Internal and Emergency Medicine
https://doi.org/10.1007/s11739-018-1835-9

IM - ORIGINAL

Major adverse cardiovascular events in non-valvular atrial fibrillation with chronic obstructive pulmonary disease: the ARAPACIS study

Valeria Raparelli[1] · Daniele Pastori[1] · Serena Francesca Pignataro[1] · Anna Rita Vestri[2] · Pasquale Pignatelli[1] · Roberto Cangemi[1] · Marco Proietti[3] · Giovanni Davì[4] · William Robert Hiatt[5] · Gregory Yoke Hong Lip[3] · Gino Roberto Corazza[6] · Francesco Perticone[7] · Francesco Violi[1] · Stefania Basili[1] · ARAPACIS Study Collaborators

Received: 20 November 2017 / Accepted: 16 March 2018

Abstract
Chronic obstructive pulmonary disease (COPD) increases the risk of mortality in non-valvular atrial fibrillation (NVAF) patients. Data on the relationship of COPD to major cardiovascular events (MACE) in AF have not been defined. The aim of the study is to assess the predictive value of COPD on incident MACE in NVAF patients over a 3-year follow-up. In the Atrial Fibrillation Registry for Ankle-Brachial Index Prevalence Assessment-Collaborative Italian Study (ARAPACIS) cohort, we evaluate the impact of COPD on the following clinical endpoints: MACE (including vascular death, fatal/non-fatal MI and stroke/TIA), cardiovascular (CV) death and all-cause mortality. Among 2027 NVAF patients, patients with COPD (9%) are more commonly male, elderly and at higher thromboembolic risk. During a median 36.0 months follow-up, 186 patients experienced MACE: vascular death ($n=72$), MI ($n=57$), stroke/TIA ($n=57$). All major outcomes (including stroke/TIA, MI, vascular death, and all-cause death) are centrally adjudicated. Kaplan–Meier curves show that NVAF patients with COPD are at higher risk for MACE ($p<0.001$), CV death ($p<0.001$) and all-cause death ($p<0.001$). On Cox proportional hazard analysis, COPD is an independent predictor of MACE (Hazard ratio [HR] 1.77, 95% Confidence Intervals [CI] 1.20–2.61; $p=0.004$), CV death (HR 2.73, 95% CI 1.76–4.23; $p<0.0001$) and all-cause death (HR 2.16, 95% CI 1.48–3.16; $p<0.0001$). COPD is an independent predictor of MACE, CV death and all-cause death during a long-term follow-up of NVAF patients.

Keywords Chronic obstructive pulmonary disease · Atrial fibrillation · Cardiovascular mortality · Major cardiovascular events

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide [1, 2]. Its prevalence is steadily rising resulting in a significant economic and social burden. COPD has been considered for many years to be a predominantly respiratory disease; however,

Valeria Raparelli and Daniele Pastori contributed equally to this work.

Names of the members of the ARAPACIS Study Group are listed in the Acknowledgement section at the end of the article.

✉ Francesco Violi
francesco.violi@uniroma1.it

[1] Department of Internal Medicine and Medical Specialties, Clinica Medica, Atherothrombosis Center, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy

[2] Department of Public Health and Infections Disease, Sapienza University of Rome, Rome, Italy

[3] University of Birmingham Institute of Cardiovascular Sciences, City Hospital, Birmingham, UK

[4] Department of Medicine and Aging, University of Chieti "G. d'Annunzio, Chieti, Italy

[5] Division of Cardiology, University of Colorado School of Medicine and CPC Clinical Research, Aurora, CO, USA

[6] First Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

[7] Department of Medical and Surgical Sciences, University Magna Græcia of Catanzaro, Catanzaro, Italy

Published online: 26 March 2018

COPD is increasingly recognized as a systemic disease with significant clinical extra-pulmonary effects, leading to a worsening prognosis [1, 3, 4]. There is a growing body of evidence that COPD may be complicated by cardiovascular diseases (CVD) including right ventricular dysfunction and pulmonary hypertension, as well as coronary artery disease and dysrhythmias such as non-valvular atrial fibrillation (NVAF) [5]. Of note, a substantial proportion of deaths in patients with mild COPD are due to CVD complications [6]. Consistent with this, COPD displays a prothrombotic tendency as indicated by enhanced urinary excretion of 11-dehydro-Thromboxane B_2, a reliable marker of in vivo platelet activation [7, 8].

It appears increasingly evident that the clinical history of AF may be complicated by major adverse cardiovascular events (MACE) of atherothrombotic origin such as myocardial infarction (MI) [9, 10]. Thus, more than half of deaths in NVAF patients treated with oral anticoagulation are unrelated to systemic thromboembolism [11]. Based on epidemiological data, COPD is present in 10–15% of AF patients, and is independently associated with increased risk of cardiovascular and non-cardiovascular mortality among anti-coagulated NVAF patients [11, 12]. A recent ancillary analysis of the EURObservational Research Programme Pilot Survey on Atrial Fibrillation Registry Pilot Phase (EORP-AF), enrolling 3086 consecutive patients finds that COPD is significantly associated with all-cause death after 1 year follow-up [13].

The predictive value of COPD in NVAF patients on MACE occurrence, i.e. CV death and death from any cause over a long-term follow-up is still unknown. Therefore, we evaluate the association between COPD and MACE in the Atrial Fibrillation Registry for Ankle-Brachial Index Prevalence Assessment-Collaborative Italian Study (ARAPACIS Study) [14, 15], a large population affected by NVAF prospectively followed up for approximately 3 years.

Materials and methods

The study reports on a pre-specified secondary analysis of the ARAPACIS study. Specifically, ARAPACIS is a multicenter, observational, prospective study held by the Italian Society of Internal Medicine (ClinicalTrials.gov -NCT01161251). The methods and baseline data from the ARAPACIS study have previously been published [14, 16]. Patient enrollment started October 1st 2010 and continued until October 31th 2012. This study was conducted in accordance with the EU Guidance on Good Clinical Practice and the Declaration of Helsinki.

