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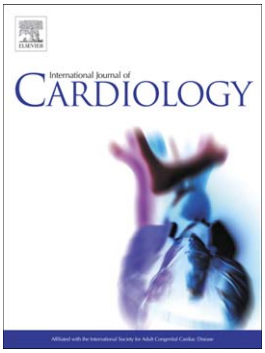


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# Aspirin and renal insufficiency progression in patients with atrial fibrillation and chronic kidney disease

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**Short title:** thromboxane and renal function

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**D Pastori:** study design and coordination, data analysis, manuscript elaboration.

**P Pignatelli:** study design and coordination, data analysis, manuscript elaboration.

**F Perticone:** writing and editing of the manuscript.

**A Sciacqua:** data collection and analysis.

**R Carnevale:** laboratory analysis, data collection.

**A Farcomeni:** statistical analysis, manuscript elaboration.

**S Basili:** writing and editing of the manuscript, data collection.

**GR Corazza:** writing and editing of the manuscript.

**G Davì**: writing and editing of the manuscript.

**GYH Lip:** writing and editing of the manuscript.

**F Violi:** study design, coordination, writing and editing of the manuscript.

**All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.**

**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/1.73m$^2$ 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/1.73m$^2$ 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/1.73m$^2$; 147 and 91 patients had incident eGFR<60 and <45 ml/min/1.73m$^2$, 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 gender (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/1.73m$^2$ 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/1.73m$^2$ (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.

**KEYWORDS:** atrial fibrillation, aspirin, chronic kidney disease, arterial hypertension, thromboxane.

## 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, typically associated with 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[10].

Aspirin, which irreversibly acetylates COX1, reduces cardiovascular events (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.

## Materials and Methods

### 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 (eg, 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].

### 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 gender 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.

**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.

**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 MI/cardiac revascularization, ischemic stroke/TIA and cardiovascular death. Definitions of CVEs have been previously reported[10].

**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 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.

**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 that would have been obtained had the treatment been randomized. 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.

**Results**

Baseline characteristics of 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, diabetes mellitus was present in 23.0%, heart failure in 18.5%, a history of MI/ CHD and Stroke/TIA in 18.6% and 12.5%, respectively (Table 1).

Median eGFR was 65.1 [52.7-76.4] ml/min/1.73 $m^2$. Distribution of eGFR classes at baseline is reported in Figure 1.

One hundred thirty-two (16.5%) AF patients were treated with low-dose of aspirin (100 mg/day), in addition to oral anticoagulants. Age, gender, heart failure and history of MI differentiated patients with and without aspirin. Conversely, no differences in median baseline eGFR and eGFR classes were detected between patients treated or not with aspirin (Table 1).

A second serum creatinine was obtained at a median of 28.0 [15.2-38.7] months. During follow-up, 147 patients showed a reduction of eGFR below 60 ml/min/1.73 $m^2$, 91 below <45 ml/min/1.73 $m^2$, and 24 below 30 ml/min/1.73 $m^2$. Marginal homogeneity test showed a significant change in eGFR classes distribution at follow-up (Figure 1, p<0.001).

Table 2 shows demographic and clinical characteristics of patients with incident eGFR<60 ml/min/1.73 $m^2$. At multivariable logistic regression analysis, age and arterial hypertension were significantly associated with incident eGFR <60 ml/min/1.73 $m^2$, while aspirin use showed no effect (Table 3, Panel A).

Patients with decline of eGFR <45 ml/min/1.73 $m^2$ were older, with a higher $CHA_2DS_2$-VASc Score, more frequently women, hypertensive and less treated with aspirin (Table 2), compared to patients with stable eGFR. Multivariate logistic regression analysis (Table 3, Panel B), showed a direct association with incident eGFR <45 ml/min/1.73 $m^2$ for female gender and arterial hypertension, while aspirin use was inversely associated.

Our findings were confirmed after propensity score adjustment (Table 4). Thus, aspirin use was inversely associated with incident eGFR <45 ml/min/1.73 $m^2$ (OR: 0.352, 95% CI 0.133-0.771, p=0.017), but not with incident eGFR <60 ml/min/1.73 $m^2$ (OR: 0.908, 95% CI 0.526-1.526, p=0.722).

