Original Paper

Patients with Atrial Fibrillation and Chronic Kidney Disease More Often Undergo Angioplasty of Left Main Coronary Artery – a 867 Patient Study

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Key Words

Atrial fibrillation • Kidney function • Estimated glomerular filtration rate • Coronary artery disease

Abstract

Background/Aims: Several studies have implicated atrial fibrillation (AF) as a contributing factor in chronic kidney disease (CKD) and cardiovascular events. The prevalence of coronary artery disease (CAD) in patients with AF varies substantially from 17% to 46.5%. There are only few studies concerning renal function in population with AF undergoing coronary angiography. The aim of the present study was to assess which type of AF is dominant in CKD population scheduled for coronary angiography and if it can influence patients' outcome, the association between renal impairment and the type of coronary procedures in AF patients and the influence of renal function on in-hospital mortality. **Methods:** We retrospectively studied 867 patients with AF hospitalized due to coronary angiography in two year time. The cut off value of CKD was eGFR ≤ 60 ml/min./1.73m² evaluated by CKD-EPI formula. **Results:** A total of 867 patients with AF (44% women; mean age 72 $\pm$ 10 years) were included in the analysis. The mean eGFR was 44 $\pm$ 11ml/min./1.73m² in patients with CKD and 89 $\pm$ 18 ml/min./1.73m² in patients with preserved renal function. Patients with CKD and AF were older ($p < 0.001$), had more often diabetes ($p = 0.009$), heart failure ($p < 0.001$) and anaemia ($p < 0.001$). Patients with CKD and AF had more often permanent type of AF ($p < 0.001$). In CKD patients CHA₂DS₂VASc score was 4.3 $\pm$ 1.5 and HAS-BLED score was 2.0 $\pm$ 1.2 and it was significantly higher as compared to population with preserved renal function ($p < 0.001$, $p = 0.02$, respectively). The

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use of oral anticoagulation was less frequent in CKD group ($p < 0.001$) although these patients had higher CHA₂DS₂VASc score. Patients with AF and CKD were more often admitted due to myocardial infarction (STEMI or NSTEMI) ($p = 0.02$, $p < 0.001$, respectively) and more often underwent percutaneous coronary intervention (PCI) ($p = 0.01$). Among coronary arteries the percutaneous coronary intervention (PCI) of left main artery was done more frequently in CKD patients ($p = 0.01$). Among CKD population in-hospital mortality was significantly higher in patients with eGFR < 30 ml/min ($p < 0.001$). **Conclusion:** Patients with CKD had more often permanent type of AF. Percutaneous interventions of the left main coronary artery, the only elective procedures influencing patients' prognosis, were done more frequently in CKD patients with AF. In-hospital mortality was significantly higher in patients with severe renal impairment. Despite the higher risk of ischaemic stroke in CKD group the use of oral anticoagulation therapy was significantly less frequent and the patients were deprived of the confirmed benefits of such treatment.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring approximately in 3% of the general population and is a well-known risk factor of cardiovascular morbidity and mortality [1-2]. Non-valvular AF frequently occurs in renal failure population and ranges from 19% to 24% rising to 27% in patients with end-stage renal disease [3-5]. Several studies have implicated AF as a contributing factor in chronic kidney disease (CKD) and cardiovascular events [6-9].

The prevalence of coronary artery disease (CAD) in patients with AF varies substantially from 17% to 46% [10-11]. There are only few studies concerning renal function in population with AF undergoing coronary angiography so the prevalence of CKD in patients with AF undergoing percutaneous coronary intervention (PCI) remains largely unknown [12]. While this is a clinically important issue because in patients with AF, CKD is associated with an increased risk of dangerous complications like ischaemic stroke, systemic emboli and bleedings [13].

The aim of the present study was to assess which type of AF is dominant in CKD population scheduled for coronary angiography and if it can influence patients' outcome. The association between renal impairment and the type of coronary procedures in AF patients and the influence of renal function on in-hospital mortality in AF population were also investigated.