In brief, the registry population comprised 2027 in- and out-patients recruited from 136 Italian centers belonging to all the three macro-regions (North, Center, South). The study was initiated at the site level after local and ethics committee's approval requirements were obtained. Patients with a diagnosis of NVAF in the preceding 12 months were consecutively enrolled, after they gave written informed consent. Exclusion criteria were: (i) acquired or congenital valvular AF, (ii) active cancer or coexistence of disease with life expectancy less than 3 years and (iii) pregnancy or hyperthyroidism.

The diagnosis of COPD was reported by each investigator in the case report form at the time of enrollment. As for other risk factors, Investigators were asked to follow international guidelines to define COPD [1]. Anthropometric data, complete medical history interview and a comprehensive pharmacological history were recorded at the baseline visit to detect the presence of cardiovascular risk factors, previous cardio- and cerebrovascular events, other comorbidities and pharmacological impact. Patients were classified using international guidelines as paroxysmal, persistent or permanent AF, and risk of ischemic stroke assessed by the CHA_2DS_2-VASc score [17, 18].

End-point definitions

The end-point of the follow-up study is to define the incidence of major adverse vascular events among the cohort of NVAF patients.

MACE includes vascular death, fatal/non-fatal MI and stroke/TIA.

Vascular death includes: cardiac decompensation, heart failure, sudden or unwitnessed death, dysrhythmia, venous thromboembolism, procedure related death and presumed cardiovascular deaths (i.e. those for which a non-cardiovascular cause had not been clearly established).

The diagnosis of myocardial infarction was made according to the definition proposed by the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation (ESC/ACCF/AHA/WHF) Task Force [19]. If a patient died within 4 weeks of MI, this event was recorded as fatal MI. Ischemic stroke was determined on clinical manifestations and confirmed by radiological findings [20]. Even in this case, if a patient died in 4 weeks from stroke, this event was classified as fatal.

Cardiovascular death was defined as an outcome including vascular death, fatal MI and fatal stroke. Non-cardiovascular death (including cancer, intracranial bleeding, infectious disease, acute respiratory failure, unexplained, other) were centrally adjudicated.

Validation of events

Data on MACE and death were prospectively collected during follow-up by each center. Details on every vascular

event, as well as death certificates, hospital discharge letter, copy of the medical records of hospitalization, were obtained from patients, or in case of death, from patients' relatives or general practitioner and were retained in each enrolling center.

A blinded committee composed by internal medicine, neurology and cardiology seniors (F.P., P.E.P., M.L.S.) adjudicated events. When the two evaluators agreed, the event was adjudicated. Otherwise, whenever the two evaluators were discordant, the event was adjudicated after a collegial discussion among the study Steering Committee.

Statistical analysis

Details on study design have already been published [14]. Variables are reported as mean and standard deviation (SD), or as median and interquartile range (IQR) as appropriate. Comparisons between groups were performed by *t* test or Mann–Whitney *U* test or Chi-square test or Fisher's exact test. Separate Kaplan–Meier curves were built for clinical endpoints according to the presence of COPD. Log-rank test was performed to analyze differences in survival distributors between subgroups. Multivariate Cox models were used to assess clinically relevant variables and COPD effect on the endpoints. A forward stepwise model selection procedure based on the Akaike Information Criterion (AIC) was used to select the best multivariate regression model [21].

Subgroup analysis of warfarin-treated patients. To exclude that a sub-optimal antithrombotic treatment may influence the association between COPD and MACE, we performed a subgroup analysis in 467 patients treated with vitamin K antagonists (VKAs), for whom the time in therapeutic range (TTR) was obtained as previously described [22]. For this analysis, patients were divided into four groups according to TTR values: group 1: 0–50%, group 2: 51–60%, group 3: 61–70%, group 4: > 70%.

Subgroup analysis of urinary excretion of 11-deydhrothromboxane (Tx) B_2. To investigate the potential mechanism accounting for MACE occurrence, we measured urinary excretion of 11-deydhro-TxB_2 (U-TxB_2), a validated marker of platelet activation, which has been shown to predict MACE in NVAF [23]. Urine sample was available in 624 AF patients, in whom TxB_2 was measured as previously described [24]. All patients were treated with VKAs only. For Cox regression analysis, values of U-TxB_2 were log-transformed.

A two-sided p value < 0.05 was considered as statistically significant. All analyses were performed using SPSS v. 22 (IBM, NY, USA) and R v. 3.0.2 (R development core team, Vienna, Austria).

Results

Demographic and clinical characteristics of the population have been previously reported [14]. In brief, mean age is 73 ± 10 years, and 55% are male. Permanent NVAF is observed in 44.5% of patients. Among cardiovascular risk factors, hypertension, dyslipidemia and diabetes mellitus are present in 82.5, 38.5 and 23.0% of patients, respectively. Three hundred twenty-eight patients (16.2%) have had a previous MI and 11.6% have experienced a previous stroke/TIA. Median CHA_2DS_2-VASc is 3 (2–4), with 84.4% of patients showing a CHA_2DS_2-VASc value ≥ 2. Concerning stroke prevention, 1,935 patients (60.7%) were treated with oral anticoagulants (OAC), while antiplatelet agents (AP) and a combined therapy including AP and OAC were recorded in 19.2 and 4.5% of patients, respectively.

Of the overall population, 185 patients (9%) have COPD. Table 1 summarizes clinical characteristics of patients with or without COPD. Patients with COPD are significantly older and more frequently male. Previous MI and heart failure (HF) is more prevalent amongst patients with COPD (Table 1). Median CHA_2DS_2-VASc values are significantly higher in patients with COPD as well as the proportion at high thromboembolic risk (CHA_2DS_2-VASc ≥ 2). Beta-blockers were less prescribed and digoxin more used amongst COPD patients (Table 1).

Follow-up and clinical outcomes

All patients were followed for a median of 36.0 (IQR 22–36) months yielding 4768 patient-years of observation. At follow-up, 186 patients have experienced MACE as follows (3.9%/year): vascular death ($n = 72$), fatal ($n = 16$) or non-fatal MI ($n = 41$), fatal ($n = 22$) or non-fatal stroke/TIA ($n = 35$). NVAF patients with COPD have higher rates for MACE, CV death, and all-cause death (Table 2 and Figs. 1, 2).

