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Platelet reactivity in stable cardiovascular patients with chronic kidney disease

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Abstract

The study aimed to evaluate antiplatelet drug responsiveness in stable outpatients with cardiovascular disease and chronic kidney disease (CKD) and examine whether impaired antiplatelet drug responsiveness is associated with worse clinical outcomes in this population. Stable cardiovascular patients (n = 771) were enrolled at least one month after an acute ischemic atherothrombotic event. Antiplatelet drug responsiveness was assessed with specific assays (serum TxA_2 for aspirin, the VASP assay for clopidogrel) and other aggregation-based assays using different agonists. All patients were followed until the first occurrence of a major adverse cardiovascular event. The 133 CKD patients were found to have higher activity of von Willebrand factor and higher fibrinogen levels. After a median follow-up of 33 months, 88 events occurred in patients without CKD and 31 events in patients with CKD (5.0 events and 8.7 events per 100 patient years, respectively, HR = 1.75 (95% CI 1.16–2.63; p = 0.008). The prevalence of poor aspirin and clopidogrel responsiveness and high platelet reactivity as assessed with different aggregation-based assays was similar in patients with estimated GFR ≥ 60 ml/min, 45–59 ml/min, and < 45 ml/min. No significant interaction for CKD vs. non-CKD was observed for events occurrence in patients with or without high platelet reactivity on several assays, with the exception of collagen-induced aggregation. In stable cardiovascular patients, CKD is not associated with higher platelet reactivity. Decreased antiplatelet drug responsiveness is not associated with worse clinical outcomes in CKD patients.

Keywords

Aspirin, chronic kidney disease, clopidogrel, high platelet reactivity, major adverse cardiovascular events

History

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Introduction

Chronic kidney disease (CKD) is associated with significant cardiovascular morbidity and mortality. The incidence of major adverse cardiovascular events (myocardial infarction, stroke, sudden cardiac death) and the concomitant reduction in life expectancy increase as CKD progresses [1].

CKD is also responsible for a thrombotic predisposition and a bleeding diathesis [2]. Different mechanisms have been proposed for the underlying platelet dysfunction. However, most data come from end-stage renal disease patients and are, at least in part, based on methods that have now become obsolete [3].

Antiplatelet agents are widely used for the management of CKD patients with cardiovascular disease. A recent meta-analysis showed that antiplatelet treatment reduces the risk of myocardial infarction, but does not alter the risk of stroke and does not lower all-cause mortality in patients with CKD [4].

The impact of renal function on the efficacy of antiplatelet agents has been evaluated by different studies over the last five years (Table I) [5–16]. Most of them were designed to assess platelet inhibition in patients undergoing percutaneous coronary or intravascular intervention (PCI) for stable coronary artery disease (CAD) or acute coronary syndrome (ACS), usually after a loading dose of clopidogrel [5–12]. Three of them also reported clinical outcomes [6,7,12]. Low responder status was more common in CKD patients and/or was associated with worse clinical outcomes in the acute setting.

Five studies assessed platelet function in stable patients with CKD receiving long-term single or dual antiplatelet therapy (DAPT) [5,13–16]. Although higher platelet reactivity was reported in CKD patients in all but one of these studies [5], no clinical outcomes were available.

The main objective of the present study, a subgroup analysis of the ADRIE study [17,18], was to evaluate antiplatelet drug responsiveness in stable cardiovascular outpatients with CKD and to examine whether impaired antiplatelet drug responsiveness, measured with specific or aggregation-based assays, is associated with higher incidence of adverse cardiovascular events during a prospective follow-up of this specific population.

Methods

The Antiplatelet Drug Resistances and Ischemic Events (ADRIE) study was a cohort study that prospectively evaluated the association between platelet reactivity and ischemic atherothrombotic events (ClinicalTrials.gov identifier NCT00501423). The Central Ethics Committee of Geneva University Hospitals in Switzerland,

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Table I. Studies assessing platelet function in chronic kidney disease (CKD) patients.

