but their direct effects on the composition of carotid artery atherosclerotic plaques are unknown. To investigate the association of antithrombotic treatment with carotid artery plaque composition, with a specific focus on an intraplaque haemorrhage (IPH).

Methods and results From the population-based Rotterdam Study, 1740 participants with carotid atherosclerosis on ultrasound (mean age 72.9 years, 46.0 women) underwent magnetic resonance imaging of the carotid arteries to assess plaque composition. Information on the use of oral anticoagulants [vitamin K antagonists (VKA)] and antiplatelet agents (salicylates), including duration of use and dosage, was obtained from pharmacy records for all participants. We used logistic regression models to assess the association between the use of anticoagulants and antiplatelet agents, and the different plaque components adjusting for confounders. Current and past use of VKA [adjusted odds ratio (OR): 1.88, 95% confidence interval (CI): 0.74–4.75 and OR 1.89, 95% CI: 0.91–3.93] and antiplatelet agents (OR: 1.22, 95% CI: 0.91–1.62), and (OR: 1.23, 95% CI: 0.86–1.75) showed positive trend with a higher presence of IPH. Also, a longer duration of use was associated with a higher frequency of IPH (OR: 3.15, 95% CI: 1.23–8.05) for the use of VKA, and longer duration of the use for antiplatelet agents showed a positive trend (OR: 1.21, 95% CI: 0.88–1.67). We also found that higher levels of international normalized ratio above 2.97 for VKA (OR: 1.48, 95% CI: 1.03–2.15) and higher daily defined dosage than 1.0 for antiplatelet agents (OR: 1.50, 95% CI: 1.21–1.87) were related to a higher frequency of IPH. We found no association with lipid core or calcification.

Conclusions The use of antithrombotic treatment relates to a higher frequency of IPH in carotid atherosclerotic plaques.

Keywords Carotid artery • Vitamin K antagonists • Antiplatelet agents • Intraplaque haemorrhage • Atherosclerosis • Epidemiology

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Introduction

Atherosclerotic disease in the carotid artery is considered a key risk factor for ischaemic stroke. In recent years, considerable efforts have been put in the development of strategies to prevent the occurrence of both new and recurrent ischaemic strokes.[1–5] An important cornerstone of these strategies is the prescription of oral anticoagulants and antiplatelet agents, given their beneficial effect on lowering the risk of cardiovascular events, including strokes.[6] Despite this benefit of oral anticoagulants and antiplatelet agents,[7] their effects on the development or changes in already existing atherosclerotic carotid plaque are unknown.[8] Emerging technological development in magnetic resonance imaging (MRI) enables a detailed characterization of carotid plaque components like intraplaque haemorrhage (IPH), lipid core and calcification,[8–10] which play an important role in future thromboembolic events.[11–14] Recently, in a relatively small sample of symptomatic patients, it was highlighted that antithrombotic treatment may exert a potentially harmful effect on the composition of carotid atherosclerotic plaques.[8] Specifically, the use of antiplatelet agents was related to a higher presence of IPH, which is a plaque component that is known to be more prevalent in plaques that are prone to rupture.[8] However, several important questions on this topic remain as previous studies were in symptomatic patients with advanced atherosclerosis. First, the influence of using vitamin K antagonists (VKA), which is also frequently prescribed for prevention of cardiovascular events of cardiac origin like as atrial fibrillation, on the composition of carotid atherosclerosis remains unclear. Second, the duration and dosage of use of VKA or antiplatelet agents may substantially affect the carotid plaque composition but has not been studied before. Therefore, we investigated in a large sample of subjects with subclinical atherosclerosis from the Rotterdam Study, the associations between oral antithrombotic treatment and carotid plaque composition, with a special focus on IPH.