On Cox proportional hazard analysis, age > 75 years [Hazard Ratio (HR): 2.02, 95% Confidence Intervals (CI) 1.37–2.98; $p < 0.0001$], vascular disease (MI, PAD and complex aortic plaque) (HR 1.97, 95% CI 1.44–2.69; $p < 0.001$), COPD (HR 1.77, 95% CI 1.20–2.61; $p = 0.004$) and HF (HR 1.56, 95% CI 1.12–2.15; $p = 0.008$), previous Stroke/TIA (HR 1.55, 95% CI 1.06–2.26; $p = 0.024$) and antithrombotic therapy use (i.e. VKAs alone or combined with AP versus no treatment) (HR 0.57, 95% CI 0.40–0.80; $p = 0.001$) are independent predictors of MACE in a model adjusted for gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, beta-blockers, ACEs, digoxin, clearance creatinine, statins, ARBs, and anti-dysrhythmic agents.

Table 1 Baseline clinical characteristics and pharmacological treatments according to COPD presence

	Patients without COPD $n=1842$	*P*	Patients with COPD $n=185$
Age, years (mean ± SD)	73.1 ± 10.1	< 0.0001¶	76.2 ± 8.6
Age classes < 65, *n* (%) 65–74, *n* (%) ≥ 75, *n* (%)	(29.2) (24.7) (46.1)	0.006*	(21.6) (20.0) (58.4)
Females, *n* (%)	847 (46)	0.04762*	71 (38)
AF type Paroxysmal, *n* (%) Persistent, *n* (%) Permanent AF, *n* (%)	758 (41) 266 (15) 818 (44)	0.18237*	84 (45) 18 (10) 83 (45)
Arterial Hypertension, *n* (%)	1521 (83)	0.88834*	152 (82)
Dyslipidaemia, *n* (%)	705 (38)	0.45448*	76 (41)
Smoking Habit, *n* (%)	278 (15)	0.70615 *	26 (14)
Diabetes, *n* (%)	420 (23)	0.52485*	46 (25)
Previous MI, *n* (%)	288 (16)	0.03507 *	40 (22)
Previous stroke/TIA, *n* (%)	214 (11)	0.91406*	21 (11)
Heart failure, *n* (%)	349 (19)	< 0.0001*	63 (34)
BMI, Kg/m^2 (mean ± SD)[a]	27.8 ± 5.0	0.64183¶	27.7 ± 5.3
Clearance creatinine (MDRD), ml/min (mean ± SD)[b]	74.7 ± 25.1	0.30213¶	72.4 ± 26.2
CHA_2DS_2-VASc, (median [IQR])	3 [2–4]	0.00074§	4 [3–5]
CHA_2DS_2-VASc classes Score 0, *n* (%) Score 1, *n* (%) Score ≥ 2, *n* (%)	78 (4) 221 (12) 1543 (84)	0.01436*	1 (0) 16 (9) 168 (91)
Concomitant therapies			
Antithrombotic therapy NONE, *n* (%) APs, *n* (%) OAC, *n* (%) OAC + APs, *n* (%)	278 (15) 357 (19) 1118 (61) 89 (5)	0.6022*	38 (20) 32 (17) 112 (61) 3 (2)
Statins, *n* (%)	368 (36)	0.89450*	68 (37)
Antiarrhythmics, *n* (%)	495 (27)	0.55612 *	46 (25)
Beta-blockers, *n* (%)	761 (41)	0.02762 *	61 (33)
ACEIs, *n* (%)	651 (35)	0.83928*	64 (35)
ARBs, *n* (%)	636 (34)	0.18938*	55 (30)
Calcium channel blockers, *n* (%)	496 (27)	0.41408 *	55 (30)
Diuretics #, *n* (%)	704 (55)	0.46032*	56 (51)
Nitrates, *n* (%)	247 (13)	0.43055*	31 (17)
Digoxin, *n* (%)	339 (18)	0.00452*	50 (27)
Oral antidiabetics, *n* (%)	271 (15)	0.87712*	28 (15)
Insulin, *n* (%)	100 (5)	0.74579*	9 (5)
PPI, *n* (%)[c]	267 (21)	0.07639	15 (14)
Politherapy (> 5 drugs), *n* (%)[c]	691 (54)	0.27760	53 (49)
Adherence, *n* (%)[d]	836 (66)	0.72930	70 (65)
Groups of TTR, *n* (%)[e]		$p=0.025$*	
Group 1: 0–50%.	93 (21.9)		18 (41.9)
Group 2: 51–60%	82 (19.3)		4 (9.3)
Group 3: 61–70%	96 (22.6)		8 (18.6)
Group 4: > 70%	153 (36.1)		13 (30.2)

ACEIs angiotensin-converting enzyme inhibitors, *APs* anti-platelets, *ARBs* angiotensin II receptor blockers, *BMI* body mass index, *#C* Congestive heart failure (or Left ventricular systolic dysfunction) (Points:1), *H* Hypertension (Points:1), A_2 Age ≥ 75 years (Points:2), *D* diabetes mellitus (Points:1), S_2 Prior Stroke or

Table 1 (continued)

TIA or thromboembolism (Points: 2), *V* Vascular disease (previous MI, peripheral arterial disease or aortic plaque) (Points: 1), *A* Age 65–74 years (Points: 1), *Sc* Sex category (female gender) (Points:1), *DVT* deep vein thrombosis, *IQR* interquartile range, *MI* myocardial infarction, *NS* not significant, *OAC* oral anticoagulants, *PE* pulmonary embolism, PPI protonic pump inhibitors, *TIA* transient ischemic attack, *TTR* time in therapeutic range