Study	Population	Drug	Tests	Control group	Intervention groups	Biological outcome	Clinical outcome
Thromb Res 2010; 126: e400–2[5]	NSTE-ACS patients	ASA 75 mg Clopidogrel 150 mg	- PRI VASP - LTA with ADP 10 μM	Cockroft-Gault CrCl ≥ 60 $N = 179$	CrCl < 60 $N = 44$	-12h post loading dose: ADP-aggregation 48.9% vs. 49.8% ($p = 0.71$); PRI-VASP 48.4% vs. 44.6% ($p = 0.22$) - ADP-Ag 52.5% vs. 55.4%, $p = 0.26$ at 1 month - PRI VASP 43.8% vs. 10.5%, $p = 0.31$ at 1 month	—
J Am Coll Cardiol 2011; 57: 399–408[6]	Consecutive patients undergoing PCI for ACS or stable CAD (urgent in 76%)	≥ 6 h after clopidogrel loading dose (300–600 mg)	- PRI VASP (cutoff ≥ 61% for non-responders)	MDRD eGFR ≥ 60 $N = 314$	eGFR 15–59 $N = 126$	- Median PRI 55.7% vs. 55.8% ($p = 0.53$) - Low responders 40% vs. 42% ($p = 0.75$)	- All cause mortality at 9 ± 2 months: 3.2% vs. 12.1% ($p = 0.001$) - Low responder status (as compared with responders) associated with higher mortality only in CKD - Interaction between CKD-low response: independent predictor of cardiac mortality
J Am Soc Nephrol 2011; 22: 627–33[7]	Consecutive patients undergoing PCI for ACS or stable CAD	≥ 6 h after clopidogrel loading dose (300–600 mg)	- ADP-induced platelet aggregation (low responders if > 75 percentile)	Stage I & II (eGFR ≥ 60)	Stage III- V (eGFR < 60)	- Significant trend of low responders among CKD stage III-V	- Higher cumulative event rate in patients with eGFR< 30 ml/min compared with eGFR ≥ 30 ml/min - Higher incidence of events in low responders to clopidogrel
Heart Vessels 2012; 27: 480–5[8]	Male patients undergoing PCI (ACS in 51%)	ASA 100 mg Clopidogrel 300 mg once	20-24h post PCI: - PFA-100 - LTA with E, ADP 5 μM, collagen, ristocetin	Patients without CKD $N = 18$	Cockroft-Gault CrCl < 60 $N = 19$	- Poor responders (as per PFA-100 assay) more frequently among CKD - No difference between groups with the 4 LTA aggregation tests	—
Am J Cardiol 2012; 109: 620–3[9]	Patients undergoing PCI	Clopidogrel 600 mg once	- PRI VASP 20 ± 4 h post clopidogrel loading dose	Cystatin-C based eGFR >90 $N = 52$	eGFR ≤ 90 $N = 223$	Non-responders to clopidogrel (PRI ≥ 50%): 31.9% vs. 34.4% ($p = 0.702$)	—
Nephrol Dial Transplant 2013; 28: 2116–22[10]	Patients undergoing PCI	ASA 100 mg Clopidogrel 75 mg	- IIb/IIIa platelet surface expression - VerifyNow P2Y12 & ASA - LTA (ADP 10 μM, AA)	MDRD eGFR ≥ 60 $N = 226$	eGFR < 60 $N = 90$	-Higher IIb/IIIa expression in CKD at baseline & after exposure to ADP-AA - Higher platelet reactivity in CKD with VerifyNow P2Y12-AA assays - Higher platelet reactivity as per LTA in response to ADP-AA in CKD patients - Higher HRPR-ADP with both assays in CKD	—

(*Continued*)

Table I. (Continued).

