Treatment with prophylactic oral anticoagulants and the risk of mortality in COVID-19 patients: a nationwide cohort study

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Shareable abstract (@ERSpublications)
In individuals with SARS-CoV-2, pre-existing treatment with OAC was not associated with prophylactic benefits in the prevention of hospital admission, ICU admissions or death. Prescription patterns should remain unchanged. https://bit.ly/40Gafwp

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Abstract

Background Venous thromboembolism has been reported in patients with coronavirus disease 2019 (COVID-19). It remains unclear if premorbid use of prophylactic oral anticoagulation, for reasons other than COVID-19, protects against death in patients with COVID-19. The aim of this study was to estimate if the risk of all-cause mortality, hospital admission or intensive care unit (ICU) admission for individuals with verified SARS-CoV-2 was lower if patients used oral anticoagulant (OAC) therapy prior to a positive COVID-19 status.

Methods Data were obtained using national health registries. Cohort entry was the day of a positive SARS-CoV-2 test, and individuals were followed for 14 days or until death or hospital admission. Adjusted Cox proportional hazard regressions and competing risk analyses were used to estimate the risk of all-cause mortality, hospital admission and ICU admission in OAC users compared with patients with no use of OAC.

Results In this nationwide cohort study a total of 244 522 individuals were included (median age 35 years (interquartile range 21–52); 124 095 (51%) female), among whom 3710 (1.5%) were OAC users. In the adjusted Cox regression cohort, there was no difference in risk of all-cause mortality in OAC *versus* non-OAC users. (hazard ratio (HR) 1.13, 95% CI 0.99–1.30). Hospital admission risk (HR 1.11, 95% CI 1.02–1.20) was slightly increased in OAC users, and there was no difference between the groups regarding the risk of ICU admission (HR 0.96, 95% CI 0.74–1.24).

Conclusions In individuals with confirmed SARS-CoV-2, pre-existing treatment with OAC was not associated with prophylactic benefits in the prevention of hospital admission, ICU admissions or death. Prescription patterns should remain unchanged.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread and infected nearly 596 million individuals globally, resulting in almost 6.5 million deaths [1]. The disease has been associated with increased risk of thrombosis [2, 3]. Increased neutrophil-to-lymphocyte ratio, high expression of inflammatory cytokines and thrombosis are observed in hospitalised COVID-19 patients [4]. This is in accordance with previous knowledge that inflammatory cytokines and delayed neutrophil apoptosis are associated with thrombosis [5]. SARS-CoV-2 seems to induce platelet activation, endothelial dysfunction, excessive inflammation and stasis, causing patients to be predisposed to thrombosis [4, 6, 7]. The World Health Organization and the US Centres for Disease Control and Prevention recommend a prophylactic dose of unfractionated heparin or low-molecular-weight heparin for the prevention of thrombosis in hospitalised adults and adolescents with severe COVID-19 disease [8, 9].

Complicated COVID-19 with arterial oxygen desaturation, hospital admission, intensive care unit (ICU) admission and death may be more frequent among COVID-19 patients who suffer from pulmonary embolisms. It is unclear whether patients who, for other indications, are on regular oral anticoagulation treatment are protected against complicated COVID-19 due to the prophylactic effect against venous thromboembolism. Some studies have been conducted on the subject, with contradicting conclusions [10–17].

The aim of the current study was to evaluate among individuals with verified SARS-CoV-2 whether premorbid treatment with oral anticoagulant therapy (OAC) for other indications was associated with a lower risk of all-cause mortality, hospital admissions and ICU admission.

Materials and methods

Study design

This was a nationwide observational cohort study comprising all individuals with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 in Denmark from 27 February 2020 (first confirmed case of SARS-CoV-2 in Denmark) to 1 March 2021. Cohort entry was defined as the day of testing positive for SARS-CoV-2. The follow-up period for all outcomes was 14 days. This period was chosen due to the risk of acute myocardial infarction and stroke, which were reported to be highest during this interval [18]. For all-cause mortality, individuals were followed until death or for 14 days, whichever came first. For hospital admission individuals were followed until admission to hospital (>12 h), death or 14 days, whichever came first. For ICU admission individuals were followed until admission to ICU, death or 14 days, whichever came first. OAC was the exposure of interest. Primary outcome was all-cause mortality. Secondary outcomes were hospital admission for more than 12 h and admission to ICU.