¶ = *t* test; * χ^2 = test; § = Mann–Whitney U Test

[a]BMI available in 1971 patients

[b]Clearance creatinine (MDRD) available in 1691 patients

[c]Politherapy, PPI and diuretics are available in 1388 patients

[d]Adherence available in 1366 patients

[e]TTR available in 467 patients

Table 2 Events during the follow-up according to COPD presence

Events	Patients without COPD n = 1842	P^*	Patients with COPD n = 185
Fatal MI, *n* (%)	11 (1)	0.00204	5 (3)
Fatal stroke, *n* (%)	17 (1)	0.02594	5 (3)
Vascular death, *n* (%)	55 (3)	0.00001	17 (9)
Cardiac decompensation, heart failure	38		15
Sudden or unwitnessed death	13		2
Dys-arrhythmia	1		0
Other vascular event	3		0
Cardiovascular mortality, *n* (%)	83 (4)	< 0.00001	27 (15)
Non-fatal MI, *n* (%)	38 (3)	0.68437	3 (4)
Non-fatal Stroke/TIA, *n* (%)	34 (2)	0.11938	1 (1)
Composite Endpoint/MACE, *n* (%)	155 (8)	0.00018	31 (17)
Non-Cardiovascular death, *n*	50 (3)	0.40164	7 (4)
Acute respiratory failure	0		2
Cancer	5		1
Infectious disease	8		0
Other	8		0
Unexplained	29		4
All-cause death, *n* (%)	133 (7)	<0.00001	34 (18)

MI myocardial infarction, *Cardiovascular mortality* Fatal MI plus fatal stroke plus vascular death, *MACE* major adverse cardiovascular events, *TIA* transient ischemic attack

* χ^2 test

Cardiovascular death

On Cox proportional hazard analysis, age > 75 years (HR 3.92, 95% CI 2.14–7.17; $p < 0.0001$), COPD (HR 2.73, 95% CI 1.76–4.23; $p < 0.0001$), HF (HR 1.84, 95% CI 1.23–2.75; $p = 0.003$), vascular disease (HR 1.82, 95% CI 1.22–2.71; $p = 0.003$), previous Stroke/TIA (HR 1.67, 95% CI 1.03–2.70; $p = 0.036$) and antithrombotic therapy (i.e. VKAs alone or combined with AP) (HR 0.36, 95% CI 0.24–0.55; $p < 0.0001$) are independent predictors of cardiovascular death in a model adjusted for gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, beta-blockers, ACEs, digoxin, clearance creatinine, statins, ARBs, and anti-dysrhythmic agents.

All-cause death

On Cox proportional hazard analysis, age > 75 years (HR 5.03, 95% CI 2.90–8.71; $p < 0.001$), age 65–74 years (HR 2.52, 95% CI 1.33–4.75; $p = 0.004$), COPD (HR 2.16, 95% CI 1.48–3.16; $p < 0.0001$), HF (HR 2.02, 95% CI 1.47–2.80; $p < 0.001$), previous Stroke/TIA (HR 1.55, 95% CI 1.04–2.29; $p = 0.030$), vascular disease (HR 1.41, 95% CI 1.00–1.98; $p = 0.047$) and antithrombotic therapy (i.e. VKAs alone or combined with AP versus no treatment) use (HR 0.44, 95% CI 0.31–0.62; $p < 0.0001$) are independent predictors of all-cause death in a model adjusted for gender, hypertension, diabetes mellitus, dyslipidemia, smoking habit, prior Stroke/TIA, beta-blockers, ACEs,

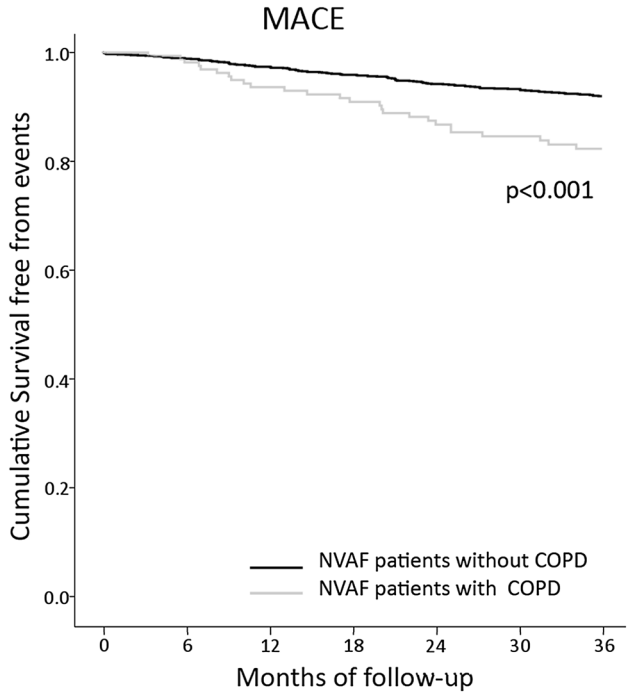

Fig. 1 Comparisons of cumulative MACE incidences between NVAF patients with or without COPD. Survival has been expressed as Cumulative Survival free from Events; *COPD* chronic obstructive pulmonary disease

digoxin, creatinine clearance, HF, statins, ARBs, and antidysrhythmic agents.

Subgroup of VKAs-anticoagulated NVAF patients for whom TTR was recorded

In the 467 NVAF patients treated with VKAs, 10.5% have COPD. Demographic, clinical and therapeutic characteristics are similar to the overall population (mean 72.4 ± 8.0 years, 41.5% women, 86.3% hypertensive, 18.0% diabetic, 22.7% previous cardiac events, 7.5% previous cerebrovascular events and 16.7% heart failure). During the follow-up, 53 MACE events were recorded. The mean TTR is $63.0 \pm 17.8\%$. After dividing the cohort into four groups according to TTR values, (group 1: 0–50%, group 2: 51–60%, group 3: 61–70% and group 4: > 70%), we find a higher percentage of low TTR in COPD compared to non-COPD patients (group 1 vs. 4, $p = 0.034$).

Kaplan–Meier curves show that the presence of COPD is significantly associated with MACE (log-rank test $p = 0.025$). On multivariate analysis, COPD is independently associated with MACE (HR: 2.27, 95% CI 1.18–4.35; $p = 0.014$), after adjustment for TTR < 70% and CHA_2DS_2Vasc score.