Materials and Methods

Study population

We retrospectively studied 867 consecutive patients with the diagnosis of non-valvular AF hospitalized due to coronary angiography (elective or due to acute coronary syndrome) in the Department of Cardiology and the Department of Invasive Cardiology in Białystok, Poland and in the Cardiology Department, Ioannina University Hospital, Ioannina, Greece in two consecutive years. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the local ethics committee. At the study entry medical history was recorded, all patients underwent physical examination, resting ECG, routine transthoracic echocardiography and coronary angiography. We excluded patients after kidney transplantation as they take drugs causing atherosclerotic changes [14].

CHA₂DS₂VASc and HAS-BLED scores were calculated for every patient. The CHA₂DS₂VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female)) is widely used to assess thrombotic complications. HAS-BLED score (hypertension, abnormal renal and liver function, stroke, bleeding, labile

INR, elderly, drugs or alcohol) is very often used to assess bleeding risk in patients who have indication for oral anticoagulation treatment [1].

The patients were divided into two groups according to the renal function. Clinical characteristics, type of AF and occurrence of CAD were compared between the two groups.

The primary end-point was in-hospital mortality.

Definition of non-valvular atrial fibrillation

We defined non-valvular AF according to 2016 ESC guidelines for the management of patients with atrial fibrillation except for AF in rheumatic mitral stenosis and in mechanical heart valve [1].

Assessment of renal function

Baseline laboratory values were obtained on admission. Renal function was assessed using glomerular filtration rate (GFR) estimated by the CKD Epidemiology Collaboration (CKD-EPI) equation [15]. The CKD-EPI equation, expressed as a single equation, is: $GFR = 141 * \min(Scr/\kappa, 1)^\alpha * \max(Scr/\kappa, 1)^{-1.209} * 0.993Age * 1.018$ [if female] $* 1.159$ [if black] Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. CKD was defined as $eGFR \leq 60$ ml/min.

Anaemia

Anaemia, based on World Health Organisation (WHO) criteria, was defined as baseline haemoglobin concentration < 13 g/dL in males and < 12 g/dL in females [16, 17].

Echocardiographic analysis

Left ventricular ejection fraction (LVEF) was assessed in transthoracic echocardiography using the modified biplane Simpson's method (Philips Ultrasound System Sonos 5500, equipped for harmonic imaging with a 3.6 MHz transducer) and was derived in accordance with the recommendations of the European Society of Echocardiography [18]. Left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson's rule from orthogonal apical long-axis projections.

Coronary angiography

In all patients the coronary angiography and angioplasty procedures were performed by an experienced invasive cardiologist. Arterial access was gained via a radial or femoral artery and hemostasis was obtained according to local practice. Selective coronary arteriography and left ventriculography were performed using standard techniques. Lesions were treated according to contemporary interventional methods. The infarct-related artery (IRA) was identified based on coronary anatomy, regional left ventricular dysfunction and ECG changes. The angioplasty procedure was considered successful when the residual stenosis was $< 30\%$, and occurred in the absence of dissection and/or thrombosis. Bare metal stents (BMS) and drug eluting stents (DES) were used. Pharmacological treatment in the catheterization laboratory included intravenous heparin in doses related to weight. Low-molecular weight heparins, bivalirudin and glycoprotein IIb/IIIa inhibitors were administered entirely at the operator's discretion. Medication at discharge was at the treating physician's decision.

Statistical analysis

Data are expressed as means and standard deviations (SD). Relative frequencies are used to present categorical variables. The Student's t test, the Wilcoxon rank-sum test and chi-square test was used for statistical analysis where applicable. Logistic regression was used to test associations between variables and outcomes. Multinomial logistic regression was used to evaluate the association between variables and in-hospital mortality. A p value of less than 0.05 was considered as statistically significant. The statistic software, StataIC (data analysis of statistical software) version 13, was used.