Data sources

We collected data from several nationwide registries and linked these through a unique identification number given at birth or immigration. This ensures complete follow-up. Data were obtained from the following registries:

- The Danish National Patient Registry contains information on all hospital admissions in Danish hospitals and outpatient clinic visits. Each visit has a primary diagnosis, and some have one or more secondary diagnoses which are coded according to International Classification of Diseases, 10th revision Clinical Modification Code (ICD-10) [19].
- The Danish National Prescription Registry contains information on filled prescriptions in all Danish pharmacies. The registry includes information on the date of dispensation, strength of drug, number of tablets and the Anatomical Therapeutic Chemical classification of each prescription [20].
- The Danish Central Personal Registry contains data on citizens of Denmark, including vital status, sex and age.
- The Danish Microbiology Database contains information on laboratory analyses, and registration of the national SARS-CoV-2 surveillance data carried out by the Danish Departments of Clinical Microbiology and Statens Serum Institut.

Study population

The study population was individuals residing in Denmark who had a positive SARS-CoV-2 PCR test result. Exclusion criteria were individuals with malignant neoplasm (ICD-10 codes: C00–C97) within 5 years prior to cohort entry, and individuals who had a bleeding diagnosis (ICD-10 codes: K920-22, N930-939, R319A, R040-049, I60-62, H313) within 1 year prior to cohort entry. The cohort was classified into: anticoagulant users (exposure group) and non-anticoagulant users (control group) (figure 1). Use of anticoagulants was defined as pre-existing anticoagulant therapy with the following treatments at cohort entry: direct oral anticoagulants (DOACs): apaxiban, edoxaban, dabigatranetexilat, rivaroxaban and the vitamin K-antagonist warfarin (supplementary table S2). We defined individuals with pre-existing anticoagulant therapy as individuals who had medication available at cohort entry. We had information on the date of dispensation, strength of drug and number of tablets but not the prescribed dosage of the drug. Therefore, we used the date of collected prescriptions and calculated whether the patients had tablets available at the time of the positive SARS-CoV-2 PCR test result. We expected that the treatment followed the Danish national guidelines recommended dosages: apixaban and dabigatranetexilat – two tablets a day, in which all the doses were available for the medication; edoxaban and rivaroxaban: one tablet a day, in which all the doses were available for the medication. For warfarin we calculated the dosage of each prescription by calculating the mean dose given for three consecutive prescriptions.

Comorbidities were classified according to the Charlson comorbidity index [21]. Comorbidities were based on diagnoses from The Danish National Patient Registry. Diagnoses were from Danish hospitals and

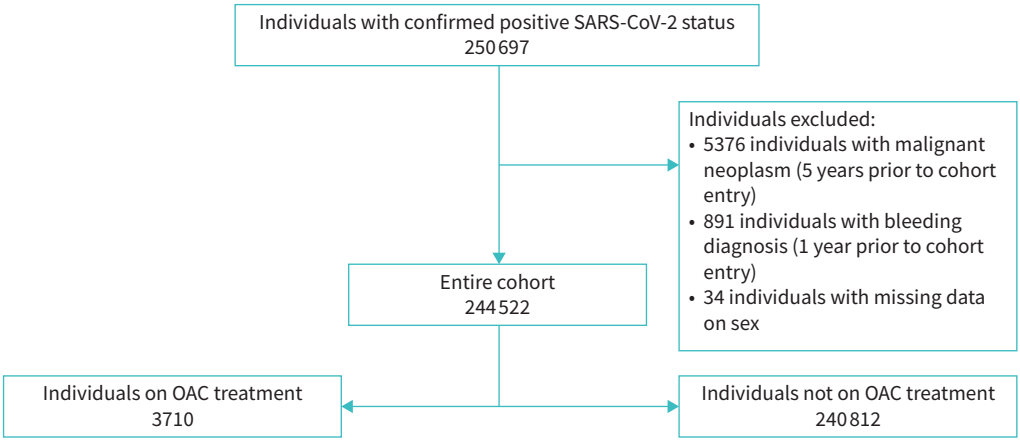

FIGURE 1 Study flowchart. OAC: oral anticoagulant therapy.

outpatient clinic visits, respectively, from 1977 until baseline and from 1995 until baseline, coded according to ICD-10 (illustrated in supplementary table S1).

