International Journal of Cardiology 240 (2017) 8–13

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Impact of point-of-care pre-procedure creatinine and eGFR testing in patients with ST segment elevation myocardial infarction undergoing primary PCI: The pilot STATCREAT study☆

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ARTICLE INFO

Article history:
Received 14 November 2016
Received in revised form 23 March 2017
Accepted 31 March 2017
Available online 5 April 2017

Keywords:
STEMI
Primary PCI
Contrast-induced AKI
Point-of-care testing

ABSTRACT

Background: Contrast-induced acute kidney injury (CI-AKI) is a recognised complication during primary PCI that affects short and long term prognosis. The aim of this study was to assess the impact of point-of-care (POC) pre-PPCI creatinine and eGFR testing in STEMI patients.
Methods: 160 STEMI patients (STATCREAT group) with pre-procedure POC testing of Cr and eGFR were compared with 294 consecutive retrospective STEMI patients (control group). Patients were further divided into subjects with or without pre-existing CKD.
Results: The incidence of CI-AKI in the whole population was 14.5% and not different between the two overall groups. For patients with pre-procedure CKD, contrast dose was significantly reduced in the STATCREAT group (124.6 ml vs. 152.3 ml, $p = 0.015$). The incidence of CI-AKI was 5.9% ($n = 2$) in the STATCREAT group compared with 17.9% ($n = 10$) in the control group ($p = 0.12$). There was no difference in the number of lesions treated (1.118 vs. 1.196, $p = 0.643$) or stents used (1.176 vs. 1.250, $p = 0.78$). For non-CKD patients, there was no significant difference in contrast dose (172.4 ml vs. 158.4 ml, $p = 0.067$), CI-AKI incidence (16.7% vs. 13.4%, $p = 0.4$), treated lesions (1.167 vs. 1.164, $p = 1.0$) or stents used (1.214 vs. 1.168, $p = 0.611$) between the two groups.
Conclusions: Pre-PPCI point-of-care renal function testing did not reduce the incidence of CI-AKI in the overall group of STEMI patients. In patients with CKD, contrast dose was significantly reduced, but a numerical reduction in CI-AKI was not found to be statistically significant. No significant differences were found in the non-CKD group.

1. Introduction

Contrast induced acute kidney injury (CI-AKI) is a recognised complication of coronary angiography and percutaneous coronary interventions (PCI) [1]. Although its incidence in low-risk patients undergoing elective procedures is <3.5% [2], it dramatically increases to 16% to 19% in ST-elevation myocardial infarction (STEMI) patients undergoing primary PCI (PPCI) [3,4]. Left ventricular systolic dysfunction and systemic hypotension in the context of STEMI, along with difficulties in implementation of renal prophylactic measures before exposure to contrast media probably explain the increased incidence compared to stable patients [5,6]. Its development is not a benign condition but is associated with increased short-term and long-term morbidity and mortality, prolonged hospitalisation, and long-term renal impairment [7,8,9]. In patients with STEMI undergoing PPCI, correlation with adverse prognosis is even stronger [4,10]. Several risk factors for CI-AKI have been identified such as old age, chronic kidney disease (CKD), diabetes mellitus, anaemia, impaired left ventricular systolic function, hemodynamic instability and contrast media volume used [11]. Its pathogenesis is not completely understood, but there is evidence that CI-AKI occurs as a combination of oxidative stress, ischemic injury, direct toxicity, and obstruction of the renal tubular epithelium [12]. Based on this knowledge multiple strategies for CI-AKI risk reduction have been tested in clinical studies: various hydration protocols, ministration of *N*-acetylcysteine, use of ascorbic acid, different contrast agents, haemofiltration protocols and statin

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcard.2017.03.147

therapy [13–19]. The results for most of these studies are mixed and conflicting. Hydration with normal saline starting 12 h pre and continuing up to 24 h post procedure is the only recommended intervention for prevention of CI-AKI in the recent ESC/EACS guidelines on myocardial revascularisation, while pre-treatment (starting 12–48 h pre-procedure) with high dose statins should be considered [20]. It is obvious that none of these pre-planned interventions can be implemented in the acute setting of PPCI, making prevention of CI-AKI in STEMI patients a challenge. Alternative ways of preventing CI-AKI in this particular population are needed.

Over the last few years there has been miniaturisation of devices measuring biochemical parameters and now creatinine and estimated glomerular filtration rate (eGFR) can be estimated rapidly at point-of-care with a near patient device [21]. The aim of this study was to assess the impact of point-of-care pre-procedure creatinine and eGFR measurements with immediate feedback to the operator on patients presenting with ST segment elevation myocardial infarction undergoing primary PCI.