Results

Baseline characteristics

A total of 867 patients with AF (381 women, 44%; mean age 72 ± 10 years) were included in the analysis. Paroxysmal AF was present in 44% ($n=381$), persistent in 16% ($n=139$), permanent in 40% ($n=345$) of the patients. Hypertension was present in 77% ($n=668$), diabetes (DM) in 27% ($n=234$), CKD in 26% ($n=225$), and chronic heart failure (CHF) in 58% ($n=503$), anaemia in 27% ($n=234$) of the patients. The history of myocardial infarction (MI) was present in 21% ($n=182$) and history of coronary artery by-pass grafting (CABG) in 5% ($n=43$) of the patients. The mean LVEF assessed by echocardiography was $45 \pm 13\%$, mean left atrium diameter was 47 ± 8 mm.

Eleven percent ($n=95$) of the patients were admitted due to non-ST elevation myocardial infarction (NSTEMI), 9% ($n=78$) of the patients due to ST elevation myocardial infarction (STEMI), and 4% ($n=35$) due to unstable angina (UA). The rest of the investigated population had scheduled coronary angiography due to either exacerbated angina or the need of coronary vessel assessment before valve replacement or valve repair. CHA₂DS₂VASc score was 3.6 ± 1.6 and HAS-BLED score was 1.8 ± 1.1 .

In the study population the in-hospital mortality was 1,6% ($n=14$). Clinical characteristics of the population is shown in Table 1.

Comparison of patients with chronic kidney disease and preserved renal function

Patients with chronic kidney disease and AF had more often permanent type of AF ($p<0.001$). They were older ($p<0.001$), also suffered more frequently from DM ($p=0.009$), CHF ($p<0.001$) and anaemia ($p<0.001$). The history of MI and CABG was more often observed in patients with CKD ($p<0.001$, $p=0.001$, respectively).

The mean eGFR evaluated by CKD-EPI formula was 44 ± 11 ml/min./1.73m² in patients with CKD and 89 ± 18 ml/min./1.73m² in patients with preserved renal function.

In CKD patients CHA₂DS₂VASc score was 4.3 ± 1.5 and HAS-BLED score was 2.0 ± 1.2 and it was significantly higher as compared to population with preserved renal function ($p<0.001$, $p=0.02$, respectively) (Table 1).

Table 1. Clinical characteristics of the population and comparison between patient with CKD and preserved renal function. CKD- chronic kidney disease; AF-atrial fibrillation; ASA-acetylsalicylic acid; CABG-coronary artery bypass graft; eGFR-estimated glomerular filtration rate; NOAC-non-vitamin K oral anticoagulants; NSTEMI-non-ST segment elevation myocardial infarction; PCI-percutaneous coronary intervention; STEMI-ST-segment elevation myocardial infarction; TIA-transient ischemic attack; UA- unstable angina, CHA₂DS₂VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female)); HAS-BLED score (hypertension, abnormal renal and liver function, stroke, bleeding, labile INR, elderly, drugs or alcohol)

Variable	All patients N=867	eGFR > 60 ml/min/1.73m ² N=642	eGFR ≤ 60 ml/min/1.73m ² N=225	p value
Females (%)	381(44)	276(43)	101(45)	0.7477
Age (years)	71±10	69±10	76±9	0.0001
Body mass index (kg/m ²)	29±5	28±5	28±5	0.7403
In-hospital mortality (%)	17 (2)	6(1)	7(3)	0.0637
Type of AF				
Permanent (%)	342(40)	231(36)	112(50)	0.0003
Paroxysmal (%)	381(44)	302(47)	79(35)	0.0017
Persistent (%)	113(13)	90(14)	27(12)	0.4278
CHA ₂ -DS ₂ -VASc score	3.6±1.6	3.3±1.6	4.3±1.5	0.0001
HAS-BLED score	1.8±1.1	1.8±1	2.0±1	0.0227
eGFR (ml/min/1.73m ²)	77.6±26	89.6±19	44.3±12	0.0001
Anaemia (%)	234(27)	141(22)	94(42)	0.0001
Hypertension (%)	667(77)	488(76)	180(80)	0.1370
Chronic heart failure (%)	503(58)	379(59)	128(57)	0.7179
Coronary artery disease (%)	503(58)	353(55)	153(68)	0.0007
Diabetes (%)	234(27)	160(25)	76(34)	0.0094
Previous CABG (%)	43(5)	26(4)	20(9)	0.0016
Previous PCI (%)	104(12)	77(12)	25(11)	0.8032
Previous TIA/stroke (%)	104(12)	64(10)	34(15)	0.0343
Previous myocardial infarction (%)	182(21)	115(18)	67(30)	0.0001
Left atrial diameter (mm)	44±8	44±8	45±8	0.6895
Ejection fraction (%)	45±13	47±12	42±13	0.0001
Admitted due to:				
STEMI (%)	78(9)	51(8)	27(12)	0.0264
NSTEMI (%)	95(11)	51(8)	38(17)	0.0003
UA (%)	34(4)	25(4)	16(7)	0.0644
Treatment				
Oral anticoagulation (%)	589(68)	462(72)	132(59)	0.0002
Warfarin (%)	225(26)	173(27)	54(24)	0.3653
NOAC (%)	69(8)	51(8)	13(6)	0.3547
ASA alone (%)	217(25)	141(22)	76(34)	0.0003