Comorbidities or groups of comorbidities with an occurrence of equal to or >5% within the study population were included. Comorbidities were grouped as follows: pulmonary disease as defined per the Charlson comorbidity index, and in addition, interstitial pulmonary diseases were included. Cardiovascular disease includes peripheral vascular disease, ischaemic heart disease, cerebrovascular disease and heart failure. Liver disease includes mild, moderate and severe liver diseases. Furthermore, diabetes with and without complications, dementia and systemic connective tissue disorders were included.

Analyses

For descriptive statistics, continuous variables were presented as median values and interquartile range. Categorical variables were reported as frequencies and proportions. For continuous variables, testing was done using a t-test or Wilcoxon rank sum test, depending on the distribution of data. For categorical variables, comparison was done using a Chi-square test. If the expected number of observations was below 5, Fisher's exact test was used.

Adjusted Cox proportional hazards regression models were used to assess the risk of all-cause mortality, hospital admission and ICU admission. For the admission outcomes, individuals dying before admission were censored. The models were adjusted for age, sex, possible confounding diagnoses based on previous literature in the field [22–24] and suspected confounding diagnoses: cardiovascular diseases, chronic respiratory diseases, diabetes mellitus, chronic renal disease, systemic connective tissue disorders, dementia, mechanic aortic valve, thrombophilia and previous venous thromboembolism (supplementary table S1). The threshold for statistical significance was set at 5%. The Cox models were tested for the assumptions of proportional hazards and linearity. If linearity was not achieved, the variable was converted to a categorical variable.

The adjusted number needed to harm (NNH) was calculated as described by Altman [25].

For sensitivity analyses, competing risk regressions were performed. Based on the cumulative incidence function, we applied a direct binomial regression for competing risks data with censoring adjustment (using a logit link) [26] to both the hospital and ICU admission outcomes, respectively, at the 14 days timepoint. Both regression models were subject to the same adjustment sets as previously described. If the independent censoring assumption was violated, the model was fitted to allow for censoring weights to depend on the covariates in question.

As explorative analysis, a Cox proportional hazards regression model was fitted to the outcome of admissions with bleeding, using the aforementioned adjustment sets and model validations.

As explorative analysis, a propensity score-matched population was conducted. The population was matched using a Greedy matching algorithm with a 1:3 case:control ratio. Variables used for the matching

were the same variables used to adjust the Cox proportional hazards regression analysis. The matching was done based on the logit of the propensity score, with a caliper of 0.25. An extended common support region was used. Unadjusted Cox proportional hazards regression models were performed in the propensity score-matched population.

Statistical analyses were performed using SAS Analysis Software version 9.4 (SAS Institute, Cary, NC, USA) apart from the predicted survival plot and binomial regression model with censoring adjustment, which were performed using R 4.2.2 with the timereg (version 2.0.5), survival (3.5-0) and binreg function of the mets (version 1.3.2) packages.

Scripts used for analyses can be accessed at GitHub *via* https://gist.github.com/SALTARAIHI/1882f2d18ec9915c2f1588953cbb5a5b

Results

Descriptive analyses

A total of 244 522 individuals with PCR-confirmed SARS-CoV-2 were included in the study, of whom 3710 (44.1% female) were OAC users. Baseline characteristics are presented in table 1. The group receiving OAC were older with a median age of 77.0 years (67–85) *versus* 35 years (21–52) and had a higher proportion of males (55.9% *versus* 49.1%). Furthermore, the OAC group had a higher prevalence of cardiovascular disease, pulmonary disease, chronic kidney disease and diabetes (for p-values see table 1).

Outcomes

The study had a 100% follow-up on the primary and secondary outcomes.

During the 14-day follow-up period, a total of 1370 (0.56%) patients died. Of these, 319 (23.28%) deaths occurred in the OAC group. No difference was observed in risk of all-cause mortality between OAC users *versus* non-OAC users (hazard ratio (HR) 1.13, 95% CI 0.99–1.30) (table 2, figure 2).