Study	Population	Drug	Tests	Control group	Intervention groups	Biological outcome	Clinical outcome
J Thromb Thrombolysis 2013; 36:14–7[11]	Non-diabetics with stable CAD	ASA 80 mg Clopidogrel 600 mg once	- PRI VASP - LTA with ADP 5 & 20 μM at 0, 2, 24 h	Cockroft-Gault CrCl ≥ 60 $N = 30$	CrCl < 60 $N = 30$	- Similar baseline platelet reactivity - No difference between groups at all time points for all tests	—
POPULAR Thromb Haemost 2014; 112: 1174–81[12]	Documented CAD undergoing elective PCI	ASA 80–100 Clopidogrel 75 mg ≥ 5 d, or 300 mg ≥ 1 d, or 600 mg ≥ 2 h before PCI	- LTA (ADP 5 μM, AA) - PRU with VerifyNow (with AA or ADP and PGE_1)	MDRD eGFR ≥ 60 $N = 808$	eGFR<60 $N = 180$	- LTA ADP5 39 vs. 43% ($p = 0.02$) - PRU 207 vs. 226 ($p = 0.004$) - LTA AA 29.9 vs. 28.7 ($p = 0.002$) - ARU 453 vs. 477 ($p = 0.02$)	- Composite end-point[a] incidence higher in CKD - Cumulative event-rate highest in patients with HCPR & CKD - TIMI major or minor bleeding 4.5% vs. 9.4% ($p = 0.01$)
Am J Cardiol 2009; 104: 1292–5[13]	Patients post coronary angiography or PCI-PVI (no recent acute events)	ASA 100 mg Clopidogrel 75 mg (I-II), 150 mg (III) for 4 weeks	- PRU with VerifyNow	Group I: Cockroft-Gault CrCl > 60 $N = 23$	Groups II-III: creatinine ≥ 3 mg/dl for ≥ 6 months $N = 18$ for each group	- PRU 240 vs. 309 vs. 303 ($p = 0.013$) - Mean % inhibition at 4 weeks: 35 vs. 21 vs. 23 ($p = 0.026$)	—
J Am Coll Cardiol 2010; 55: 1139–46[14]	Diabetics with angiographically documented CAD, no acute events in the last 3 months	ASA 100 mg Clopidogrel 75 mg for ≥ 30 days	- LTA with ADP 20 μM & collagen 6 μg/ml	Cockroft-Gault CrCl ≥ 60 $N = 222$	CrCl < 60, HD patients excluded $N = 84$	- ADP-induced aggregation: 52 vs. 60% ($p = 0.001$) - Collagen-induced aggregation: 41 vs. 49% ($p = 0.004$) - $HPPR_{ADP}$ 21% vs. 36% ($p = 0.007$) - $HPPR_{COLL}$ 22% vs. 33% ($p = 0.043$)	—
PIANO-2 CKD Am Heart J 2011; 162: 1018–25[15]	Chronic HD patients undergoing PCI for stable CAD (no recent acute events)	ASA 100 mg Clopidogrel loading dose 300 mg, then 75 or 150 mg	Day 0 & 14: - LTA with ADP 5 & 20 μM - PRU with VerifyNow	Patients with normal kidney function (on clopidogrel 75 mg) $N = 50$	HD patients (on 75 or 150 mg of clopidogrel) $N = 74$	- Significantly higher platelet aggregation at 14 days in HD pts ($p < 0.01$) - Maximal IPA is lower in HD patients ($p < 0.05$) - Lower HOPR rate and PRU value in controls	—
Am J Kidney Dis 2012; 59: 777–85[16]	Stable patients admitted in cardiology- nephrology	Clopidogrel 75 mg for at least 8 days	- PRI VASP - PRU (with 20 μmol ADP) with VerifyNow	CKD-EPI eGFR ≥ 60 $N = 29$	4 groups for CKD stage 3a, 3b, 4, 5 $N = 21$–26-14–36 respectively	- PRI higher in CKD5 (61%) vs. eGFR ≥ 60 (44%), ($p = 0.002$) - Mean PRU 268 (stage 5), 238 (stage 4) vs. 150 (control), $p < 0.001$ & 0.02	—