***Renal function and cardiovascular events***

During follow-up, 70 CVEs were recorded. Aspirin use was not associated with CVEs in the whole cohort (log-rank test, p=0.368). No association was found between incident eGFR <60 ml/min and CVEs (not shown). CVEs occurred in 16/91 and 43/599 patients with and without incident eGFR <45 ml/min, respectively.

Incident eGFR <45 ml/min was associated with a significant increased rate of CVEs (log-rank test p=0.009), and at univariate Cox regression analysis, (HR: 2.11, 95%CI 1.19-3.76, p=0.011) was predictive of CVEs. This association remained significant at multivariable analysis (Table 5).

***Analysis of urinary excretion of Thromboxane $B_2$***

In a subgroup of 401 AF patients, in whom urine sample was collected, we measured baseline urinary excretion of $TxB_2$. In this group, median $TxB_2$ was 98.0 [55.0-162.5] ng/mg creatinine, while median eGFR was 64.4 [52.1-75.2] ml/min/1.73 $m^2$. At baseline, 247 (61.6%) AF patients had an eGFR between 90-60 ml/min/1.73 $m^2$, 97 (24.2%) between 59-45 ml/min/1.73 $m^2$, 43 (10.7%) between 44-30 ml/min/1.73 $m^2$, and 14 (3.5%) below 30 ml/min/1.73 $m^2$, similar to those of the entire population.

We found no difference in $TxB_2$ levels in patients with (n=95, median $TxB_2$ 90.0 [50.0-180.0]) and without (n=152, median $TxB_2$ 98.0 [50.5-180.0]) incident eGFR<60 ml/min/1.73 $m^2$ (p=0.573). Conversely, $TxB_2$ was higher in patients with incident eGFR <45 ml/min/1.73 $m^2$ (n=63, median $TxB_2$ 123.0 [68.0-257.0]), compared to those without incident eGFR <45 ml/min/1.73 $m^2$ (n=280, median $TxB_2$ 90.0 [50.5-160.0], p=0.031, Figure 2). Among the 401 patients 48 were aspirin users; they had significantly lower levels of $TxB_2$ (median $TxB_2$ 72.5 [45.0-120.0] compared to those aspirin-free (n=353, median $TxB_2$ 100.0 [60.0-175.5], p=0.014).

Univariate logistic regression analysis confirmed that $TxB_2$ levels were significantly associated with incident eGFR<45 ml/min/1.73 $m^2$ (log $TxB_2$ OR 2.239, 95%CI 1.056-4.747, p=0.036), with no interaction with the use of aspirin (p=0.5122), suggesting that the negative association between $TxB_2$ and renal function is similar in aspirin users and non-users. Log- $TxB_2$ was significantly associated with CVEs (n=47, HR: 1.86, 95%CI 1.30-2.65, p=0.001).

**Discussion and conclusions**

This study provides the first evidence that in patients with AF, the use of aspirin was associated with a less decline of renal function, and suggests that $TxA_2$ plays a role in the progression of renal failure.

Prior studies investigated the relationship between $TxA_2$ and renal function in patients with renal disease showing that the balance of prostacyclin/$TxA_2$ is crucial for an optimal renal function[15]. In particular, an inverse association between biosynthesis of prostacyclin, which is a vasodilator molecule, and creatinine clearance was detected in patients with chronic glomerular disease[15]. Furthermore, in patients with lupus nephritis, the acute infusion of a selective thromboxane receptor antagonist resulted in an increased renal clearance[5]. Similar finding was observed in patients with heart failure treated with picotamide, a dual antiplatelet molecule inhibiting $TxA_2$ synthase and acting as $TxA_2$ receptor antagonist[16]. Thus, patients given picotamide for 8 days showed an improvement of renal flow and glomerular filtration rate along with a decrease of vascular

resistance compared to placebo suggesting that inhibiting $TxA_2$ synthase or activity improves renal function by interfering with renal perfusion[4]. While these data are in favor of a role of $TxA_2$ as molecule associated with worsening renal function, few prospective data exist on the relationship between $TxA_2$ and renal function on a long-term follow-up.