2. Methods

2.1. Study design and population

This is a pre and post interventional study comparing two cohorts of STEMI patients who underwent primary PCI in a high volume tertiary centre. In the intervention group, point of care pre-primary PCI creatinine and eGFR were measured with the results available instantly and feedback to the operator (STATCREAT group). This group was then compared with a retrospective group used as control (Control group). We expected a benefit from point-of-care testing in patients with pre-PCI renal dysfunction, so for the purpose of the analysis patients were further divided into subjects with or without pre-existing CKD.

2.2. STATCREAT group

Patients presenting with chest pain for >30 min and ST elevation ≥2 mm in ≥2 contiguous chest leads or ≥1 mm in ≥2 contiguous limb leads or new left bundle branch block (LBBB) due to undergo primary PCI were enrolled. Recruitment took place in a period of 5 months (March to August 2014) depending on availability of point-of-care testing. Patients with cardiogenic shock were excluded. Routine blood samples were taken at the time of sheath insertion as per hospital protocol. Creatinine and eGFR were tested using the Nova Biomedical STAT SENSOR (MA, USA). The amount of blood required with this device is 1.2 μl, while processing time is 30 s. The operator was informed of the result and continued with the procedure. Patients in whom angiography showed no significant atherosclerotic lesions or were referred for emergency coronary artery bypass grafting (CABG) were excluded from the analysis. PCI was performed according to international guidelines. Radial access was used as the default approach. Patients were loaded with 300 mg aspirin and 600 mg clopidogrel or 60 mg Prasugrel or 180 mg Ticagrelor. They received a bolus of 70–100 IU/kg of unfractionated heparin at the start of the procedure. Use of glycoprotein IIb/IIIa inhibitors was at the discretion of the PCI operators on the basis of the clinical condition. Creatinine and eGFR were measured on admission and at 24, 48 and 72 h.

2.3. Control group

The Control group consisted of consecutive STEMI patients undergoing PPCI in a previous 6 month period (June 2013 to December 2013). The same inclusion and exclusion criteria applied. For these patients a point of care blood test was not performed and the operator was unaware of the baseline creatinine and eGFR. PCI procedure and subsequent patient's management followed the same standards as the STATCREAT group.

STATCREAT and control groups were further divided into subjects with chronic kidney disease (CKD) prior to PCI (eGFR < 60 ml/min) or subjects with normal renal function (eGFR > 60 ml/min). For both groups the diagnosis of CKD was based on the blood results from the sample taken immediately prior to PPCI during their index admission: the point-of-care tested sample for the STACREAT group and the laboratory values were made available later for the control group.

2.4. Definitions

CI-AKI was defined as an absolute increase of serum creatinine ≥ 0.5 mg/dl (44 mmol/l) or relative increase ≥25% from baseline value at 72 h post intervention [22]. CKD was defined as eGFR < 60 ml/min per 1.73 m^2 pre-PCI [23].

2.5. Study outcomes

Primary endpoints were total volume of contrast media used and incidence of CI-AKI. Number of lesions treated and number of stents implanted were used to assess impact of pre-procedure renal function measurements in interventional treatment strategy. Procedure duration and fluoroscopy time was also documented.

2.6. Statistical analysis

Categorical variables are expressed as percentages and were compared by Fisher's exact test. Continuous variables are presented as mean with standard deviation. Differences between means have been tested using a two-sample, two-sided *t*-test, and the *p*-values have been obtained using a Monte Carlo approach with 10,000 permutations, using the R package perm. This approach avoids strong distributional assumptions, such as the normality of data, in the statistical inferences. A *p*-value of <0.05 was considered as statistically significant. All statistical analyses have been carried out using the computer program R (R CRAN 2016).

3. Results

A total of 454 patients were included, 160 in the STATCREAT group and 294 in the control group. Baseline characteristics for the two cohorts are shown in Table 1. Mean age was 64 years and 20% of patients were above 75 years for both groups. In both cohorts the patients were predominantly male (73.1% vs. 71.2%, $p = 0.662$). There was no statistically significant difference in the presence of major cardiovascular risk factors. For both groups, the door to balloon time was 39 min. Left anterior descending artery (LAD) was the culprit vessel in 38.4% of patients in the control group and in 43.1% in the STATCREAT group ($p = 0.367$). Both groups had similar numbers of patients with pre-procedure CKD (19% vs. 21.3%, $p = 0.622$). The incidence of CI-AKI in the whole population of our study was 14.5% and it was not different between the two groups (14.4% vs. 14.6%, STATCREAT and control groups respectively $p = 0.942$). For the overall STATCREAT group, contrast dose was 162.2 ml compared to 157.2 ml for the overall control group ($p = 0.869$).