Methods

Study population

This study is embedded within a prospective population-based cohort, The Rotterdam Study.[15] Between the year 2007 and 2012 participants with carotid atherosclerosis were invited to undergo an MRI scan of the carotid arteries. Previously, participants were selected on the basis of a carotid artery ultrasound examination (intima-media thickness ≥2.5 mm in one or both carotid arteries) performed in all participants of the Rotterdam Study. From the 2666 invited participants, 684 did not undergo MRI scan, and 1982 did (74%). From them, 242 participants were excluded and 1740 were included in this study (*Figure 1*). The Rotterdam Study has been approved by the Medical Ethical Committee of the Erasmus MC and by the Dutch Ministry of Health, Welfare and Sports, implementing the 'Wet Bevolkings Onderzoek: ERGO (Population Screening Act: Rotterdam Study)'. All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Carotid scanning and analysis of plaque components

A 1.5 Tesla scanner (GE Healthcare, Milwaukee, WI, USA) with a dedicated bilateral phase-array surface coil (Machnet, Eelde, the Netherlands) was used to perform bilateral imaging of the carotid artery, with a standardized scanning protocol, which required an approximate total scanning time of 30 min. The protocol included four sequences in axial plane: a proton density weighted (PDw)-fast spin echo (FSE)-black blood (BB) sequence (in-plane resolution 130/160 × 130/128 = 0.8 × 1 cm); a PDw-FSE-BB with an increased in-plane resolution (in-plane resolution 130/224 × 130/160 = 0.5 × 0.8 cm); a PDw-echo planar imaging (EPI) sequence (in-plane resolution 130/160 × 70/160 = 0.8 × 0.4 cm); a T2-weighted-EPI sequence (in-plane resolution 130/160 × 70/160 = 0.8 × 0.4 cm) and two three-dimensional (3D) sequences: a 3D-T1-weighted (T1w)-gradient echo sequence (in-plane resolution 180/192 × 180/180 = 0.9 × 1 cm), and a 3 D phased-contrast magnetic resonance angiography (3D-PC-MRA) (in-plane resolution 180/256 × 180/128 = 0.7 × 1.4 cm).[16] More details of the scanning protocol, reading procedure, and reproducibility are described in detail elsewhere.[17] The images of the carotid were evaluated for the presence of three different plaque components: IPH, lipid core, and calcification. Calcification was defined as the presence of a hypointense region in the plaque on all sequences.[16,18,19] Intraplaque haemorrhage was defined as the presence of a hyperintense region in the atherosclerotic plaque on 3D-T1w-GRE.[20,21] Lipid core presence was defined as a hypointense region, not classified as IPH or calcification, in the plaque on PDw-FSE or PDw-EPI and T2w-EPI images or a region of relative signal intensity drop in the T2w-EPI images compared with the PDw-EPI images.[18,19,22] Two independent MRI readers, with 3 years of experience, not being aware of any of the clinical characteristics of the participants, including the medication recorded subjects as positive for the presence of any plaque component if the component was identified in one or both carotid arteries. Testing the intra-subject variability, 40 participants underwent a second MRI scan (average time between scans 15 ± 9 days).[17] For an interobserver reproducibility analysis, MRI examinations were selected randomly ($n = 50$) and read by a second independent observer with three years of experience. Further, using Cohens' Kappa statistics interobserver and an intra-scan agreement was calculated. The intra-subject agreement was good for all measurements. The Kappa value for the presence of IPH was 0.95 (95% CI 0.88–0.99); for lipid core was 0.85 (95% CI 0.74–0.96) and for calcification was 0.91 (95% CI

