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Aspirin and renal insufficiency progression in patients with atrial fibrillation and chronic kidney disease☆

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ABSTRACT

Background: In experimental models, thromboxane (Tx)A_2 reduced renal perfusion and accelerated renal failure. The aim of the study was to investigate the association between the use of aspirin, which inhibits TxA_2 production, and the incidence of an estimated Glomerular Filtration Rate (eGFR) <60 and <45 ml/min/1.73 m^2 in patients with atrial fibrillation (AF) and chronic kidney disease (CKD).
Methods: Prospective multicentre observational cohort study including 800 anticoagulated AF patients; CKD was defined as an eGFR <90 ml/min/1.73 m^2 by CKD-EPI formula; eGFR was measured at baseline and after a median of 28.0 months. Urinary 11-dehydro-TxB_2, was measured in 401 patients. The incidence of cardiovascular events (CVEs) was also registered.
Results: Baseline eGFR was 65.1 ml/min/1.73 m^2; 147 and 91 patients had incident eGFR < 60 and <45 ml/min/1.73 m^2, respectively; 16.5% patients received a concomitant treatment with aspirin 100 mg/day. Multivariate logistic regression analysis showed a direct association with incident eGFR < 45 ml/min/1.73 m^2 for female sex (odds ratio [OR]:1.910, p = 0.005) and hypertension (OR: 7.589, p = 0.047), while aspirin use was inversely associated (OR: 0.347, p = 0.016). Propensity score adjustment confirmed this association (p = 0.017). Patients with incident eGFR < 45 ml/min/1.73 m^2 had higher TxB_2, compared to those without (123.0 vs. 90.0 ng/mg creatinine, p = 0.031); TxB_2 was inversely associated with incident eGFR < 45 ml/min/1.73 m^2 (log TxB_2 OR 2.239, p = 0.036). Incident eGFR < 45 ml/min was associated with an increased rate of CVEs (HR: 2.211, p = 0.01).
Conclusion: Aspirin use was associated with a less decline in eGFR in our cohort of AF patients with CKD. Our findings suggest that TxA_2 may be implicated in renal function deterioration in AF.

1. Introduction

Thromboxane (Tx) A_2 is an unstable eicosanoid deriving from arachidonic acid metabolism by cyclooxygenase (COX)-1 activation. TxA_2 is produced by several cell lines such as platelets, in which it acts as aggregating molecule; at level of kidney, its production by glomerular and renal artery cells contributes to arterial vasoconstriction [1,2].

Experimental models demonstrated that TxA_2 over-production may have a deleterious effect on renal function, as inhibition of TxA_2 biosynthesis and/or TxA_2 receptor antagonism are associated with improvement of renal perfusion and a delay of renal insufficiency progression [3–5]. Patients with mild to moderate renal failure, i.e. those with creatinine clearance of approximately 50–60 ml/min/1.73 m^2, have enhanced production of TxA_2 compared to controls [6]. However, it is unclear if such over-production is associated with deterioration of renal failure on long-term follow-up.

Atrial fibrillation (AF) is a common cardiac arrhythmia with a high prevalence in the elderly population, and is typically associated with

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arterial hypertension and chronic kidney disease (CKD) [7] as shown by the REGARDS Study [8]. Moreover, a rapid decline of renal function is associated with a higher incidence of cardiovascular outcomes [9].

This population is a suitable clinical setting to investigate the role of TxA_2 in the progression of renal disease, as TxA_2 production in AF patients is associated with progression of vascular disease and cardiovascular events (CVEs) [10].

Aspirin, which irreversibly acetylates COX1, reduces CVEs in hypertensive CKD patients [11]. A dose of aspirin of 50–325 mg/day [12] has been shown to be effective in inhibiting TxA_2 production [13]. The relationship between TxB_2 excretion and in vivo renal function, as well as the potential effect of low-dose aspirin on kidney function has never been explored in AF.

Therefore, we performed a multicentre observational study to assess the relationship between low-dose (100 mg/day) aspirin treatment and changes in renal function in an elderly AF population affected by CKD.