ACS, acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; PVI, peripheral vascular intervention; ASA, aspirin; NSTE-ACS, non-ST segment elevation acute coronary syndrome; CrCl, creatinine clearance in ml/min; eGFR, estimated glomerular filtration rate in ml/min.1.73m^2; PRI, platelet reactivity index; VASP, VAsodilator-Stimulated Phosphoprotein; PRU, P2Y12 reaction units; HD, hemodialysis; LTA, light transmittance aggregometry; μM, μmol/l; IPA, inhibition of platelet aggregation defined as the % decrease in aggregation values (at baseline and after treatment); HOPR, high on-treatment platelet reactivity, defined as 5 μM of ADP-induced maximal percent change of light transmission >50%; PFA, platelet function analyzer; E, epinephrine; AA, arachidonic acid; HRPR-ADP, high on-treatment residual ADP-inducible platelet reactivity, defined as PRU > 235 for the VerifyNow P2Y12 assay, and as maximal aggregation >67% for LTA ADP; $HPPR_{ADP}$, high post-treatment platelet reactivity to ADP, defined as the upper quartile of platelet aggregation; $HPPR_{COLL}$, high post-treatment platelet reactivity to collagen, defined as the upper quartile of platelet aggregation; PGE_1, prostaglandin E_1; HCPR, high on clopidogrel platelet reactivity, defined as >236 PRU; d, day.

a. all-cause mortality, non-fatal myocardial infarction, definite stent thrombosis, and ischemic stroke at one-year.

the Montpellier St-Eloi Ethics Committee in France approved the original study protocol. The current study was also approved by the McGill University Health Centre Research Ethics Board. All participants provided informed consent. The authors adhere to the *Declaration of Helsinki* principles.

The study protocol has been presented in detail elsewhere [17,18]. In summary, 771 consecutive patients with known CAD, cerebrovascular disease, or peripheral artery disease were enrolled at three different centers in France and Switzerland, at least one month after the last documented ischemic atherothrombotic event. All patients had to be treated with aspirin and/or clopidogrel for less than 5 years. They should not be treated with anticoagulants, non-steroidal anti-inflammatory drugs, or other antiplatelet agents.

The following platelet function assays were performed at two outpatient visits, between one and three months apart: serum thromboxane (Tx) B2 (the stable breakdown product of TxA2), vasodilator-stimulated phosphoprotein (VASP) phosphorylation status and the derived platelet reactivity index (PRI), the PFA-100 (Siemens, Marburg, Germany), and light transmission aggregometry using four different agonists (arachidonic acid (AA) 1 mmol/l, adenosine diphosphate (ADP) 5 and 20 μmol/l, or collagen 1 μg/ml). An automated method was used for fibrinogen assay, von Willebrand factor (vWF) ristocetin cofactor assay (Siemens, Marburg, Germany), and high sensitivity C- reactive protein (CRP) (Beckman Coulter, Paris, France).

Poor aspirin responsiveness was defined as a TxB2 level ≥ 12 ng/ml. Poor clopidogrel responsiveness was defined as a VASP-PRI ≥ 50% [17]. For aggregation-based assays, high platelet reactivity was defined as maximal aggregation ≥ 20% with arachidonic acid, maximal aggregation ≥ 90th percentile of the distribution with collagen 1 μg/mL, and maximal aggregation ≥ 55% with ADP 20 μmol/L and ≥ 42% with ADP 5 μmol/L. For the PFA-100 assay, the cutoff of <190 sec was used [18].

Creatinine values upon inclusion were available for 769 out of the 771 patients. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation. CKD was defined as an eGFR < 60 ml/min.1.73 m^2.

All patients were followed until the first occurrence of an adverse cardiovascular event, which was defined as acute myocardial infarction, unstable angina, hospitalization for revascularization, acute limb ischemia, ischemic stroke, transient ischemic attack, or cardiovascular death. The physicians following the patients were blinded to all platelet function test results. An independent committee adjudicated all adverse cardiovascular events [18]. Patients were also asked to report bleeding events that were subsequently recorded as minor or major bleedings according to the definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients [19].

Statistical analysis

Results are presented as mean ± standard deviation, or median (interquartile range) for continuous variables, or frequencies (percentage) for categorical variables. To compare baseline characteristics of patients with or without CKD, the χ^2 test was used for categorical variables, and the t-test or the Mann–Whitney test for continuous variables.

To assess the effect of CKD on antiplatelet drug responsiveness, patients were divided into three groups according to the eGFR values (≥ 60, 45–59, and < 45 ml/min.1.73 m^2), and the χ^2 test for trend was used.

Kaplan–Meier and log-rank methods were used to evaluate the association of CKD with adverse cardiovascular events. Cox proportional hazard models were used to determine hazard ratios for adverse cardiovascular events in patients with high or normal platelet reactivity, stratified by the presence or absence of CKD (cutoff of 60 ml/min.1.73 m^2).