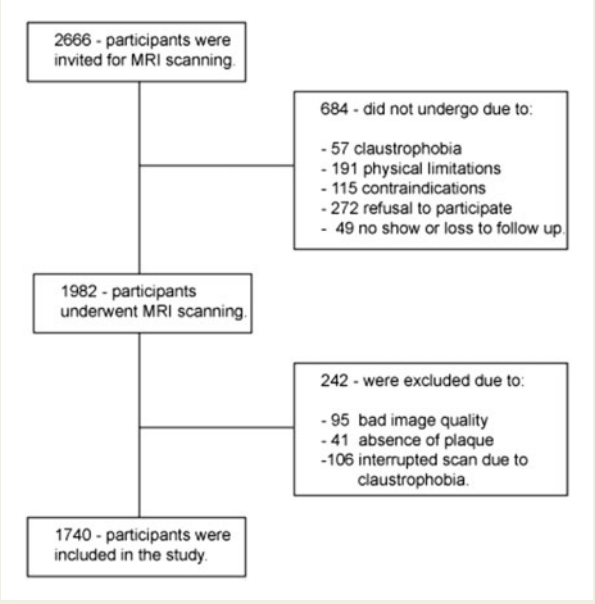


Figure 1 Flowchart of the study population.

0.82–0.99).[17] The interobserver agreement was good for all measurements. The Kappa value for IPH was 0.86 (95% CI 0.72–0.99); for lipid core presence 0.86 (95% CI 0.72–0.99) and for calcification 0.94 (95% CI 0.86–0.99).[17]

Assessment of antithrombotic treatment

Dispensing information for the VKA and antiplatelet agents [acetylsalicylic acid (ATC code B01AC06) and carbasalate calcium (ATC code B01AC08)] was obtained using a computerized platform linking the study database and the pharmacies in the study area. All prescriptions for VKA and antiplatelet agents from 1 January 1991 to 26 October 2012, included the product name of the drug, the anatomical therapeutic chemical code (ATC code), the amount dispensed, the prescribed dose regimen, and the date of dispensing.[23,24] The average measured international normalized ratios (INRs)[25] were obtained for VKA use and daily defined dosage (DDD) was obtained for antiplatelet agents use.[26] Among the antithrombotic users, we distinguished the main therapeutic indications such as atrial fibrillation, recent coronary or cerebrovascular events.

At the time of the MRI, all subjects were classified into one of the following mutually exclusive categories: 'current user' if the subject was an active user at time of MRI; 'past user' if the subject discontinued the use before the MRI scan date, or 'never user' if subject never used any of these drugs. We used tertiles for the duration of use to classify the use of VKA and antiplatelet agents. This resulted in the VKA duration of use ≤3 months; duration of use 3–11 months, duration of use >11 months, and for the antiplatelet agents' duration of use ≤30 months; duration of use 30–72 months, duration of use >72 months since the end of the last prescription episode. To facilitate direct dose-dependent relation between drugs from the same therapeutic drug group, we used the INRs[25] for the VKA use and a daily dose of antiplatelet agents expressed in DDD.[26] We created three categories of measured INR and DDD and compared them separately with never use. The INRs categories were set based on tertiles and antiplatelet DDD categories were set based on the median. Only five subjects, previously treated with VKA due to atrial fibrillation and with the recent coronary syndrome, were in concomitant use of dual therapy at the time of MRI and none in past use category. Considering the prolonged effect of anticoagulation medication, we have not reallocated any subject from past use into current use categories among VKA users as a minimum discontinuation period was 22 days but we reclassified three subjects in past use category, among antiplatelet agent users, to current use category since the minimum discontinuation period was 3–5 days.[25,27]

Other risk factors in the Rotterdam Study

Information on the other cardiovascular risk factors as relevant measurements was obtained by interview, physical examination, and blood sampling.[15] Among the other measures smoking status was categorized into never, the past, and current smoking, diabetes mellitus was defined as fasting blood glucose >6.9 mmol/L, nonfasting glucose >11.0 mmol/L, or use of glucose-lowering medication, systolic and diastolic blood pressure was measured using a random-zero sphygmomanometer on the right arm and two measurements were performed and the average of the two was used in the analyses. Body mass index was calculated based on weight in kilograms divided by height in metres squared. Serum total cholesterol and high-density lipoprotein levels were measured using standard laboratory techniques. We were able to consider the use of antihypertensive medication and statin use, which were obtained from pharmacy records.[15]