In total, 7094 (2.90%) individuals experienced a hospital admission during the follow-up period, of whom 789 (11.12%) were in the OAC group. OAC use was associated with a slight increased risk of hospital admission (HR 1.11, 95% CI 1.02–1.20). ICU admission occurred in 845 patients (0.35%) in the whole population; 73 (8.64%) in OAC users. No difference was observed in the risk of ICU admission between OAC users and non-OAC (HR 0.96, 95% CI 0.74–1.24). The results of risk of all outcomes in a propensity score-matched population can be seen in supplementary tables S10 and S11.

TABLE 1 Demographic and clinical characteristics of the study population at baseline

	Entire cohort[#]		p-value
	OAC users	Non-OAC users	
Patients n	3710	240 812	
Male sex, n (%)	2075 (55.9)	118 352 (49.1)	<0.0001
Age years			
Mean±SD	74.8±14.2	36.9±20.1	<0.0001
Median (interquartile range)	77.0 (67.0–85.0)	35.0 (21.0–52.0)	
Previously known diagnosis, n (%)			
Pulmonary disease	599 (16.1)	10 168 (4.2)	<0.0001
Cardiovascular disease	1707 (46.0)	8193 (3.2)	<0.0001
Renal disease	265 (7.1)	1221 (0.5)	<0.0001
Dementia	292 (7.9)	1443 (0.6)	<0.0001
Systemic connective tissue disorder	190 (5.1)	1688 (0.7)	<0.0001
Diabetes mellitus	641 (17.3)	5981 (2.5)	<0.0001
Liver disease	52 (1.4)	1709 (0.7)	<0.0001
Venous thromboembolism	443 (11.7)	972 (0.4)	<0.0001
Mechanical aortic valve	225 (6.1)	210 (0.1)	<0.0001
Thrombophilia	34 (0.9)	38 (0.0)	<0.0001
Oral anticoagulant use, n (%)			
DOAC	2946 (79.4)	0 (0.0)	<0.0001
Warfarin	795 (21.4)	0 (0.0)	<0.0001

OAC: oral anticoagulant therapy; DOAC: direct oral anticoagulant therapy. [#]: n=244 522.

TABLE 2 Cox regression hazards estimates for risk of death, hospital admission and ICU admission with use of oral anticoagulation

Outcome	Cox regression hazards, OAC *versus* non-OAC use				Competing risk analysis, OAC *versus* non-OAC use	
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
All-cause death	20.53 (18.10–23.26)	<0.0001	1.13 (0.99–1.30)	0.07		
Hospital admission >12 h	9.1 (8.45–9.80)	<0.0001	1.11 (1.02–1.20)	0.02	1.11 (1.00–1.23)	0.05
ICU admission	6.34 (4.99–8.06)	<0.0001	0.96 (0.74–1.24)	0.74	0.95 (0.72–1.26)	0.74

Cox regression hazards adjusted for: cardiovascular diseases, chronic respiratory diseases, diabetes mellitus, chronic renal disease, systemic connective tissue disorders, dementia, mechanical aortic valve, thrombophilia and previous venous thromboembolism. Competing risk analyses, for hospital admission and ICU admission: variables adjusted for same variables as for Cox regression hazards. Parameter for the adjusting variables can be seen in supplementary tables S4–S8. OAC: oral anticoagulant therapy; HR: hazard ratio; OR: odds ratio; ICU: intensive care unit.

The NNH for death between the OAC and the non-OAC groups was 1769 (95% CI 793–∞). NNH regarding hospital admission was 352 (95% CI 194–1935). NNH regarding ICU admission was −7800 (95% CI (−1200)–1300).

Sensitivity analyses

Applying the binomial regression model for competing risk data revealed an odds ratio (OR) for hospitalisation in the OAC group of 1.11 (95% CI 1.00–1.23). For ICU admission the OR was 0.95 (95% CI 0.72–1.26).

Explorative analyses

A total of 39 (0.02%) patients were hospitalised with a bleeding episode in the study period, with 4 (10.26%) in the OAC group. OAC use was not associated with admissions due to bleeding in the study period (HR 1.35, 95% CI 0.41–4.45) (supplementary table S9).