Patients on DAPT were stratified according to the absence or presence of poor response to one or both antiplatelet agents. The χ^2 test for trend was used to estimate the effect of renal function on antiplatelet drug resistance. Hazard ratios for adverse cardiovascular events in patients with absence or presence of resistance to one or both antiplatelet agents, stratified by the presence or absence of CKD (cutoff of 60 ml/min.1.73 m^2), were calculated with Cox proportional hazard models.

Results

Seven hundred sixty-nine patients had available creatinine values at baseline and were included in this analysis. Among them, 133 patients (17.3%) had CKD: 88 with eGFR of 45–59 and 45 with eGFR less than 45 ml/min.1.73m^2. Median eGFR was 52 ml/min.1.73m^2 in the CKD group and 88 ml/min.1.73m^2 in the non-CKD group. Patients with CKD were older, with a higher proportion of females, and had higher prevalence of hypertension, lower albumin and higher CRP levels (Table II). These differences reflect the higher morbidity of CKD patients. CKD patients

Table II. Baseline characteristics in patients with and without chronic kidney disease.

	eGFR ≥ 60 ml/min.1.73m^2	eGFR < 60 ml/min.1.73m^2	*p*
N	636	133	
Male sex	530 (83.3%)	93 (69.9%)	<0.001
Age (years)	60.9 ± 11.6	72.4 ± 9.7	<0.001
Race (blacks)	8 (1.3%)	1 (0.8%)	0.62
Hypertension	328 (51.6%)	109 (82%)	<0.001
Diabetes	130 (20.4%)	37 (27.8%)	0.06
Coronary disease	464 (73.0%)	92 (69.2%)	0.74
DAPT	363 (57.1%)	74 (55.6%)	0.76
Albumin (g/l)	39.9 ± 3.9	38.6 ± 3.1	0.01
Creatinine (μmol/l)	79 (69–89)	116 (106–142)	<0.001
eGFR (ml/min.1.73m^2)	88 (75–98)	52 (41–56)	<0.001
CRP (mg/l)	1.8 (0.7–4.4)	2.7 (1.1–6.7)	0.001
PLT count (x 10^9/L)	224 (191–268)	219 (187–276)	0.80
Fibrinogen (g/L)	3.4 (3.0–4.0)	3.8 (3.3–4.5)	<0.001
vWF: RCo (%)	135 (97–166)	166 (137–224)	<0.001

Results are presented as mean ± standard deviation, or median (interquartile range), or number of patients (percentage). *N*, number of patients in each group; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate (CKD EPI equation); CRP, C-reactive protein; PLT, platelet; vWF: RCo, von Willebrand factor ristocetin cofactor.

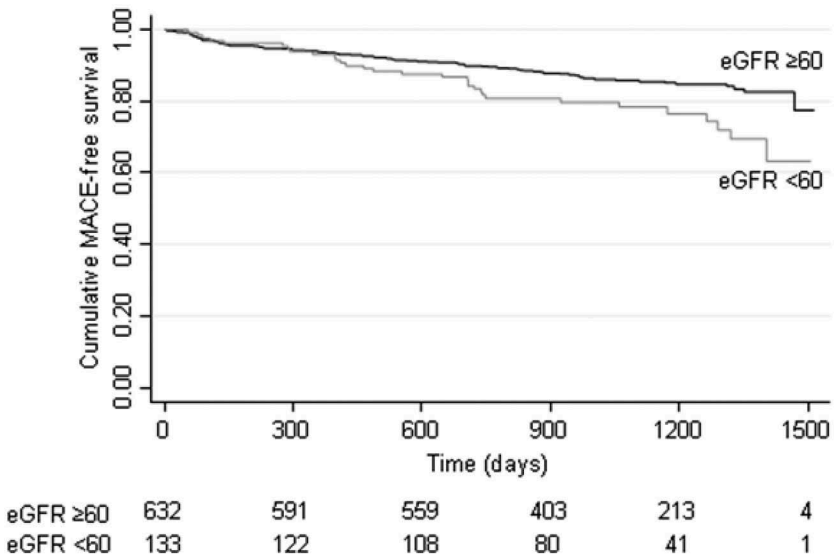

Figure 1. Major adverse cardiovascular events in patients with and without chronic kidney disease (HR 1.75, 95% CI 1.16–2.63) eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events.

were also found to have higher activity of von Willebrand factor and higher fibrinogen levels compared with non-CKD patients (Table II).