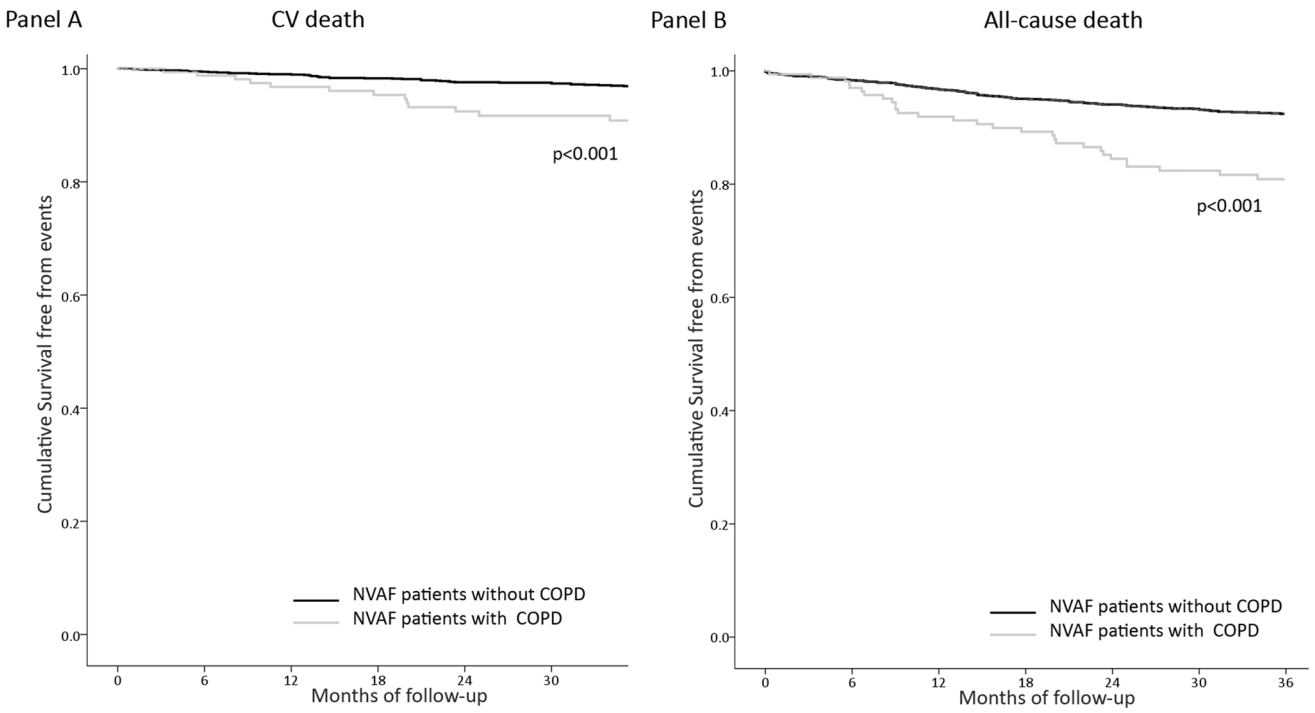

Fig. 2 Comparisons of cumulative incidences between NVAF patients with or without COPD: Panel A) CV death; Panel B) All-cause death. Survival has been expressed as Cumulative Survival free from Events; *COPD* chronic obstructive pulmonary disease

Subgroup analysis of urinary excretion of 11-deydhro-TxB_2

In a subgroup of 624 patients with available urine sample, 75 (12.0%) had COPD. This subset of patients has similar characteristics of the entire cohort (data not shown). Median U-TxB_2 is 100.0 [58.0–180.0] ng/mg of urinary creatinine. Patients with COPD show significant higher U-TxB_2 levels compared to those without COPD, 140.0 [70.7–350.0] vs 100.0 [55.0–170.0] ng/mg of urinary creatinine, $p < 0.001$). A multivariable linear regression model showed that COPD (Beta: 0.176, $p < 0.001$) is associated with U-TxB_2 and also after adjustment for CHA_2DS_2-VASc score (Beta:0.080, $p = 0.043$).

Ninety-four MACE, in particular vascular death ($n = 29$), fatal/non-fatal MI ($n = 39$), fatal/non-fatal stroke/TIA ($n = 26$), occurred in this subgroup. Median U-TxB_2 values are higher in patients experiencing CV death ($p < 0.001$), MI ($p = 0.002$) and stroke ($p = 0.026$). Log U-TxB_2 values are predictive of MACE on univariate Cox regression analysis (HR 2.12, 95% CI 1.65–2.72, $p < 0.001$).

Discussion

In the present study, we show that COPD is independently associated with an increased risk of MACE, CV death and all-cause mortality in a cohort of NVAF patients, prospectively followed up for 3 years.

The rate of cardiovascular events in this study is comparable to previous ones; [10, 25] in particular, the rate of cardiovascular and non-cardiovascular deaths is comparable to that reported in the XANTUS registry [26].

Previous studies on this topic focused on the relationship between COPD and risk of total and CV mortality in NVAF patients (summarized in Table 3). For example, a post hoc analysis of the ARISTOTLE study [12] investigates if the coexistence of COPD increases the risk of stroke or systemic embolism in AF patients. The prevalence of COPD was similar to that observed in our study (11%); however, no significant differences in the risk of cerebrovascular events were detected in AF patients with or without COPD during 1-year follow-up, although

Table 3 Comparisons among trials reporting evidence on AF patients with COPD

	Aristotle	Rocket AF	EORP AF	Arapacis
Study design	RCT	RCT	OBSERVATIONAL	OBSERVATIONAL
Antithrombotic therapy	APIXABAN 5 mg vs WARFA	RIVAROXABAN 20 mg vs WARFA	78.5% VKA 4.4% NOAC 5.6% Heparin 40.1% Any AP	61% VKA 19% AP 16% No Therapy 4% OAC + AP
TTR	62	55[a]	NR	63
Patients (*n*)	18,134	14,171	3086	2027
Follow-up (years)	1.8	1.9	1.0	2.9
Age	72 (65–77)	73[a]	72.5 ± 10.2	76.2 ± 8.6
Female (%)	30.3	40.0[a]	35.4	38
COPD Prevalence (%)	11	10	11	9
COPD definition	Anamnestic	Anamnestic	Anamnestic	Anamnestic
Comorbidities (%)				
Diabetes	27.8	40.0	29.7	25.0
Hypertension	86.9	90.0	74.9	82.0
Dyslipidemia	NR	NR	51.0	41.0
Valvular disease	NO	NO	69.7	NO
Previous MI	20.9	NR	20.9	22.0
Previous stroke/TIA	19.7	NR	12.2	11.0
HF	46.9	NR	63.3	34.0
$CHADS_2$ at inclusion	> 1	> 2*	Any	Any
CHA_2DS_2VASC (median)	NR	NR	4	4
CV mortality (%/year)	1.91	3.0*	6.3	2.3
All-cause mortality (%/year)	3.73	4.2*	12.8	3.5
MACE (%)	NR	NR	13.5 (+ bleeding)	3.9