Statistical analysis

We used the means [standard deviations (SDs)], medians [interquartile ranges (IQRs)] and percentages to describe the distribution of continuous and categorical variables, respectively. To investigate the association between antithrombotic treatment and plaque components, IPH, lipid core, and calcification, a three-step statistical analysis approach was used. Initially, we prepared three models, using logistic regression, to assess the association of antithrombotic treatment (never, current, past) with the presence of each component in one or both carotid arteries. In the first model, we adjusted these analyses for age and sex and in second model we adjusted for other risk factors. Additionally, in model three for VKA users, we adjusted for the INRs levels. Further, as a second step, we examined whether the duration of antithrombotic treatment was associated with any of the plaque components. Third, we assessed whether the INRs levels for VKA and DDDs for antiplatelet agents were associated with each plaque component. Finally, we performed sensitivity analyses and stratified analyses. First, to address confounding by indication, we restricted analyses among subjects without known cardiovascular diseases (CVD), only by excluding the participants with known CVD history and performed the propensity-score matching for untreated and treated participants. Cardiovascular diseases were defined as known and verified the history of stroke, myocardial infarction or coronary heart disease. Second, we performed stratified analyses for sex and age below and above 70 years of age, to investigate whether associations are different between sex and age groups. Antithrombotic treatment is usually prescribed to subjects at risk for or with a history of CVD.

All analyses were carried out using IBM SPSS Statistical package version 21 (Chicago, IL, USA).

Results

The study population characteristics are provided in *Table 1*. The mean age of the population was 72.9 years (SD: 9.1 years) and 46.0% were women. At the time of MRI, a total of 6.8% of the participants was using VKA treatment and 29.9% used antiplatelet (salicylates) treatment. The median VKA use was 11 months (IQR 3–43 months), and median antiplatelet agents use was 72 months (IQR 30–123 months). The IPH was more frequently found in the users of antithrombotic treatment compared to never-users (*Table 2*).

Antithrombotic therapy and carotid plaque composition

Table 3 summarizes the associations of oral VKA and antiplatelet agents use with the three plaque components. Although not statistically significant, we found a trend that current and past use of VKA [adjusted odds ratio (OR): 1.88, 95% confidence interval (CI): 0.74–4.75 and OR 1.89, 95% CI: 0.91–3.93, respectively] (*Table 3*) and current and past use of antiplatelet agents (OR: 1.22, 95% CI: 0.91–1.62 and OR: 1.23, 95% CI: 0.86–1.75, respectively) related to a higher presence of IPH (*Table 3*). We found no associations between antithrombotic treatment with a lipid core or calcification.

Duration of use and dosage of antithrombotic therapy

The use of VKA for 3 months or less was not associated with the presence of IPH whereas the use of VKA for more than 3 months was significantly related to the presence of IPH. This relation became more prominent when we additionally adjusted for INRs levels

Table 1 Baseline characteristics of the study population ($n = 1740$)

Age (years)	72.9 ± 9.1
Women (%)	46.0
Smoking, current (%)	31.5
Diabetes mellitus (%)	14.4
Systolic blood pressure (mmHg)	145 ± 21
Diastolic blood pressure (mmHg)	80 ± 11
BMI (kg/m^2)	27.3 ± 3.5
Total cholesterol (mmol/L)	5.6 ± 1.0
HDL cholesterol (mmol/L)	1.4 ± 0.3
Use of antihypertensive medication (%)	39.3
Use of statins (%)	29.0
Vitamin K antagonists (%)	
Current	6.8
Past	9.0
Antiplatelet agents use (%)	
Current	29.9
Past	11.9
Wall thickness (mm)	3.2 ± 0.6
Degree of stenosis (%)	14.4 (0.0–26.8)
History of stroke (%)	6.3
History of coronary heart disease (%)	11.4

Values are presented as means (standard deviations) or median (interquartile ranges) for continuous variables and percentages for dichotomous or categorical variables.
BMI, body mass index; CHD, coronary heart disease; HDL, high-density lipoprotein; IPH, intraplaque haemorrhage.