The use of oral anticoagulation was less frequent in CKD group ($p < 0.001$) although these patients had higher CHA₂DS₂VASc score. ASA alone was used more often in CKD patients ($p = 0.003$). The use of anticoagulation together with ASA was similar between both groups ($p = 0.81$). In patients who had anticoagulant treatment there were no differences in use of warfarin or non-vitamin K oral anticoagulant antagonists (NOACs) between CKD patients with eGFR > 30 mL/min. and those with preserved renal function.

Comparison between the two groups is shown in Table 1.

Chronic kidney disease and coronary artery disease

Patients with AF and CKD were more often admitted due to MI (STEMI or NSTEMI) ($p = 0.02$, $p < 0.001$, respectively) and more often underwent PCI ($p = 0.01$). Among coronary arteries the PCI of left main artery was done more frequently in CKD patients ($p = 0.01$). Comparison between the two groups is shown in Table 2.

Patients with CAD who had PCI were older ($p < 0.001$), had more often paroxysmal type of AF ($p = 0.04$), CKD (0.01), anaemia ($p < 0.001$) and history of MI ($p < 0.001$) or PCI ($p = 0.003$). The CHA₂DS₂VASc score was higher in CAD population ($p < 0.001$).

In multivariate logistic regression model, odds of PCI were significantly higher in older patients (OR = 1.04; 95%CI: 1.01-1.06; $p < 0.001$), with paroxysmal AF (OR = 1.42; 95%CI: 1.01-1.99; $p = 0.04$) and with history of MI (OR = 1.89; 95%CI: 1.26-2.83; $p = 0.002$) or previous PCI (OR = 2.05; 95%CI: 1.27-3.29; $p = 0.003$) (Table 3).

Anaemia

Anaemia on admission was present in 27% ($n = 234$) of the patients. Patients with CKD and AF had more often anaemia ($p < 0.001$). Patients with admission anaemia were significantly older ($p < 0.00001$), had lower BMI ($p = 0.002$), more often had paroxysmal AF ($p = 0.002$) and CKD ($p < 0.0001$). They were more frequently admitted due to NSTEMI ($p < 0.0001$) and had a history of MI ($p < 0.0001$) and CABG ($p = 0.03$). In this population CHA₂DS₂VASc score was higher (4.0 ± 1.5 vs 3.4 ± 1.6 ; $p < 0.0001$), but not HAS-BED score (1.9 ± 1.2 vs 1.8 ± 1.0 ; $p = 0.07$).

Patients with admission anaemia had more frequently PCI ($p < 0.00001$) and angioplasty of the right coronary artery ($p = 0.002$), ramus circumflex ($p = 0.02$) and left main ($p = 0.02$) was performed more often in this population.

In-hospital mortality

The in-hospital mortality was higher in elderly patients ($p < 0.001$), female ($p = 0.04$), with DM ($p < 0.01$), higher CHA₂DS₂VASc score ($p = 0.006$) and with history of MI ($p < 0.01$).