In this study, we focused on patients with AF, a condition that is associated with CKD[8]. For instance, Roldàn et al[17] found a moderate renal impairment in 28% out of 978 patients affected by AF[17], with a reduction in the eGFR ≥10 ml/min in 21% of patients after 2 years.

In our cohort of AF patients with CKD, we found that an incident eGFR <60, <45 and <30 ml/min were detected in 18%, 11% and 3%, respectively, with age, female gender and arterial hypertension significantly associated with a decline in the renal function.

The fact that most of our AF patients were hypertensive is in keep with the work by Roldàn et al[17] in which 82% of AF patients were hypertensive, and reinforces the role of arterial hypertension as risk factor for AF[18] and CKD[19].

Similarly to previous reports[17], approximately 17% of our AF population was on treatment with aspirin. The prevalence of heart failure and previous cardiovascular event was higher in aspirin users, suggesting that physicians tend to associate oral anticoagulants to antiplatelet drugs after an acute cardiovascular event.

One novel finding of the present study is the significant association between aspirin use and delay in renal function progression. In particular, aspirin use was associated with lower incident eGFR <45 ml/min, while no association has been found with incident eGFR <60ml/min.

When we analysed the relationship between baseline urinary excretion of $TxB_2$, which is a reliable marker of $TxA_2$ biosynthesis, and renal function deterioration, we found that patients with incident eGFR <45ml/min had significantly higher urinary excretion of $TxB_2$ compared with those with values >45 ml/min providing indirect evidence on a $TxA_2$ role in progression to moderate-severe renal failure.

The study has implications and limitations. Previous study demonstrated that patients with hypertension have enhanced production of $TxB_2$[20], but it has never been investigated if hypertension elicits renal dysfunction also via $TxB_2$ over-production. As >90% of our patients were hypertensive, it is possible that aspirin delays renal dysfunction by blunting hypertension-related $TxB_2$ over-production.

The study has been done in an elderly population with AF and therefore, results cannot be extrapolated to other settings affected by chronic renal disease. Moreover, as all patients included in the study were Caucasian, these data cannot be generalized to other ethnic groups. The lack of randomization is an intrinsic limitation of the study, although propensity-adjusted analysis confirmed our findings. Finally, a limitation of the study is in a relatively low number of patients in G3b stage.

In conclusion, the study provides evidence that aspirin use is associated with a delay in the renal function deterioration in AF patients, suggesting $TxA_2$ as a molecule favouring progression of renal disease. This finding may represent a valid rationale for planning interventional trials with aspirin or $TxA_2$ receptor antagonist in this setting.

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**Figure legends**

**Figure 1. Sequential changes in eGFR classes distribution during follow-up compared to baseline.**

**Figure 2. Median value of urinary excretion of 11-dehydro-$TxB_2$ in the all cohort (left column), and in patients with (middle column) and without (right column) incident eGFR <45 ml/min/ 1.73 $m^2$.**

**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/1,73m$^2$)** [#] | **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**[#] | **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)*** | **98.0 [55.0-162.5]** | **100.0 [60.0-175.5]** | **72.5 [45.0-120.0]** | **0.014** |

[#]data expressed as median and interquartile range; *****data in 401 AF patients