Table 2 Presence of the components in the carotid artery plaque according to antithrombotic treatment

	IPH	Lipid core	Calcification
Vitamin K antagonists			
Never use	31.9	43.6	82.0
Current use	50.4	47.9	87.4
Past use	48.1	44.9	81.4
Antiplatelet agents			
Never use	28.6	43.8	78.7
Current use	42.5	44.4	87.9
Past use	44.4	44.0	86.0

Values are presented as percentages.
IPH, intraplaque haemorrhage.

(adjusted OR: 3.15, 95% CI: 1.23–8.05) (*Table 4*). The use of antiplatelet agents for less than or more than 30 months was not related to the presence of IPH (adjusted OR: 1.21, 95% CI: 0.88–1.67) (*Table 4*).

Furthermore, when considering the effect of INRs and DDDs, the dose-response relation was found in both groups. Among oral vitamin K antagonist users, INRs levels higher than 2.97 were significantly associated with the presence of IPH, whereas among the antiplatelet users DDDs levels higher than 1.0 were significantly associated with the presence of IPH (*Table 5* and *Figure 2*). When restricting our analyses only to subjects without a history of CVD, we found a prominent positive trend with IPH, among current and past users of VKA, and a positive trend with IPH among current and past users of antiplatelet agents (Supplementary material online, *Table S1*). Further, propensity-score matched analyses yielded similar results (Supplementary material online, *Table S2*).

Additionally, investigating for age differences, we found a more prominent association of VKA current use with IPH in the younger age group ≤70 for both drug groups (Supplementary material online, *Table S3*). Moreover, when investigating the sex differences, we found a prominent trend between VKA use and IPH in females compared to males and similar trend between antiplatelet agents use and IPH for both sexes (Supplementary material online, *Table S4*).

Discussion

In this large population-based sample of individuals with subclinical carotid atherosclerosis, we observed that current and past use of antithrombotic treatment is associated with IPH in the carotid artery plaques. Moreover, we found that longer duration of use and higher dosages of antithrombotic treatment were related to a higher frequency of IPH.

The association of antithrombotic treatment with IPH in atherosclerotic plaques has been studied before, but only in high risk, symptomatic patients. In these studies, it was found that the use of antithrombotic treatment related to the presence of IPH.[8,28,29] Moreover, a histopathological study on carotid endarterectomy specimens demonstrated an effect of antithrombotic treatment on the presence of IPH, in particular of VKA.[28] Apart from this, the earlier study also found that before surgical intervention the users of antiplatelet agents, suffered a higher presence of multiple haemorrhages in plaques (68% compared with 17%) compared with patients who did not use.[29] Finally, a recent report from the PARISK-study highlighted an association of antiplatelet agents with IPH.[8] Our results further elucidate the effect of antithrombotic treatment on IPH in carotid atherosclerosis on multiple levels and corroborate findings of studies with symptomatic high-risk patients. First, we demonstrated that already in the subclinical phase of carotid atherosclerosis there is a prominent association of antithrombotic treatment. Second, duration of use is important with regard to the presence of IPH. Third, independently of other risk factors higher levels of INRs and DDDs influence on the presence of IPH.

One of the main mechanisms underlying the relation of antithrombotic treatment with a higher presence of IPH may be the leakage of neovessels (neovascularization) in the plaque under influence of antithrombotic treatment.[8] Histological observations suggest that IPH arises from the adventitia,[30] as inward sprouting neovessels towards the plaque and neovessels are considered immature and highly susceptible to leakage.[31] In this context, we hypothesize that antithrombotic treatment may predispose persons to extended leakage from neovessels, due to their antithrombotic effects. Additionally, our findings may be explained through prior histopathological evidence, which suggests that oral VKA relate to haemorrhage from the neovessels within the plaque whereas antiplatelet agents increase densities of these neovessels.[32,33] Similarly, a capillary bleeding in