Among CKD population in-hospital mortality was significantly higher in patients with eGFR < 30 mL/min ($p < 0.001$).

Table 2. Percutaneous coronary procedures in patients with and without CKD. CKD – chronic kidney disease; PCI – percutaneous coronary intervention

PCI	Odds Ratio	p value	Confidence interval
Age	1.04	< 0.001	1.01-1.06
Paroxysmal AF	1.42	0.04	1.01-1.99
CHA ₂ -DS ₂ -VASc score	0.92	0.28	0.81-1.06
Anaemia	1.38	0.86	0.95-2.00
CKD	1.06	0.74	0.72-1.57
History of MI	1.89	0.002	1.26-2.83
History of PCI	2.05	0.003	1.27-3.29

Table 3. Factors associated with PCI. AF-atrial fibrillation; CKD-chronic kidney disease; MI-mycardial infarction; PCI-percutaneous coronary intervention; CHA₂DS₂VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female))

PCI	Odds Ratio	p value	Confidence interval
Age	1.04	< 0.001	1.01-1.06
Paroxysmal AF	1.42	0.04	1.01-1.99
CHA ₂ -DS ₂ -VASc score	0.92	0.28	0.81-1.06
Anaemia	1.38	0.86	0.95-2.00
CKD	1.06	0.74	0.72-1.57
History of MI	1.89	0.002	1.26-2.83
History of PCI	2.05	0.003	1.27-3.29

In multivariate logistic regression, odds of in-hospital death were higher in elderly patients (OR=1.15; 95% CI: 1.04–1.26; $p=0.004$) but not with CKD (OR=4.18; 95%CI: 0.45–38; $p=0.2$) (Table 4).

Discussion

The novelty of the paper stays on the fact that the type of AF can influence outcome of the CKD patients scheduled for coronary angiography. Patients with CKD and AF had more often permanent type of AF. Among population with advanced renal impairment in-hospital mortality was significantly higher. According to Mlodawska et al. CKD was more often observed in patients with valvular AF. In population with non-valvular AF like ours decreased eGFR was associated with permanent type of AF and with higher CHA₂DS₂VASc and HAS-BLED score. Among valvular AF patients there were no differences in type of AF between patients with and without CKD while there was significant correlation between CKD and AF perpetuation in non-valvular population [19].

Patients with AF often have coexistent CAD and are treated with PCI [20]. In two registries EORP-AF (the EURObservational Research Programme AF Pilot General Registry) and PREFER in AF (PREvention of thromboembolic events—European Registry in AF), which together collected prospective data from 16 participating European countries (over 10 000 patients), approximately 20% to 35% of the patients were found to have CAD [21, 22]. In several studies, either new-onset or pre-existing AF was shown to have a negative impact on prognosis in patients with CAD treated with PCI [23–26].

CKD is present in 10%–15% of AF patients [27]. Atrial fibrillation and CKD share a number of risk factors, including increasing age, pre-existing cardiovascular disease, hypertension, DM, CAD and CHF [28–30] and are associated with a worse outcome [31]. In the randomized AMADEUS trial, that compared renal function and outcomes in anticoagulated patients with AF, patients with CKD had more often history of stroke/TIA, and higher CHA₂DS₂VASc and HAS-BLED score [32]. In our study patients with CKD were frequently admitted due to myocardial infarction and more often underwent PCI.

We think that our data on CKD patients is of value as such patients are often excluded from clinical trials. We analyzed relatively large group of patients and all of them were investigated invasively if it comes to CAD. In our two-center study we showed that among patients with AF and CAD a lot of them had also CKD – according to our population 26%. In the group with AF decreased eGFR was similarly associated with CHF, higher CHA₂DS₂VASc and HAS-BLED score. We also observed more frequently CAD and history of MI and CABG. Several studies have implicated that renal failure may increase the risk of AF-related cardiovascular complications [33]. It was shown that the risk of death, the composite end point of death from cardiovascular causes or stroke increases 8-times with declining eGFR [33]. Anavekar et al. reported that each 10 unit reduction of eGFR was associated with a 10% increase in the relative risk of death or non-fatal cardiovascular complications [34]. In our study in-hospital all-cause mortality was significantly higher in patients with severe CKD.