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

**Table 2. Demographic and clinical characteristics of patients with incident eGFR <60 and <45 ml/min/1.73 $m^2$.**

| | Incident eGFR <60 ml/min/1.73 $m^2$ | | p | Incident eGFR <45 ml/min/1.73 $m^2$ | | p |
|---|---|---|---|---|---|---|
| | No (n=351) | Yes (=147) | | No (n=599) | Yes (=91) | |
| **Age (years)** | **71.2±8.5** | **73.4±8.1** | **0.006** | **72.8±8.6** | **75.2±6.6** | **0.002** |
| **Women (%)** | **38.2** | **49.0** | **0.028** | **42.4** | **59.3** | **0.003** |
| **Body Mass Index (kg/$m^2$)** | **28.0±4.6** | **27.5±4.5** | **0.277** | **27.8±4.6** | **27.7±4.6** | **0.885** |
| **Paroxysmal AF (%)** | **57.5** | **56.5** | **0.843** | **57.1** | **56.0** | **0.910** |
| **$CHA_2DS_2$-VASc Score[#]** | **3.0 [2.0-4.0]** | **3.0 [2.0-4.0]** | **0.656** | **3.0 [2.0-4.0]** | **4.0 [3.0-5.0]** | **0.027** |
| **Arterial Hypertension (%)** | **90.9** | **96.6** | **0.025** | **92.7** | **98.9** | **0.021** |
| **Diabetes mellitus (%)** | **23.1** | **17.7** | **0.191** | **22.7** | **23.1** | **0.937** |
| **History of MI/ CHD (%)** | **17.4** | **16.3** | **0.896** | **17.9** | **20.9** | **0.469** |
| **Heart Failure (%)** | **17.9** | **10.2** | **0.031** | **17.5** | **18.7** | **0.769** |
| **History of Stroke/TIA (%)** | **12.0** | **12.9** | **0.766** | **13.0** | **12.1** | **0.804** |
| **Aspirin (%)** | **18.5** | **15.6** | **0.520** | **17.5** | **6.6** | **0.006** |
| **Statins (%)** | **43.0** | **44.2** | **0.843** | **44.4** | **53.8** | **0.113** |
| **Thromboxane $B_2$ (ng/mg creatinine)*** | **98.0 [50.5-180.0]** | **90.0 [50.0-180.0]** | **0.573** | **90.0 [50.0-160.0]** | **123.0 [68.0-257.0]** | **0.031** |

[#]data expressed as median and interquartile range; *data on 247 AF patients for incident 60 ml/min, and on 343 for incident 45 ml/min.

**AF: atrial fibrillation,** CHD: coronary heart disease, eGFR: estimated glomerular filtration rate, MI: myocardial infarction, TIA: transient ischemic attack.

**Table 3. Stepwise multivariable logistic regression analysis of factors associated with incident eGFR <60 ml/min/1.73 $m^2$ (Panel A) and <45 ml/min/1.73 $m^2$ (Panel B).**

| **Panel A** | **p** | **OR** | **95% CI** |
|---|---|---|---|
| **Age** | **0.008** | **1.034** | **1.009-1.061** |
| **Arterial Hypertension** | **0.040** | **2.783** | **1.050-7.381** |
| After adjustment for female gender, diabetes, heart failure, history of Stroke/TIA, history of MI/CHD, aspirin, statins and body mass index, type of AF (paroxysmal vs. persistent/permanent AF) | | | |
| **Panel B** | **p** | **OR** | **95% CI** |
| **Female gender** | **0.005** | **1.910** | **1.214-3.005** |
| **Arterial Hypertension** | **0.047** | **7.589** | **1.029-55.982** |
| **Aspirin** | **0.016** | **0.347** | **0.147-0.819** |
| After adjustment for age, diabetes, heart failure, history of Stroke/TIA, history of MI/CHD, statins and body mass index, type of AF (paroxysmal vs. persistent/permanent AF) | | | |

AF: atrial fibrillation, CHD: coronary heart disease, eGFR: Estimated Glomerular Filtration Rate, MI: myocardial infarction, TIA: transient ischemic attack.

**Table 4. Baseline characteristics of AF cohort with baseline eGFR>60 (Panel A) and >45 (Panel B) ml/min/1.73 $m^2$, according to the use of aspirin after propensity score adjustment. A standardized difference (SD) < 10% indicates balance of the two groups after adjustment.**