Discussion

In this nationwide observational cohort study with complete follow-up for all outcomes, we did not observe prophylactic benefits in the prevention of death, hospital admission or admission to an ICU associated with pre-existing treatment with OAC. There was no significant difference between OAC users

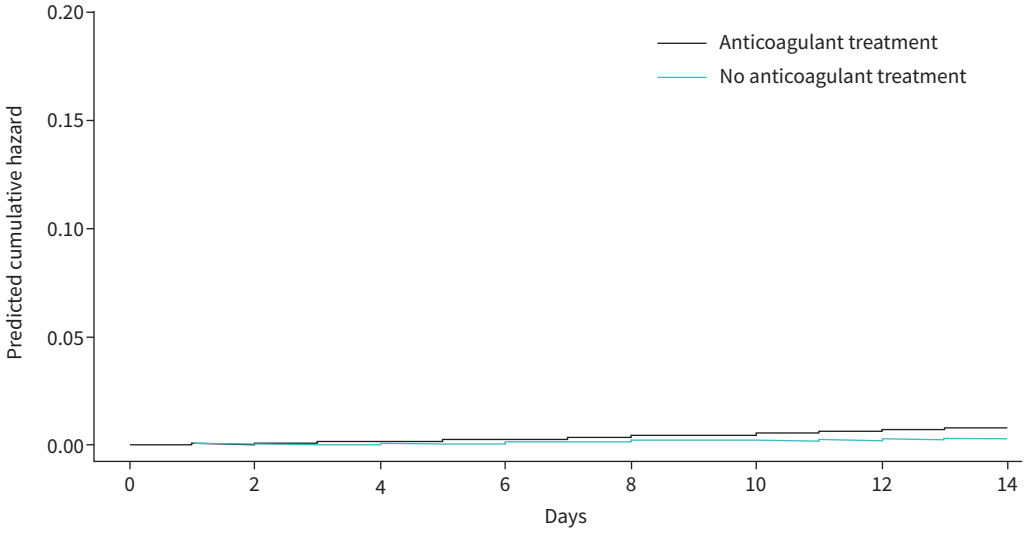

FIGURE 2 Predicted cumulative hazard for all-cause mortality (hazard ratio 1.13, 95% CI 0.99–1.30).

and non-OAC users in the risk of death and ICU admission in either Cox proportional hazards regressions or the competing risk sensitivity analyses. Whereas the risk of hospital admission was slightly increased for OAC users in the Cox proportional hazards regression, this was attenuated to just below statistical significance in the competing risk sensitivity analysis. The reason behind the lack of noteworthy difference we observe in our study between OAC users and non-OAC users in death and hospital admission are difficult to deduce. In exploratory analyses, we did not find increased risk of admissions due to bleeding in the OAC group (supplementary table S9). However, it could be due to residual confounding, even though we adjusted for known and suspected confounders.

Amidst the pandemic there has been a focus on controlling the hypercoagulative state that has been seen in hospitalised COVID-19 patients, and therefore guidelines on usage of heparins have been published [8, 9, 27, 28]. Data on oral anticoagulants as a prophylactic drug are lacking, and those published have varied results.

Some smaller studies and case series have indicated that pre-existing oral anticoagulant treatment was beneficial for COVID-19 patients [10–12, 29]. A study involving patients admitted to medical wards of French hospitals and a study simulating an intention-to-treat clinical trial both found that OAC treatment in COVID-19 patients was associated with a better prognosis [10, 11]. Furthermore, two cohort studies have concluded that COVID-19 patients on OAC medication may have a lower risk of death compared to COVID-19 patients not on OAC [12, 29].

Conversely, some studies had results in congruence with the findings in this study. Several studies compared patients taking OAC medication with patients who did not take OAC medication at the time of infection with SARS-CoV-2 and concluded that there was no noteworthy difference in mortality risk [13–15]. Several large cohort studies had the same findings, including a Swedish nationwide cohort study and a large cohort study with data from TriNetx [16, 17]. Furthermore, a recently published randomised study did not demonstrate an impact of rivaroxaban on disease progression in adults with mild COVID-19 [30].