2. Materials and methods

2.1. Study design

Prospective observational multicentre cohort study including 800 non-valvular AF patients affected by CKD, defined as a baseline estimated glomerular filtration rate (eGFR) <90 ml/min/1.73 m^2.

AF patients were recruited from the Atherothrombosis Centre of I Clinica Medica of "Sapienza" University of Rome, from the Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Italy), and from the cohort of the Ankle-brachial Index Prevalence Assessment: Collaborative Italian Study (ARAPACIS) study [14].

All patients were treated with vitamin K antagonists (recommended INR range 2.0–3.0). Exclusion criteria were the presence of prosthetic heart valves, chronic infections or autoimmune systemic disease, any active cancer or liver insufficiency (e.g., cirrhosis), acute ischemic cerebrovascular and cardiovascular events in the previous year. At baseline, anthropometric data as well as comorbidities and concomitant therapies were collected. Cardiovascular risk factors were defined as previously described [10].

2.2. Definition of renal function

At baseline, serum creatinine (mg/dl) was obtained for all patients, and eGFR was calculated using the 2009 chronic kidney disease epidemiology collaboration (CKD-EPI) formula. Thus, according to the CKD-EPI formula, eGFR was adjusted for sex and race. Patients were classified into eGFR categories according to the 2013 Kidney disease: improving global outcomes (KDIGO) guidelines: normal eGFR (>90 ml/min/1.73 m^2, Stage G1), mild decrease in eGFR (90–60 ml/min/1.73 m^2, Stage G2), mild to moderate decrease in eGFR (59–45 ml/min/1.73 m^2, Stage G3a), moderate to severe decrease in eGFR (44–30 ml/min/1.73 m^2, Stage G3b) and severely decreased eGFR (<30 ml/min/1.73 m^2, Stage G4). A second serum creatinine was collected during follow-up.

2.3. Primary endpoint

The study end-point was the incidence of an eGFR <60 and <45 ml/min/1.73 m^2 during follow-up, amongst aspirin users or non-users.

2.4. Secondary endpoint

As secondary endpoint, we investigated if the incidence of an eGFR <60 and <45 ml/min/1.73 m^2 was associated with an increased risk of CVEs during follow-up. The outcome was a composite endpoint of fatal/non-fatal MI or cardiac revascularization, fatal/non-fatal ischemic stroke or TIA and cardiovascular death. Definitions of CVEs have been previously reported [10].

2.5. Laboratory analysis

The analysis of urinary 11-dehydro-TxB_2 was performed in a subgroup of 401 AF patients, as in the ARAPACIS study and in the Catanzaro cohort, it was not mandatory to collect a biological sample at baseline. The collection of urine samples was concomitant with the assessment of renal function. Excretion of urinary 11-dehydro-TxB_2 was measured by an ELISA commercial kit (Cayman). Data were expressed as ng/mg urinary creatinine. Intra- and inter-assay coefficients of variation were 4.0% and 3.6%, respectively. Analyses were performed in a blinded manner.