AP Antiplatelet, *COPD* chronic obstructive pulmonary disease, *CV* cardiovascular, *HF* heart failure, *MI*, myocardial Infarction, *NOAC* new oral anticoagulants, *NR* not reported, *TTR* time in therapeutic range, *WARFA* warfarin

[a]Data referred to overall population as specific data on AF patients with COPD are not reported

COPD was independently associated with an increased risk of all-cause and CV mortality. A post hoc analysis of the ROCKET AF trial [11] shows that COPD is a significant predictor of all-cause mortality, but not of CV mortality in a follow-up of 1.9 years of 14,171 patients. Finally, the EORP-AF registry [13] reports a similar prevalence of COPD (11%), which is independently associated with all-cause mortality at 1-year follow-up.

In our cohort, the annual rate of overall and CV mortality are 3.5%/year and 2.3%/year, respectively, similar to those observed in the ARISTOTLE (3.73%/year for all-cause and 1.91%/year for CV death) [12] and ROCKET-AF (4.2%/year for all-cause and 3.0%/year for CV death) trials (Table 3) [11]. Furthermore, the annual rate of MACE in our cohort is 3.9%/year, which is consistent with previous reports from our cohort (3.43%/year) [27] and other groups (3.67%/year) [28].

Among the mechanisms potentially accounting for the association between COPD and MACE, platelet activation might have a role as suggested by previous studies reporting enhanced platelet aggregation and urinary excretion of 11-dehydro-TxB_2, a marker of in vivo platelet activation, in patients with COPD [8, 29]. The present study supports these previous studies, as urinary excretion of 11-dehydro-TxB_2 is more elevated in NVAF with COPD compared to NVAF alone, suggesting that platelet hyperactivation is a frequent feature of COPD [30]. In addition, in this specific sub-set, urinary excretion of 11-dehydro-TxB_2 is associated with poor vascular outcomes, which is consistent with a key role played by platelets in cardiovascular events occurring in NVAF patients [23].

To exclude that the increased risk of MACE was due to a different quality of antithrombotic treatment, we performed a subgroup analysis on VKAs-anticoagulated patients for whom TTR was available. This shows no difference in TTR between NVAF with and without COPD, indicating that the increased rate of MACE is not affected by anticoagulation quality.

Furthermore, we confirm that anticoagulation therapy exerts a protective effect in terms of adverse outcome regardless of other covariates. Interestingly, the percentage of AF patients properly treated with anticoagulants in ARAPACIS cohort was is higher than that reported in another multicenter study in Italy (around 40%) [31] reinforcing the relevance of a guidelines-adherent approach as best strategy for reducing adverse outcomes in AF patients. The difference between these two studies may rely on the fact that in the REPOSI study all patients were recruited during a hospital stay, while in the ARAPACIS study most were recruited from outpatient clinics.

Clinical implications and limitations

The main limitation of the ARAPACIS study is its observational study design, which does not allow establishing a cause-effect relationship between the presence of COPD and MACE occurrence. The lack of an objective assessment of COPD and the absence of any further details about clinical and severity of airways obstruction (based on spirometry as recommended by GOLD guidelines) is another major limitation.

Hence, a careful assessment of atherosclerotic co-morbidities should be part of routinely evaluation of AF patients, to improve cardiovascular risk stratification in AF, allowing an early identification of patients at higher risk for MACE. In this context, the ARAPACIS registry would suggest that COPD may be part of AF workup to identify patients at risk of vascular events.

Despite our data indicating a higher degree of platelet activation in AF patients with concomitant COPD, no interventional trials have been performed thus far to suggest a potential benefit of combination therapy of anticoagulation and antiplatelet in this subgroup of patients. Moreover, results may be different in patients treated with the non-vitamin K oral anticoagulants, as some of them (i.e. anti-factor Xa inhibitors) inhibit thromboxane urinary excretion [32]. Finally, even if thromboxane urinary excretion is considered a validated marker of platelet activation, it may reflect the activity of different enzymatic systems. [33, 34].

In conclusion, COPD is an independent predictor of MACE, CV death and all-cause death during a long-term follow-up of NVAF patients.

Acknowledgements Dr. Hiatt reports grants from Bayer, Janssen and AstraZeneca, outside the submitted work. ARAPACIS STUDY Collaborators Alessandri C., Serviddio G., Palange P., Greco E., Bruno G., Averna M., Giammanco A., Sposito P., De Cristofaro R., Carulli L., De Gennaro L., Pellegrini E. Cominacini L., Mozzini C., Pasini A.F.; Sprovieri M., Spagnuolo V., Cerqua G., Cerasola G., Mulé G., Barbagallo M., Lo Sciuto S., Monteverde A., Saitta A., Lo Gullo A., Malatino L., Cilia C., Terranova V., Pisano M., Pinto A., Di Raimondo D., Tuttolomondo A., Conigliaro R., Signorelli S., De Palma D., Galderisi M., Cudemo G., Galletti F., Fazio V., De Luca N., Meccariello A., Caputo D., De Donato M. T., Iannuzi A., Bresciani A., Giunta R., Utili R., Iorio V., Adinolfi L.E., Sellitto C., Iuliano N., Bellis P., Tirelli P., Sacerdoti D., Vanni D., Iuliano L., Ciacciarelli M., Pacelli A., Palazzuoli A., Cacciafesta M., Gueli N., Lo Iacono C., Brusco S., Verrusio W., Nobili L., Tarquinio N., Pellegrini F., Vincentelli G.M., Ravallese F., Santini C., Letizia C., Petramala L., Zinnamosca L., Minisola S., Cilli M., Colangelo L., Falaschi P., Martocchia A., Pastore F., Bertazzoni G., Attalla El Halabieh E., Paradiso M., Lizzi E.M., Timmi S., Battisti P., Cerci S., Ciavolella M., Di Veroli C., Malci F., De Ciocchis A., Abate D., Castellino P., Zanoli L., Fidone F., Mannarino E., Pasqualini L., Oliverio G., Pende A., Artom N., Ricchio R., Fimognari F.L., Alletto M., Messina S., Sesti G., Arturi F., Succurro E, Fiorentino T.V., Pedace E., Scarpino P.E., Carullo G., Maio R., Sciacqua A., Frugiuele P., Spagnuolo V., Battaglia G., Atzori S., Delitala G., Angelucci E., Sestili S., Traisci G., De Feudis L., Di Michele D., Fava A., Balsano C., De Ciantis P., Desideri G., Camerota A., Mezzetti M.,