3.1. Patients with CKD

Results for patients with pre-procedure CKD are shown in Table 2. 34 (21.2%) patients in the STATCREAT group and 56 (19.0%) in the Control group were found to have CKD pre-procedure. Contrast media volume used was reduced in the STATCREAT group by 27.7 ml (124.6 ml vs. 152.3 ml, $p = 0.015$). The incidence of CI-AKI in the STATCREAT group was 5.9% ($n = 2$) compared with 17.9% ($n = 10$) in the control group ($p = 0.12$). Similar numbers of lesions were treated (1.118 vs. 1.196, $p = 0.643$) and similar numbers of stents were placed (1.176 vs. 1.250, $p = 0.78$) in the two groups. There was no statistically significant

Table 1
Baseline patient characteristics.

	Control ($n = 294$)	STATCREAT ($n = 160$)	p Value
Age (years)	64 (13)	64 (12)	$p = 0.83$
Age > 75 (%)	59 (20.0)	33 (20.6)	$p = 0.903$
Men (%)	215 (73.1)	114 (71.2)	$p = 0.662$
DM (%)	36 (12.2)	17 (10.6)	$p = 0.649$
HTN (%)	119 (40.5)	53 (33.1)	$p = 0.13$
Hypercholesterolaemia (%)	103 (35.0)	44 (27.5)	$p = 0.115$
Smoker/ex-smoker (%)	165 (56.1)	89 (55.6)	$p = 0.922$
Previous MI (%)	34 (11.6)	18 (11.2)	$p = 1.0$
Previous PCI (%)	28 (9.5)	11 (6.9)	$p = 0.384$
Previous CABG (%)	8 (2.7)	7 (4.4)	$p = 0.412$
LAD infarct (%)	113 (38.4)	67 (43.1)	$p = 0.367$
Baseline serum Cr (mmol/l)	89 ± 35	86 ± 25	$p = 0.556$
eGFR < 60 (%)	56 (19.0)	34 (21.3)	$p = 0.622$
Hb (g/dl)	14.0 ± 1.8	14.8 ± 11.0	$p = 0.161$

Values are expressed as means (standard deviation), or percentage.
DM, diabetes mellitus, HTN, hypertension, MI, myocardial infarction, PCI, percutaneous coronary intervention, CABG, coronary artery bypass grafting, LAD, left anterior descending, Cr, creatinine, eGFR, estimate glomerular filtration rate, Hb, haemoglobin.

difference in the procedure duration (46.3 min vs. 44.4 min, $p = 0.694$) or fluoroscopy time (10.27 min vs. 9.87 min, $p = 0.779$).

3.2. Patients without CKD

For the two groups of patients with normal renal function prior to the procedure, the volume of contrast media used was numerically higher for the STATCREAT group (172.4 ml vs. 158.4 ml, $p = 0.067$), but this increase did not reach statistical significance (Table 3). There was no statistically significant difference in the incidence of CI-AKI (16.7 vs. 13.4, $p = 0.4$), the number of lesions treated (1.67 vs. 1.64, $p = 1.0$) or the number of stents used (1.214 vs. 1.168, $p = 0.611$). In the STATCREAT group, fluoroscopic time was longer by 1.51 min (10.78 min vs. 9.27 min, $p = 0.029$). Similarly, the duration of the procedure was longer for the STATCREAT patients (45.83 min vs. 41.36 min, $p = 0.027$).

4. Discussion

The present study assessed the impact of point-of-care pre-procedure creatinine and eGFR measurements in patients with ST segment elevation myocardial infarction undergoing primary PCI in a single tertiary cardiac centre. The results of these measurements were instantly available to the operator prior to PCI. Point-of-care testing did not increase door to balloon time. Incidence of CI-AKI in the whole study cohort was 14.5% and that was not different between the overall group of patients with pre-PCI renal function testing compared with the overall control group. Similarly, contrast dose between the two groups was not different when the total number of patients was compared. In the group of patients who were found to have pre-procedural CKD, contrast media volume was significantly reduced. The incidence of CI-AKI in this group of patients showed an absolute risk reduction by 12%, which was not statistically significant. In the group of patients without pre-procedural CKD, contrast volume and incidence of CI-AKI were not different, as a numerical increase was not found statistically significant.