Table 3 Association between antithrombotic treatment and carotid artery plaque composition

	IPH, OR (95% CI)	Lipid core, OR (95% CI)	Calcification, OR (95% CI)
Vitamin K antagonists			
Model 1			
Never use	Ref	Ref	Ref
Current use	1.48 (1.00–2.19)	1.01 (0.69–1.49)	0.96 (0.54–1.71)
Past use	1.55 (1.10–2.19)	0.97 (0.69–1.36)	0.66 (0.42–1.03)
Model 2			
Never use	Ref	Ref	Ref
Current use	1.34 (0.87–2.06)	1.06 (0.70–1.59)	0.88 (0.48–1.61)
Past use	1.46 (1.01–2.12)	0.99 (0.70–1.41)	0.59 (0.37–0.94)
Model 3			
Never use	Ref	Ref	Ref
Current use	1.88 (0.74–4.75)	0.87 (0.36–2.11)	1.09 (0.33–3.53)
Past use	1.89 (0.91–3.93)	0.85 (0.42–1.73)	0.70 (0.28–1.77)
Antiplatelet agents use			
Model 1			
Never use	Ref	Ref	Ref
Current use	1.46 (1.16–1.84)	0.92 (0.74–1.15)	1.51 (1.10–2.07)
Past use	1.57 (1.14–2.17)	0.94 (0.69–1.29)	1.19 (0.77–1.84)
Model 2			
Never use	Ref	Ref	Ref
Current use	1.22 (0.91–1.62)	1.00 (0.77–1.30)	1.07 (0.74–1.54)
Past use	1.23 (0.86–1.75)	0.91 (0.66–1.27)	1.03 (0.65–1.61)

Model 1 – adjusted for age, sex. Model 2 – model 1 + smoking, diabetes mellitus, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, high-density lipoprotein, antihypertensive medication use, statin use, and carotid wall thickness. Model 3 – model 2+ average INR.
CI, confidence interval; INR, international normalized ratio; IPH, intraplaque haemorrhage; OR, odds ratios.

Table 4 Association between duration of use of antithrombotic treatment and intraplaque haemorrhage in the carotid artery

	IPH		
	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
Vitamin K antagonists			
Never use duration	Ref	Ref	Ref
≤3 months	0.81 (0.48–1.37)	0.76 (0.43–1.35)	1.21 (0.51–2.86)
3–11 months	1.63 (0.99–2.69)	1.62 (0.96–2.76)	2.54 (1.11–5.82)
>11 months	1.95 (1.35–2.82)	1.74 (1.16–2.60)	3.15 (1.23–8.05)
Antiplatelet agents use			
Never use duration	Ref	Ref	
≤30 months	1.30 (0.92–1.83)	1.14 (0.78–1.66)	
30–72 months	1.54 (1.10–2.16)	1.32 (0.91–1.92)	
>72 months	1.57 (1.21–2.04)	1.21 (0.88–1.67)	

Model 1 – adjusted for age, sex. Model 2 – model 1 + smoking, diabetes mellitus, systolic blood pressure, diastolic blood pressure, body mass index, total cholesterol, high-density lipoprotein, antihypertensive medication use, statin use, and carotid wall thickness. Model 3 – model 2+ average INR.
CI, confidence interval; INR, international normalized ratio; IPH, intraplaque haemorrhage; OR, odds ratios.

humans has been found in patients using coumarin-type anticoagulation.[34] On the other hand, animal studies exhibited that capillary dilation and permeability, or capillary bleeding, increase when using coumarin-type anticoagulants.[35–37] Although VKA inhibit the vitamin K conversion cycle and salicylates inhibit the platelet aggregation and induce vasodilation, both drugs may contribute similarly with their effects in regard to IPH formation.[25,27]

These findings seem paradoxical to current knowledge as the goal of antithrombotic treatment is to prevent cardiovascular events. Of note is that the beneficial effect of antithrombotic treatment[7] is well