Gresele P., Vedovati C., Fierro T., Puccetti L., Bertolotti M., Mussi C., Boddi M., Savino A., Contri S., Degl'Innocenti G., Saller A., Fabris F., Pesavento R., Filippi L., Vedovetto V., Puato M., Fabris F., Treleani M., De Luca E., De Zaiacomo F., Giantin V., Semplicini A., Minuz P., Romano S., Fantin F., Manica A., Stockner I., Pattis P., Gutmann B., Catena C., Colussi G., Sechi L.A., Annoni G., Bruni A.A., Castagna A., Spinelli D., Miceli E., Padula D., Schinco G., Spreafico S., Secchi B., Vanoli M., Casella G., Pulixi E.A., Sansone L., Serra M.G., Longo S., Antonaci S., Belfiore A., Frualdo M., Palasciano G., Ricci L., Ventrella F., Bianco C., Santovito D., Cipollone F., Nicolai S., Salvati F., Rini G. B., Scozzari F., Muiesan M.L., Salvetti M., Bazza A., Picardi A., Vespasiani-Gentilucci U., De Vincentis A., Cosio P., Terzolo M., Madaffari B., Parasporo B., Fenoglio L., Bracco C., Melchio R., Gentili T., Salvi A., Nitti C., Gabrielli A., Martino G.P., Capucci A., Brambatti M., Sparagna A., Tirotta D., Andreozzi P., Ettorre E., Viscogliosi G., Servello A., Musumeci M., Delfino M., Giorgi A., Glorioso N., Melis G., Marras G., Matta M., Sacco A., Stellitano E., Scordo A., Russo F., Caruso A.A., Porreca E., Tana M., Ferri C., Cheli P., Portincasa P., Muscianisi G., Giordani S., Stanghellini V., Sabbà C., Mancuso G., Bartone M., Calipari D., Arcidiacono G., Bellanuova I., Ferraro M., Marigliano G., Cozzolino D., Lampitella A., Acri V., Galasso D., Mazzei F., Buratti A., Galasso S., Porta M., Brizzi M.F., Fattorini A., Sampietro F., D'Angelo A., Manfredini R., Pala M., Fabbian F., Moroni C., Valente L., Lopreiato F., Parente F., Granata M., Moia M., Braham S., Rossi M., Pesce M., Gentile A., Catozzo V., Baciarello G., Cosimati A., Ageno W., Rancan E., Guasti L., Ciccaglioni A., Negri S., Polselli M., Prisco D., Marcucci R., Ferro D., Perri L.,, Cangemi R., Saliola M., Del Ben M., Angelico F., Baratta F., Migliacci R., Porciello G., Corrao S. Data entry and Safety Monitoring Board: Proietti M., Raparelli V., Napoleone L., Talerico G., Amoroso D., Romiti G.F., Ruscio E., Toriello F., Sperduti N., Todisco T., Di Tanna G., Sacchetti M.L., Puddu P.E., Farcomeni A. Simi Young Internists Group: Anzaldi M., Bazzini C., Bianchi P.I., Boari B., Bracco C., Buonauro A., Buttà C., Buzzetti E., Calabria S., Capeci W., Caradio F., Carleo P., Carrabba M.D., Castorani L., Cecchetto L., Cicco S., Cimini C., Colombo B.M., De Giorgi A., De Vuono S., Del Corso L., Denegri A., Di Giosia P., Durante Mangoni E., Falsetti L., Forgione A., Giorgini P., Grassi D., Grembiale A., Hijazi D., Iamele L., Lorusso G., Marchese A., Marra A.M., Masala M., Miceli G., Montebianco Abenavoli L., Murgia G., Naccarato P., Padula D., Pattoneri P., Perego F., Pesce P., Piano S., Pinna M., Pinto D., Pretti V., Pucci G., Salinaro F., Salzano A., Santilli F., Scarpini F., Scicali R., Sirico D., Suppressa P., Talia M., Tassone E.J., Torres D., Vazzana N., Vecchio C.R., Vidili G., Vitale F., Zaccone V.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement of human and animal rights All procedures performed in this study involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in this study.