CI-AKI has a higher incidence in the STEMI population and leads to worse prognosis especially in patients with pre-existing chronic kidney disease [24,25]. A recent study on a large cohort of STEMI patients ($n = 2968$) showed higher rates of mortality at 30 days (8.0 vs. 0.9%, $p = 0.0001$) and 3 years (16.2 vs. 4.5%, $p = 0.0001$) for patients who developed CI-AKI [4]. Volume of contrast media used is a known risk factor for the development of CI-AKI [1]. At the emergency setting of primary PCI there is usually limited information regarding the background of the patient and most of the times previous blood test results are unavailable. Our hypothesis was that if the operators performing the PPCI knew the renal function of the patient, they would reduce the contrast volume used in patients with pre-existing kidney disease and that would lead to a reduced incidence of CI-AKI. Revascularisation is underused in patients with kidney disease, in view of concerns regarding further deterioration of renal function [26] and we wanted to control for such an effect. Thus, a specified endpoint was the comparison between the number of lesions treated and stents implanted between the two cohorts. We also documented procedural and fluoroscopic times as safety endpoints.

We recruited 454 patients with STEMI without cardiogenic shock, who underwent primary PCI with stent implantation. In our centre mechanical circulatory support (MCS) is used only in the context of cardiogenic shock, so none of the patients in this study received MCS. Cardiogenic shock by definition leads to tissue hypoperfusion resulting to renal injury. Reduction of contrast media volume to the absolute needed one is important for this group of patients, but we did not expect any detectable benefit from our intervention. The incidence of CI-AKI in the whole population of our study was 14.5%. This was in concordance with other studies focused in patients with STEMI [3,4], suggesting that our study population was a representative one.

The negative effect of contrast media in renal function has been demonstrated in animal models [27] and a clear-cut association of contrast media dose with incidence of CI-AKI has been found in patients

Table 2
Results in patients with pre-procedure chronic kidney disease (CKD).

	STATCREAT 34 patients	Control 56 patients	Difference in means	p-Value
Contrast media volume (ml)	124.6 (54.4)	152.3 (53.3)	−27.7	$p = 0.015$
% CI-AKI	5.9%	17.9%		$p = 0.12$
Number of lesions treated	1.118 (0.41)	1.196 (0.58)	−0.078	$p = 0.643$
Number of stent used	1.176 (0.76)	1.246 (0.84)	−0.074	$p = 0.78$
Procedure duration (minutes)	46.3 (26.4)	44.4 (19.4)	1.9	$p = 0.694$
Fluoroscopy time (minutes)	10.27 (7.69)	9.87 (5.56)	0.4	$p = 0.779$

Values are expressed as means ± standard deviations, or percentage.
CI-AKI, contrast-induced acute kidney injury.

Table 3
Results in patients with no pre-procedure chronic kidney disease (CKD).

	STATCREAT	Control	Difference in means	*p*-Value
Contrast media volume (ml)	172.4 (76.6)	158.4 (66.4)	14	$p = 0.067$
% CI-AKI	16.7%	13.4%		$p = 0.4$
Number of lesions treated	1.167 (0.518)	1.164 (0.48)	0.003	$p = 1.00$
Number of stent used	1.214 (0.755)	1.168 (0.715)	0.046	$p = 0.611$
Procedure duration (minutes)	45.83 (19.57)	41.36 (16.35)	4.47	$p = 0.027$
Fluoroscopy time (minutes)	10.78 (7.17)	9.27 (5.64)	1.52	$p = 0.029$

Values are expressed as means (standard deviation), or percentage.
CI-AKI, contrast-induced acute kidney injury.

during clinical studies [6,28]. Thus, the importance of minimisation of volume of contrast media for prevention of CI-AKI is emphasised in current percutaneous coronary revascularisation guidelines, especially in patients with CKD [20,29]. In our study, awareness of pre-existing CKD disease by operators led to a statistically significant reduction of contrast by 27.87 ml. This amount is not negligible as a previous study on patients with CKD undergoing coronary angiography showed that the risk of CI-AKI doubled with every 20 ml of contrast administered (incremental odds ratio of 2.12, 95% CI 1.4 to 3.4, $p = 0.0002$) [30]. In a meta-analysis of the effect of automated contrast injection devices on CI-AKI, an average reduction of 45 ml of contrast per case, led to a reduction of CI-AKI by 15% [31]. In our study, the mean total volume of contrast media used in the Control group, where pre-procedure renal function was unknown, was 152.3 ml for patients with CKD and 158.4 ml for patients without CKD. Both amounts are considerably lower compared with the 225 to 245 ml used in the subgroup of HORIZONS-AMI and the 216.1 ml in the study by Sgura et al. [4,24]. This could be the result of an individual operator's preferences, local protocols or complexity of cases. For example, in our centre routine ventriculography is not performed, as bedside transthoracic echocardiography is instantly available. If pre-procedure creatinine and eGFR testing was to be implemented in centres with higher contrast doses, maybe it would be space for a largest reduction in contrast volume leading to more pronounced reduction in CI-AKI.