| **Panel A** | **Aspirin use** | | **SD** |
|---|---|---|---|
| | No | Yes | |
| **Age (years)** | 55.7±7.4 | 55.8±7.4 | 0.018 |
| **Women (%)** | 1.6 | 1.6 | 0.042 |
| **Body Mass Index (kg/$m^2$)** | 29.4±4.6 | 29.4±4.6 | 0.009 |
| **Paroxysmal AF (%)** | 51.1 | 51.2 | 0.002 |
| **Arterial Hypertension (%)** | 99.9 | 99.9 | <0.001 |
| **Diabetes mellitus (%)** | 37.9 | 37.9 | <0.001 |
| **History of MI/ CHD (%)** | 99.8 | 99.8 | <0.001 |
| **Heart Failure (%)** | 97.6 | 97.8 | 0.003 |
| **History of Stroke/TIA (%)** | 13.9 | 14.1 | 0.014 |
| **Statins (%)** | 92.1 | 92.0 | <0.001 |
| **Panel B** | **Aspirin use** | | **SD** |
| | No | Yes | |
| **Age (years)** | 57.3±7.1 | 57.4±7.1 | 0.018 |
| **Women (%)** | 1.0 | 1.0 | 0.001 |
| **Body Mass Index (kg/$m^2$)** | 31.6±4.5 | 31.5±4.5 | 0.014 |
| **Paroxysmal AF (%)** | 53.9 | 54.1 | 0.004 |
| **Arterial Hypertension (%)** | 99.9 | 99.9 | <0.001 |
| **Diabetes mellitus (%)** | 37.3 | 37.2 | 0.001 |
| **History of MI/ CHD (%)** | 99.8 | 99.8 | 0.001 |
| **Heart Failure (%)** | 85.2 | 85.7 | 0.006 |
| **History of Stroke/TIA (%)** | 16.3 | 16.6 | 0.018 |
| **Statins (%)** | 73.6 | 73.8 | 0.003 |

**AF: atrial fibrillation, CHD: coronary heart disease, eGFR: Estimated Glomerular Filtration Rate, MI: myocardial infarction, SD: Standardized Difference, TIA: transient ischemic attack.**

**Table 5. Adjusted hazard ratios for cardiovascular events by Cox proportional hazards model according to selected variables.**

| | Hazard Ratio | 95% Confidence Interval | | p |
|---|---|---|---|---|
| ***Paroxysmal AF (vs. persistent/permanent)*** | **0.782** | **0.460** | **1.329** | **0.364** |
| ***Female gender*** | **0.772** | **0.447** | **1.334** | **0.354** |
| ***Age*** | **1.069** | **1.026** | **1.113** | **0.001** |
| ***Diabetes*** | **1.701** | **0.961** | **3.012** | **0.068** |
| ***Heart failure*** | **1.372** | **0.713** | **2.643** | **0.344** |
| ***Previous stroke/TIA*** | **1.772** | **0.902** | **3.480** | **0.097** |
| ***Previous MI/CHD*** | **2.070** | **1.165** | **3.676** | **0.013** |
| ***Antiplatelet*** | **1.126** | **0.575** | **2.205** | **0.728** |
| ***Arterial ypertension*** | **0.432** | **0.128** | **1.463** | **0.178** |
| ***Statin*** | **1.117** | **0.655** | **1.906** | **0.684** |
| ***Body mass index*** | **1.008** | **0.950** | **1.070** | **0.792** |
| ***Incident eGFR <45 ml/min*** | **2.211** | **1.207** | **4.048** | **0.010** |

AF: atrial fibrillation, CHD: coronary heart disease, eGFR: estimated glomerular filtration rate, MI: myocardial infarction, TIA: transient ischemic attack.

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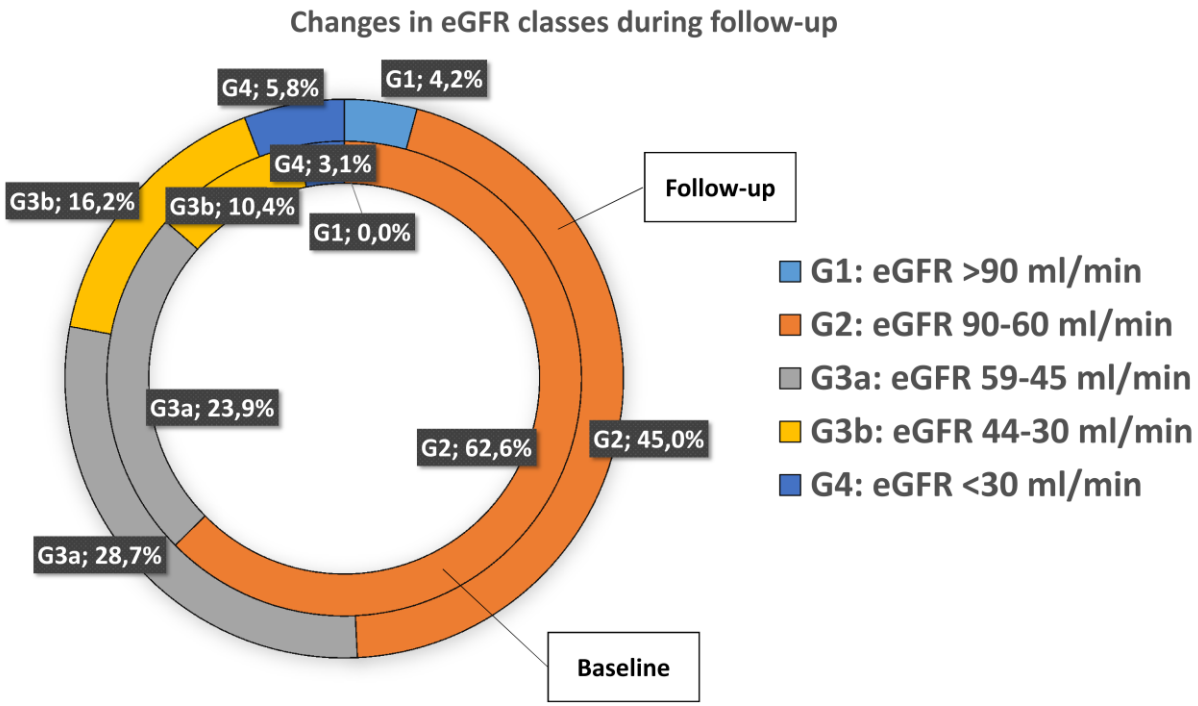