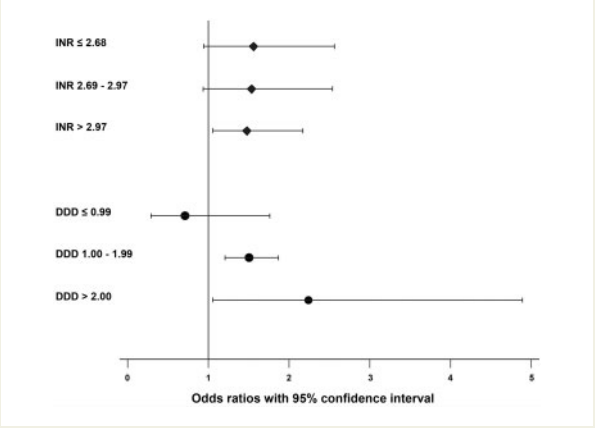
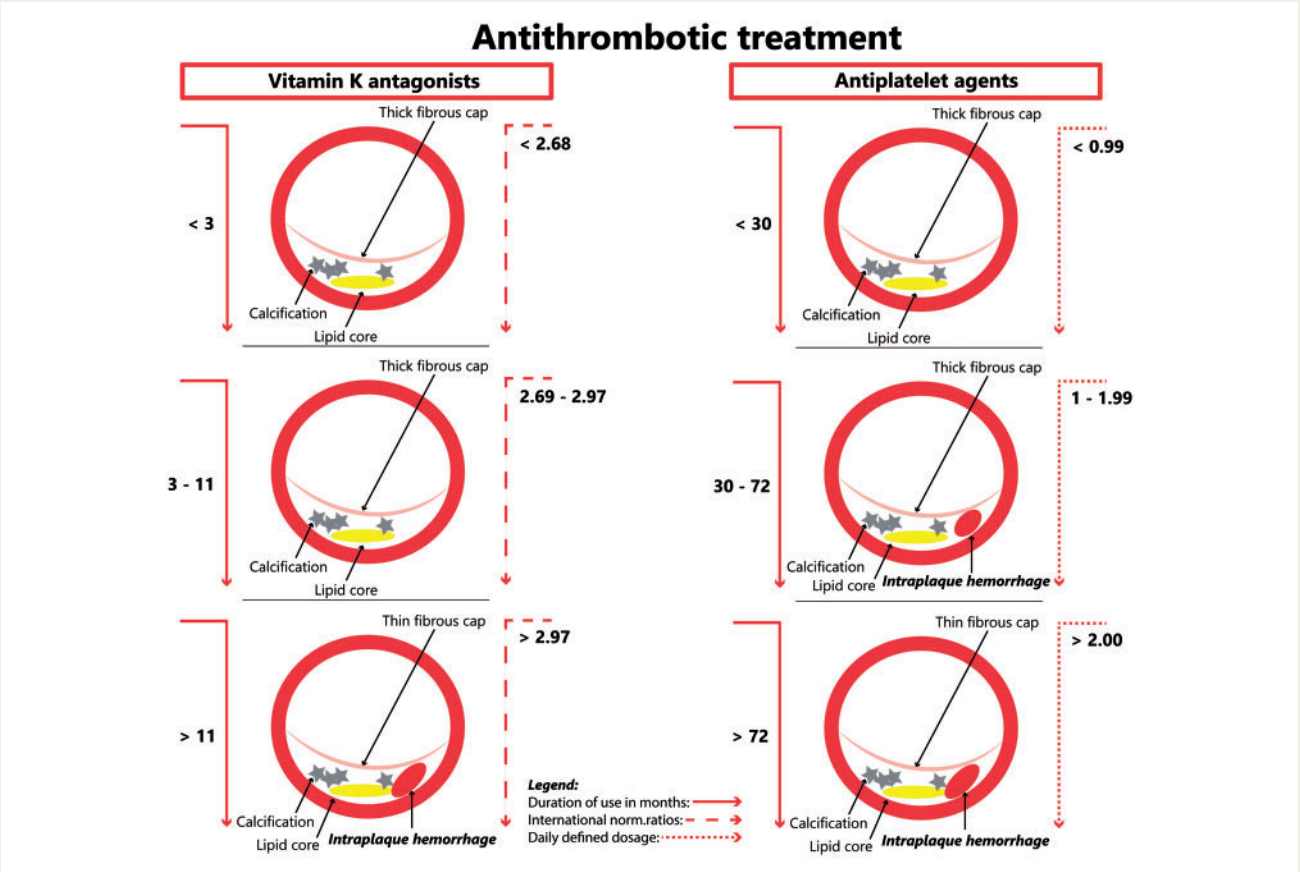