Strengths and limitations

The large nationwide cohort we follow in our study is among the strengths of our study. Furthermore, we had access to complete collection of OAC prescriptions in the cohort. Additionally, we had complete (100%) follow-up for death, hospital admission and ICU admission, and all individuals included had confirmed SARS-CoV-2. However, there were some limitations to our study design. First, information about OAC medication usage was obtained through prescriptions collected. We did not have information about patient adherence to treatment, though this is assumed. However, we did include patients who had medication available at the time of confirmed SARS-CoV-2. Additionally, we assumed DOAC prescriptions followed the Danish national guidelines on recommended dosages.

Second, non-OAC users were generally more healthy participants, and although we adjusted for known and suspected confounders, residual confounding may be present. Atrial arrythmias were not adjusted for, as they are not necessarily registered in the Danish National Patient Registry, since they are often treated in private primary care. However, we have adjusted for the remaining main indications for anticoagulation, as we have complete data on these, as they are treated in the hospitals. These include previous venous thromboembolism and mechanical aortic valve. Furthermore, data on risk factors such as lifestyle (*e.g.* physical activity, alcohol consumption) were not available. Third, we did not have data on SARS-CoV-2 vaccination status; however, vaccination rollout started in Denmark on 27 December 2020, and at the end of our study period <4.5% of the Danish population had completed the initial vaccination protocol [31]. This was mainly health workers and nursing home residents [31], and thus, given the small number of vaccinated individuals in the population during the study period, we do not believe this could have influenced the main signal of the study. Fourth, we did not have data on causes of death, preventing us from investigating specific causes of death, especially bleeding. However, in exploratory analyses, we did not find any increase in admissions due to bleeding in the OAC group. Finally, the non-experimental nature of the study limits the capability to infer causation, though a protocol on the plan and study design preceding collection of data and analyses was made.

In conclusion, our data did not indicate any prophylactic benefits in preventing death or hospital admission associated with pre-existing treatment with oral anticoagulants. However, we did notice a statistically significant, but clinically not meaningful, increased risk of hospital admission among OAC users. Thus, our study does not support the use of oral anticoagulants as prophylaxis against mild COVID-19 to prevent COVID-19 complications. Importantly, our data do not indicate that ongoing anticoagulant therapy for

other indications should be stopped during COVID-19 episodes. Neither do our data eliminate the possible benefit of other anticoagulants such as heparins in COVID-19 patients.

Provenance: Submitted article, peer reviewed.

Informed consent statement: The study has been approved by the Danish Data Protection Agency. In Denmark, retrospective use of register data does not require ethical approval or patient consent.

Data availability statement: We believe that knowledge sharing increases the quantity and quality of scientific results. Sharing of relevant data will be discussed within the study group upon reasonable request.

Author contributions: Conceptualisation, P. Sivapalan and J-U. Jensen; methodology, S. Altaraihi, P. Kamstrup, P. Sivapalan and J-U. Jensen; software, S. Altaraihi and P. Kamstrup; formal analysis, S. Altaraihi and P. Kamstrup; investigation, S. Altaraihi, P. Kamstrup, P. Sivapalan, J. Eklöf and J-U. Jensen; resources, P. Sivapalan, J. Eklöf and J-U. Jensen; data curation, S. Altaraihi, P. Kamstrup and P. Sivapalan; writing (original draft preparation), S. Altaraihi; writing (review and editing), S. Altaraihi, P. Kampstrup, J. Eklöf, N. Dyrby Johansen, T. Biering-Sørensen, P. Sivapalan and J-U. Jensen; visualisation, S. Altaraihi and P. Kamstrup; supervision, P. Kamstrup, P. Sivapalan, J. Eklöf and J-U. Jensen; project administration, P. Kamstrup, P. Sivapalan, J. Eklöf and J-U. Jensen; funding acquisition, J-U. Jensen and P. Sivapalan. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: S. Altaraihi, P. Kamstrup, J. Eklöf, N. Dyrby Johansen, P. Sivapalan and J-U. Jensen have no conflict of interest. T. Biering-Sørensen received speaker payments from Bayer, Sanofi Pasteur, GSK and Novartis; is on advisory boards for Sanofi Pasteur, Amgen and GSK; received research grants from GE Healthcare and Sanofi Pasteur; and is a steering committee member in trials financed by Amgen, Sanofi Pasteur and Boston Scientific Corporation.

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