In addition, factors associated with renal disease such as uremic toxins, inflammation, hyperparathyroidism, elevated calcium-phosphate product, fluid overload, and anemia contribute to the severity and extent of the coronary atherosclerosis as well as the higher adverse event rates [35].

Among the patients hospitalized due to coronary artery disease 5–7% are diagnosed with left main coronary artery disease, the most severe form of CAD. Patients with left main

Table 4. Factors associated with all-cause in-hospital mortality. CKD-chronic kidney disease; MI-myocardial infarction; CHA₂DS₂VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female))

In-hospital death	Odds Ratio	p value	Confidence interval
Age	1.14	0.004	1.05–1.26
CHA ₂ -DS ₂ -VASc score	0.52	0.04	0.28–0.97
History of MI	4.92	0.032	1.14–21.11
Diabetes	14.76	0.001	3.11–69.97
CKD	4.18	0.2	0.45–38.14

coronary artery disease require urgent revascularization, either a CABG operation or PCI [36, 37]. In our study percutaneous interventions of the left main coronary artery, the only elective procedures positively influencing patients' prognosis, were done more frequently in CKD patients with AF. Presence of chronic kidney disease in these patients increases the risk of complications and mortality connected with cardiac procedures [38]. Moreover cardiac operation in the group with CKD correlates with higher mortality and higher risk of acute kidney injury which requires dialysis [39, 40].

Reflecting our findings, patients in the AFCAS study with severe renal insufficiency had more often high-risk baseline characteristics such as multivessel and left main disease and underwent more often emergency PCI due to acute coronary syndrome [41].

It was not surprising that patients with CKD and AF had more often anaemia. Anaemia is present in 12-30% of patients with acute coronary syndromes (ACS) undergoing coronary angiography. Many studies have shown that admission anaemia is an independent predictor of in-hospital or short-term mortality in this group of patients [16, 17, 42]. In the present study patients with admission anaemia more often had paroxysmal AF and CKD. They were more frequently admitted due to NSTEMI and had a history of MI and CABG. Patients with admission anaemia had more frequently PCI of left main stem.

Furthermore, it was demonstrated that AF patients with CKD were treated not properly if it comes to anticoagulant therapy. Despite the higher risk of ischaemic stroke and peripheral emboli according to CHA₂DS₂VASc score the use of oral anticoagulation therapy in CKD group was significantly less frequent. The therapy in the group with AF, CAD and CKD was complex, it consisted of oral anticoagulants including NOACs (Non-Vitamin K Antagonist Oral Anticoagulants) and antiplatelet agents which raised the risk of bleeding that is why physicians were cautious about using antithrombotic drugs [43]. NOACs are preferable option for patients with moderate renal failure as they cause less major bleedings and some of them have specific reversal agents in case of life-threatening bleedings or the need of urgent procedures [44]. We revealed that this way the patients in our study were deprived of the confirmed benefits of anticoagulant therapy.

Limitations

The study has been performed in two centers of two different countries, likely with different clinical practices and treatment indications. This study has all the limitations of an observational study as the decision about PCI, the choice of stent and antithrombotic treatment has been entirely at the discretion of the treating physician. We had not enough data to analyze the rate of contrast induced nephropathy. We also cannot exclude the residual confounding in multivariate analysis. Nevertheless we think that these data are of value in the characteristics of patients with AF and undergoing PCI. The strength of our study is the inclusion of 'real-world' patients undergoing coronary angiography.

Conclusion

Patients with CKD and AF had more often permanent type of AF. Percutaneous interventions of the left main coronary artery, the only elective procedures influencing patients' prognosis, were done more frequently in CKD patients with AF. In-hospital mortality was significantly higher in patients with severe CKD. Despite the higher risk of ischaemic stroke in CKD group the use of oral anticoagulation therapy was significantly less frequent and the patients were deprived of the confirmed benefits of such treatment.

Disclosure Statements

None of the authors identify any conflicts of interest.

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