References

1. Vestbo J, Hurd SS, Agusti AG et al (2013) Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 187:347–365
2. Bousquet J, Dahl R, Khaltaev N (2007) Global alliance against chronic respiratory diseases. Eur Respir J 29:233–239
3. Ambrosino P, Lupoli R, Iervolino S, De Felice A, Pappone N, Storino A, Di Minno MND (2017) Clinical assessment of endothelial function in patients with chronic obstructive pulmonary disease: a systematic review with meta-analysis. Intern Emerg Med 12:877–885
4. Diez-Manglano J, Barquero-Romero J, Almagro P et al (2014) COPD patients with and without metabolic syndrome: clinical and functional differences. Intern Emerg Med 9:419–425
5. Roversi S, Fabbri LM, Sin DD, Hawkins NM, Agusti A (2016) Chronic obstructive pulmonary disease and cardiac diseases: an urgent need for integrated care. Am J Respir Crit Care Med 194:1319–1336
6. Cavailles A, Brinchault-Rabin G, Dixmier A et al (2013) Comorbidities of COPD. Eur Respir Rev 22:454–475
7. Catella F, Healy D, Lawson JA, FitzGerald GA (1986) 11-Dehydrothromboxane B2: a quantitative index of thromboxane A2 formation in the human circulation. Proc Natl Acad Sci USA 83:5861–5865
8. Davi G, Basili S, Vieri M et al (1997) Enhanced thromboxane biosynthesis in patients with chronic obstructive pulmonary disease. The Chronic Obstructive Bronchitis and Haemostasis Study Group. Am J Respir Crit Care Med 156:1794–1799
9. Soliman EZ, Safford MM, Muntner P et al (2014) Atrial fibrillation and the risk of myocardial infarction. JAMA Internal Med 174:107–114
10. Violi F, Soliman EZ, Pignatelli P, Pastori D (2016) Atrial fibrillation and myocardial infarction: a systematic review and appraisal of pathophysiologic mechanisms. J Am Heart Assoc 5:e003347
11. Pokorney SD, Piccini JP, Stevens SR et al (2016) Cause of death and predictors of all-cause mortality in anticoagulated patients with nonvalvular atrial fibrillation: data from ROCKET AF. J Am Heart Assoc 5:e002197
12. Durheim MT, Cyr DD, Lopes RD et al (2016) Chronic obstructive pulmonary disease in patients with atrial fibrillation: insights from the ARISTOTLE trial. Int J Cardiol 202:589–594
13. Proietti M, Laroche C, Drozd M et al (2016) Impact of chronic obstructive pulmonary disease on prognosis in atrial fibrillation: a report from the EURObservational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) General Registry. Am Heart J 181:83–91
14. Violi F, Davi G, Proietti M et al (2016) Ankle-Brachial Index and cardiovascular events in atrial fibrillation. The ARAPACIS Study, Thromb Haemost, p 115
15. Violi F, Davi G, Hiatt W et al (2013) Prevalence of peripheral artery disease by abnormal ankle-brachial index in atrial fibrillation: implications for risk and therapy. J Am Coll Cardiol 62:2255–2256
16. Raparelli V, Proietti M, Butta C et al (2014) Medication prescription and adherence disparities in non valvular atrial fibrillation patients: an Italian portrait from the ARAPACIS study. Intern Emerg Med 9:861–870
17. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 137:263–272
18. Kirchhof P, Benussi S, Kotecha D et al (2016) 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS: The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart

Rhythm Association (EHRA) of the ESCEndorsed by the European Stroke Organisation (ESO). European heart journal
19. Thygesen K, Alpert JS, White HD et al (2007) Universal definition of myocardial infarction. Circulation 116:2634–2653
20. Whisnant JP, Basford JR, Bernstein EF et al. (1990) Classification of cerebrovascular diseases III. Stroke 21:637–676
21. Miller AJ (2002) Subset selection in regression. CRC monographs on statistics and applied probability. Chapman & Hall, CRC Press
22. Pastori D, Pignatelli P, Saliola M et al (2015) Inadequate anticoagulation by vitamin K Antagonists is associated with major adverse cardiovascular events in patients with atrial fibrillation. Int J Cardiol 201:513–516
23. Pastori D, Pignatelli P, Farcomeni A et al (2015) Urinary 11-dehydro-thromboxane B2 is associated with cardiovascular events and mortality in patients with atrial fibrillation. Am Heart J 170(490–497):e491
24. Pastori D, Pignatelli P, Farcomeni A, Nocella C, Bartimoccia S, Carnevale R, Violi F (2016) Age-related increase of thromboxane B2 and risk of cardiovascular disease in atrial fibrillation. Oncotarget 7:39143–39147
25. Pastori D, Pignatelli P, Angelico F et al (2015) Incidence of myocardial infarction and vascular death in elderly patients with atrial fibrillation taking anticoagulants: relation to atherosclerotic risk factors. Chest 147:1644–1650
26. Camm AJ, Amarenco P, Haas S et al (2015) XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J 37:1145–4453
27. Pastori D, Pignatelli P, Angelico F et al (2015) Incidence of myocardial infarction and vascular death in elderly patients with atrial fibrillation taking anticoagulants: relation to atherosclerotic risk factors. Chest 147:1644–1650
28. Larsen TB, Rasmussen LH, Gorst-Rasmussen A, Skjoth F, Rosenzweig M, Lane DA, Lip GY (2014) Myocardial ischemic events in 'real world' patients with atrial fibrillation treated with dabigatran or warfarin. Am J Med 127(329–336):e324
29. Ferroni P, Basili S, Pulcinelli FM, Pettirossi G, Alessandri C, Violi F, Gazzaniga PP, Cordova C (1994) In vivo thrombin generation and platelet hyperactivity in patients with chronic obstructive pulmonary disease. Platelets 5:276–278
30. Malerba M, Clini E, Malagola M, Avanzi GC (2013) Platelet activation as a novel mechanism of atherothrombotic risk in chronic obstructive pulmonary disease. Expert Rev Hematol 6:475–483
31. Proietti M, Nobili A, Raparelli V, Napoleone L, Mannucci PM, Lip GY, Investigators R (2016) Adherence to antithrombotic therapy guidelines improves mortality among elderly patients with atrial fibrillation: insights from the REPOSI study. Clin Res Cardiol 105:912–920
32. Pignatelli P, Pastori D, Bartimoccia S, Menichelli D, Vicario T, Nocella C, Carnevale R, Violi F (2016) Anti Xa oral anticoagulants inhibit in vivo platelet activation by modulating glycoprotein VI shedding. Pharmacol Res 113:484–489
33. Mitchell JA, Knowles RB, Kirkby NS et al (2018) Kidney transplantation in a patient lacking cytosolic phospholipase A2 Proves Renal Origins of urinary PGI-M and TX-M. Circ Res 122:555–559
34. Grosser T, Naji A, FitzGerald GA (2018) Urinary prostaglandin metabolites: an incomplete reckoning and a flush to judgment. Circ Res 122:537–539