2.6. Statistical analysis

Categorical variables were reported as counts (percentage). Continuous variables were expressed as mean ± standard deviation or median and interquartile range, as appropriate. Two-sided *t* tests or Wilcoxon rank sum test, depending on the shape of the distribution curve, were used to compare means and medians. Pearson chi-square test was used to compare proportions. Bivariate analysis was performed with Pearson's linear correlation. Appropriate nonparametric tests (Mann-Whitney *U* test and Rho Spearman test) were employed for all the other variables. The marginal homogeneity test was used for comparison of categorized eGFR classes at baseline and follow-up. To test the effect of aspirin on renal function progression, we performed multivariable logistic regression analysis, to calculate the adjusted Odds Ratios (OR) of factors associated with the decrease of renal function across classes of eGFR, from Stage G1 and G2 to Stage G3a (<60 ml/min/1.73 m^2) and G3b (<45 ml/min/1.73 m^2). Multivariable analyses were determined with a forward stepwise procedure, including all variables that could potentially affect renal function, listed in Table 1, with the exception for TxB_2 and CHA_2DS_2-VASc score and using hypertension as covariate instead of single anti-hypertensive agents. As proof-of-concept, we propensity-score adjusted aspirin effect estimates and p-values. The estimated propensity score for aspirin usage was used as a predictor, together with aspirin treatment indicator, in multivariable models assessing the relationship with the outcomes. The balancing properties of propensity score adjustment have been assessed by evaluating the adjusted summaries within each treatment group. As reported in Table 4 after propensity score adjustment the two treatment arms are fairly balanced with respect to the considered baseline characteristics. Propensity score adjusted estimates can then be expected to be close to those obtained from a randomized treatment. As secondary outcome, we investigated the relationship between incident eGFR <60 and <45 ml/min and the occurrence of CVEs during follow-up. The cumulative incidence was estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test. The association with CVEs was analysed separately for the two thresholds of incident eGFR. Cox proportional hazards analyses were used to calculate the adjusted relative hazards of CVEs by each clinical variable. The multivariable analyses were determined including pre-specified variables listed in Table 5.

All tests were two-tailed and analyses were performed using computer software packages (R v3.0.2, R Development Core Team and SPSS-18.0, SPSS Inc.). Only p values < 0.05 were considered as statistically significant.

The study was approved by the local ethical board of Sapienza University of Rome (Protocol number 593/10). All patients provided written informed consent to participate in the study.

3. Results

Baseline characteristics of the 800 AF patients are listed in Table 1. Mean age was 73.7 ± 8.4 years, and 57.6% had paroxysmal AF. Most patients (94.0%) were affected by arterial hypertension; in addition,

Table 1
Baseline characteristics of AF cohort overall, and according to the use of aspirin.

	Overall (n = 800)	Aspirin use		p
		No (n = 668)	Yes (n = 132)	
Age (years)	73.7 ± 8.4	74.1 ± 8.3	71.9 ± 8.5	0.008
Paroxysmal AF (%)	57.6	58.1	55.3	0.564
Women (%)	46.0	47.9	36.4	0.017
Body mass index (kg/m^2)	27.7 ± 4.6	27.6 ± 4.6	28.1 ± 4.6	0.323
Baseline eGFR (ml/min/1.73 m^2) [a]	65.1 [52.7–76.4]	64.8 [52.7–76.1]	67.4 [54.2–80.0]	0.211
eGFR classes distribution (%)				0.248
G2	62.6	61.8	66.7	
G3a	23.9	25.1	17.4	
G3b	10.4	9.9	12.9	
G4	3.1	3.1	3.0	
CHA_2DS_2-VASc score[a]	4.0 [3.0–4.0]	4.0 [3.0–4.0]	4.0 [2.0–5.0]	0.227
Arterial hypertension (%)	94.0	93.6	96.2	0.316
ACE inhibitors/ARBs (%)	73.5	71.3	84.8	0.001
β blockers (%)	49.1	49.6	47.0	0.634
Calcium channel antagonists (%)	28.1	29.2	22.7	0.139
Diabetes mellitus (%)	23.0	22.0	28.0	0.142
History of MI/CHD (%)	18.6	15.9	32.6	<0.001
Heart failure (%)	18.5	17.2	25.0	0.049
History of stroke/TIA (%)	12.5	12.6	12.1	0.885
Aspirin (%)	16.5	–	–	–
Statins (%)	45.0	44.0	50.0	0.214
Thromboxane B_2 (ng/mg creatinine)[b]	98.0 [55.0–162.5]	100.0 [60.0–175.5]	72.5 [45.0–120.0]	0.014

ACE: angiotensin converting enzyme, AF: atrial fibrillation, ARBs: angiotensin receptor blockers, CHD: coronary heart disease, eGFR: estimated glomerular filtration rate, MI: myocardial infarction, and TIA: transient ischemic attack.

[a] Data expressed as median and interquartile range.

[b] Data in 401 AF patients.