After a median follow-up of 33 months, 88 adverse cardiovascular events occurred in non-CKD patients and 31 adverse cardiovascular events in patients with CKD (5.0 events and 8.7 events per 100 patient-years, respectively). Kaplan–Meier analysis showed a significantly higher event rate in CKD patients compared with non-CKD patients (log-rank $p = 0.007$, Figure 1). The hazard ratio for adverse cardiovascular events was 1.75 (95% CI 1.16–2.63; $p = 0.008$). Thirty-five bleeding events occurred during follow-up: 25 in non-CKD patients (1.4 events per 100 patient-years), 4 in patients with eGFR 45–60 (1.7 events per 100 patient-years), and 6 in patients with eGFR<45 ml/min.1.73m^2 (5.3 events per 100 patient-years) (χ^2 for trend = 6.3; $p = 0.01$).

Table III shows the prevalence of poor aspirin and clopidogrel responsiveness (as assessed with specific assays) and high platelet reactivity (as assessed with different aggregation-based assays) across the eGFR groups. There was no significant difference between patients with and without CKD. No significant interaction for CKD versus non-CKD was observed for adverse cardiovascular events in patients with or without high platelet reactivity on several aggregation assays, with the exception of HPR assessed with collagen-induced aggregation (Table IV). A sensitivity analysis excluding the revascularization events yielded similar results. In univariate regression analysis, vWF activity or fibrinogen levels were not associated with adverse cardiovascular events ($p = 0.10$ and $p = 0.67$, respectively).

Six hundred fifty-seven patients were on aspirin and 548 patients on clopidogrel (437 patients were on dual antiplatelet therapy [DAPT]). DAPT was used at a similar rate in patients with and without CKD (55.6% vs. 57.1%, $p = 0.76$). Among patients on DAPT ($N = 437$), 74 had CKD (16.9%). The prevalence of biological poor response to either or both antiplatelet agents was similar in patients with or without CKD (Table V).

Seventy-two adverse cardiovascular events occurred in patients on DAPT (6.1 per 100 patients-years) versus 47 in patients on a single antiplatelet agent. The events rate was not statistically different in patients on DAPT with or without CKD (8.4 events versus 5.6 events per 100 patient-years; HR 1.54; 95% CI 0.90–2.66). Twenty-three events occurred in the 144 patients responding to both agents (5.9 per 100 patient-years), 35 events in the 215 patients who were poor responders to one of the agents (6.0 per 100 patient-years), and 14 events in the 78 patients who were poor responders to both agents (6.6 per 100 patient-years). The results were similar in the CKD subgroup. There was no impact of CKD in the events rate across the groups of antiplatelet drug responsiveness (p for interaction = 0.55).

Discussion

This cohort study assessed antiplatelet drug responsiveness in stable cardiovascular outpatients with specific and aggregation-based assays using different agonists. All patients were prospectively followed until the first occurrence of an adverse cardiovascular event. We report three important findings. First, a

Table III. Prevalence of aspirin and clopidogrel poor response (as assessed with serum TxB2 and the VASP assay, respectively) and high platelet reactivity according to different aggregation-based assays.

eGFR in ml/min.1.73m^2	≥ 60	45–59	< 45	p for trend[a]
Poor aspirin responsiveness	156/542 (29%)	17/75 (23%)	8/38 (21%)	0.16
Poor clopidogrel responsiveness	238/455 (52%)	31/63 (49%)	21/30 (70%)	0.20
HPR arachidonic acid	121/635 (19%)	16/88 (18%)	6/44 (14%)	0.41
HPR ADP5	504/635 (79%)	66/88 (75%)	41/44 (93%)	0.20
HPR ADP20	442/635 (70%)	58/88 (66%)	32/44 (73%)	0.99
HPR PFA100	270/634 (43%)	43/88 (49%)	17/44 (39%)	0.87
HPR collagen	66/635 (10%)	8/88 (9%)	2/43 (5%)	0.24

eGFR, estimated glomerular filtration rate (CKD EPI equation); HPR, high platelet reactivity.
[a]Chi square test for trend.