Figure 2 Association of antithrombotic treatment with intraplaque haemorrhage, according to international normalized ratios for vitamin K antagonists and daily defined dosage for antiplatelet agents. Values on the *y*-axis represent the odds ratios and 95% confidence interval. The values are adjusted for age and sex. The *P*-trend in both groups <0.001.

Table 5 Association of antithrombotic treatment with intraplaque haemorrhage, according to international normalized ratios for vitamin K antagonists and daily defined dosage for antiplatelet agents

	IPH, OR (95% CI)
Vitamin K antagonists	
INR	
≤2.68	1.56 (0.94–2.56)
2.69–2.97	1.54 (0.93–2.54)
>2.97	1.48 (1.03–2.15)
Antiplatelet agents	
DDD	
≤0.99	0.71 (0.29–1.76)
1.00–1.99	1.50 (1.21–1.87)
>2.00	2.24 (1.03–4.87)

Values are adjusted for age and sex.
CI, confidence interval; INR, international normalized ratio; IPH, intraplaque haemorrhage; OR, odds ratios.



Take home figure Duration and dosage of use of antithrombotic treatment play important role in the presence of intraplaque haemorrhage (IPH) in the atherosclerotic plaque of the carotid artery.

documented under medical conditions such as ischaemic cardiovascular or cerebrovascular diseases.[6,38,39] Yet, our findings emphasize that antithrombotic treatment should be used with care and in low dosage[7] and not prescribed unless the clinical benefits outweigh the risks. With regard to the clinical effects of antithrombotic treatment, a meta-analysis of two large trials (International stroke trial and Chinese acute stroke trial), revealed that antithrombotic treatment reduced the risk of ischaemic stroke only in the 6–12 weeks directly after the stroke, but established no beneficial effect after this period.[40] Due to the observational nature of the study, the findings should be regarded as hypothesis generating and further confirmation is required.

The major strengths of the current study include the long follow-up time, the duration and dosage of exposure to antithrombotic treatment for all study participants, and the standardized MRI-based assessment of carotid atherosclerotic plaques. This is the first population-based study to investigate the association of antithrombotic treatment with plaque components in the carotid artery within a relatively large study sample. Moreover, the MRI enabled to characterize in great detail each specific component of the carotid plaque. Nonetheless, some limitations of our study should also be taken into account. First, we did not have data on the use of new oral anticoagulants (NOAC's). Second, as in many observational studies investigating the effect of specific medication, we should acknowledge the issue of confounding-by-indication given that antithrombotic treatment is more often prescribed to persons with an increased risk of CVD. However, sensitivity analysis did not show prominent differences in the results. Third, although salicylates are prescribed by doctors, such drugs are available 'over the counter', and used for other therapeutic indications for e.g. like analgesics. Fourth, the cross-sectional design limits our ability to draw causal inferences between antithrombotic treatment and IPH.

Conclusion

The use of antithrombotic treatment relates to a higher frequency of IPH in carotid atherosclerotic plaques. Further studies are warranted to replicate this finding in a longitudinal design.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: O.H.F. works in ErasmusAGE, a centre for aging research across the life course funded by Nestlé Nutrition (Nestec Ltd); Metagenics Inc.; and AXA. The other authors report no potential conflicts of interest.

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