Figure 1

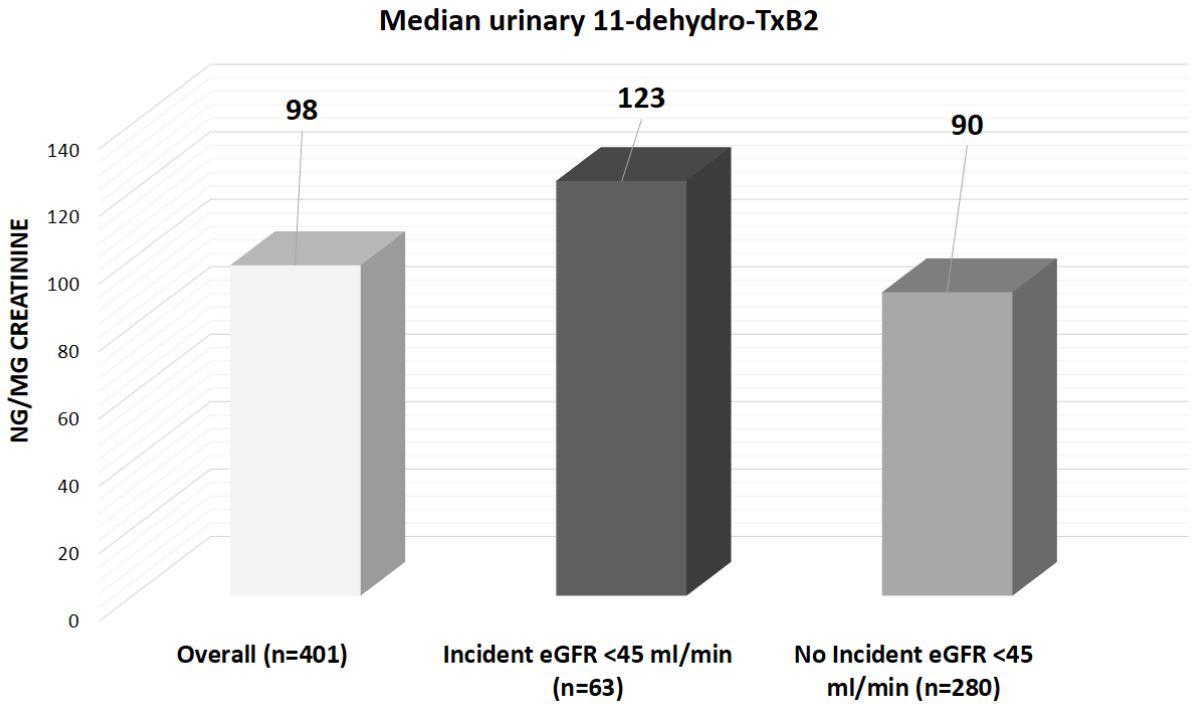


Figure 2