Table IV. Outcomes in patients with aspirin or clopidogrel poor response (as assessed with serum TxB2 and the VASP assay, respectively) or with high platelet reactivity according to different aggregation-based assays, stratified by the presence or absence of chronic kidney disease.

HPR test	CKD status	MACEs if HPR	MACEs if no HPR	HR (95% CI)	*p* for interaction
Poor aspirin responsiveness	with CKD	5 (20.0%)	19 (21.6%)	0.92 (0.34–2.48)	0.88
	without CKD	20 (12.8%)	57 (14.8%)	0.83 (0.50–1.37)	
Poor clopidogrel responsiveness	with CKD	13 (25.0%)	11 (26.8%)	0.97 (0.43–2.17)	0.95
	without CKD	34 (14.3%)	32 (14.7%)	0.94 (0.58–1.52)	
HPR arachidonic acid	with CKD	8 (36.4%)	23 (20.9%)	2.07 (0.93–4.64)	0.12
	without CKD	16 (13.2%)	72 (14.0%)	0.94 (0.55–1.61)	
HPR ADP5	with CKD	27 (25.2%)	4 (16.0%)	1.92 (0.67–5.49)	0.46
	without CKD	72 (14.3%)	16 (12.2%)	1.19 (0.69–2.05)	
HPR ADP20	with CKD	23 (25.6%)	8 (19.0%)	1.63 (0.73–3.66)	0.90
	without CKD	68 (15.4%)	20 (10.4%)	1.66 (1.01–2.74)	
HPR PFA100	with CKD	16 (26.7%)	15 (20.8%)	1.28 (0.63–2.59)	0.23
	without CKD	32 (11.9%)	56 (15.4%)	0.78 (0.51–1.21)	
HPR collagen	with CKD	4 (40.0%)	27 (22.3%)	2.09 (0.73–5.97)	0.02
	without CKD	4 (6.1%)	84 (14.8%)	0.38 (0.14–1.04)	

CKD, chronic kidney disease (defined as CKD EPI estimated glomerular filtration rate < 60 ml/min.1.73 m^2); MACEs, major adverse cardiovascular events; HPR, high platelet reactivity; HR, hazard ratio.

Table V. Poor responsiveness to antiplatelet agents in patients on dual antiplatelet therapy with and without chronic kidney disease.

eGFR in ml/min.1.73m^2	≥ 60	45–59	< 45	*p*
Absence of poor responsiveness	119/363 (33%)	20/50 (40%)	5/24 (21%)	*p* for trend = 0.63
Poor responsiveness to one agent	180/363 (50%)	21/50 (42%)	14/24 (58%)	
Poor responsiveness to both agents	64/363 (18%)	9/50 (18%)	5/24 (21%)	

eGFR, estimated glomerular filtration rate (CKD EPI equation).

confirmation that CKD patients have a higher event rate compared with non-CKD patients. Second, no significant difference was identified in the prevalence of aspirin and clopidogrel responsiveness or high platelet reactivity in patients with or without CKD. Third, no significant interaction for CKD vs. non-CKD was observed for adverse cardiovascular events in patients with or without high platelet reactivity on most assays.

High platelet reactivity has been reported to be more prevalent in CKD (Table I) [7,8,10,12–16]. Half of these studies assessed platelet reactivity in patients undergoing PCI after a loading dose of clopidogrel [7,8,10,12]. The other four studies were conducted in stable outpatients and did demonstrate higher platelet reactivity in the CKD subgroup. However, two of them included a limited number of patients [13,16]. Woo et al. [15] enrolled only individuals with normal renal function or hemodialysis patients and did not study platelet reactivity in individuals with less advanced CKD. Angiolillo et al. [14] conducted a cross-sectional study with a target group similar to that in the ADRIE (stable outpatients with diabetes mellitus and documented CAD on DAPT). In this study, antiplatelet agents effect was assessed with light transmittance aggregometry after challenge with ADP or collagen. The authors included only diabetic patients and used the upper quartile of platelet aggregation. They found that patients with CKD had higher ADP-induced and collagen-induced platelet reactivity than those without CKD. In the ADRIE study, a different cutoff was used and the cohort also included non-diabetic patients. Therefore, the results may not be comparable.

The higher incidence rate of adverse cardiovascular events in CKD patients has been well described [1]. The exact pathophysiology underlying this association is still under debate. In this report, we show a prothrombotic tendency in CKD patients, as demonstrated by a higher vWF activity and a higher fibrinogen level which may reflect an underlying pro-inflammatory state [20], and are in line with the findings in patients with advanced CKD [21]. Plasma vWF concentration has been found to be elevated in patients with impaired renal function (defined as serum creatinine >1.47 mg/dl) compared with healthy controls [22]. Spiel et al. [23] argued that vWF might be directly involved as a causative agent of myocardial infarction.

We are the first to explore the impact of concomitant high platelet reactivity and CKD on adverse cardiovascular events in stable outpatients with documented cardiovascular disease. No significant interaction for CKD presence vs. no CKD was observed for adverse cardiovascular events in patients with or without high platelet reactivity on most assays. The significant interaction identified with collagen-induced aggregation between high platelet reactivity and CKD for adverse cardiovascular events is likely a false positive finding due to multiple testing. The results were similar in patients on DAPT. This finding contrasts with the other studies assessing antiplatelet drug responsiveness and platelet reactivity in CKD in the acute setting [6,7,12]. Indeed, these latter studies assessed antiplatelet drug responsiveness and platelet reactivity in patients undergoing percutaneous coronary intervention, after a clopidogrel loading dose. It is likely that poor antiplatelet drug responsiveness has a greater impact on clinical outcomes shortly after an acute cardiovascular event or after stent implantation because of the interaction between activated platelets and the ruptured plaque or the stent. On the contrary, high platelet reactivity may be less critical in stable cardiovascular patients with lower platelet activation status [18].

We also found a higher bleeding events rate in CKD patients compared with patients with preserved renal function. The UK-HARP trial did not find any significantly increased major

bleeding risk in patients with advanced CKD who were prescribed aspirin for secondary prevention of adverse cardiovascular events vs. placebo but an increase in minor bleeding events [24]. The DOPPS study showed a similar risk of gastrointestinal bleeding in dialysis patients who were prescribed 100 mg of aspirin compared with those who were not [25]. However, a meta-analysis by Palmer et al. [26] found an increased risk for major or minor bleeding events in patients with CKD who are prescribed antiplatelet agents.

The strengths of the multicentric ADRIE cohort study, including a thorough follow-up with few patients lost, high treatment compliance and the adjudication of adverse cardiovascular events by an independent committee, have already been highlighted [27]. A major limitation of this subgroup analysis is its *post hoc* design, which may not be powered to assess clinical outcomes in a CKD subgroup. Bleeding events were not independently adjudicated and might have been under reported. We did not use several other available biological tests (VerifyNow, PFA-100 with the collagen and ADP cartridge, and the Multiplate assay). These assessments of platelet function might have had a higher predictive value among patients with stable cardiovascular disease. Chronic obstructive pulmonary disease, known to be associated with high platelet reactivity [28], was not recorded in this cohort. Furthermore, our results do not apply in patients treated with the recent antiplatelet agents (such as prasugrel or ticagrelor). These results may not apply to end-stage renal disease patients, as most of our patients had moderate CKD. Finally, our results do not extend to other platelet function assays that may be able to detect differences in platelet reactivity that would be clinically significant.

In conclusion, in stable cardiovascular patients, CKD is not associated with a higher prevalence of antiplatelet drug poor responsiveness or high platelet reactivity. Platelet reactivity, measured with specific or aggregation-based assays, is not associated with worse clinical outcomes in stable patients with CKD, in line with what was found in the whole cohort [18]. It may be more relevant in CKD patients at higher cardiovascular risk, as those presenting with an acute coronary syndrome or concomitant diabetes mellitus [29].

Declaration of interest

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