A total volume of contrast media of >350 ml or >4 ml/kg is directly related to the development of CI-AKI, but the ratio of the volume of contrast media to creatinine clearance (CV/CrCl) is a better risk predictor in individual patients [32,33]. A CV/CrCl > 3.7:1 correlated strongly with the risk of developing CI-AKI in a mixed population of stable coronary artery disease and acute myocardial infarction undergoing PCI and predicted CI-AKI and 1 month mortality in patients undergoing PPCI for STEMI [34,35]. In the context of STEMI specifically, an even lower CV/CrCL ratio of 2.5 has been shown to predict CI-AKI [36]. The above demonstrate the importance of knowing a patient's renal function in advance before performing the PCI procedure. As shown in our study, by performing point-of-care instant Cr and eGFR measurements, the operator could guide the intervention accordingly and adjust contrast dose to the one tolerated by each individual patient based on baseline renal function.

In the group of patients with pre-existing CKD there was an absolute risk reduction of 12% (5.9% vs. 17.9%), which did not reach statistical significance. This could be explained by the small number of events; with the cardiogenic shock patients excluded from the analysis, only 2 patients in the STATCREAT group developed CI-AKI. A larger study is needed to confirm the above finding.

In patients without CKD, the contrast dose in the STATCREAT group was increased (absolute mean increase by 14 ml), but this increase was not statistically significant. Equally there was no difference in the incidence of CI-AKI. Given the acute inflammation during STEMI and the high risk of peri-STEMI hemodynamic compromise, a universal "minimize dye" approach should be practiced. A potential false sense of security that would liberalise contrast use would be a pitfall for point-of-care renal function testing in the setting of PPCI. This was not shown in our study, but it should be tested as a safety endpoint in a larger randomised trial. Interestingly, in the non-CKD group of patients, fluoroscopy time and procedure time were prolonged by 1.51 and 4.47 min respectively. Importantly, this was not the result of more revascularisation as number of lesions treated and stents used was similar between the two groups.

One particular concern in the study was that the operators might underuse revascularisation in the group of patients found to have impaired renal function pre procedure. The analysis of the data did not show that effect. The number of the lesions treated and stent used was similar between the different groups. In any case, knowledge of pre-procedure renal impairment should not lead to under-utilisation of clinically needed PCI, but should prompt strategies to reduce contrast use like use of biplane angiography or intravascular ultrasound to plan and optimise stent implantation and strategies of renal protection like hydration.

5. Limitations

The present study has limitations. It is a single centre study and involves a small number of patients who developed CI-AKI. The comparison between the groups is not the result of randomisation; a group of patients recruited prospectively has been compared with a retrospective historic cohort. We hypothesised that operators were unaware of the patients' pre-procedure renal function. In the emergency setting of PPCI, history taking and clinical assessment only take place a few minutes before the procedure. We cannot exclude that some patients might have reported pre-existing renal dysfunction or that medical records were instantly available, introducing an operator bias. Furthermore, operators could have been more careful with contrast usage in patients who belonged in high-risk groups (i.e. elderly, diabetic) even without knowing the pre-PCI renal function. Hydration pre, during and post procedure can prevent CI-AKI [37]. Operators who were aware of the pre-PPCI renal function apart from reducing the amount of contrast used, might have been more aggressive with hydration in patients that could tolerate it. The amount of intravenous fluids given pre, during and post procedure has not been documented for the purpose of this study. The same applies with the use of potential nephrotoxic drugs. Their peri-procedural use might have been reduced in the group of patients with documented pre-PCI CKD. In our study, we used a specific point-of-care analyser for renal function testing. There are multiple devices in the market and the technology itself has limitations compared with standard laboratory testing [38], but this discussion is out of the scope of this paper. The device used in our study has been tested and proved reliable in other studies [39]. In our centre, for the first 130 patients we compared the point-of-care creatinine results with the laboratory ones. As shown in Fig. 1, point-of-care results were adequately accurate. In any case, point-of-care renal function testing in the context of PPCI, does not substitute standard laboratory analysis, but provides information prior to the procedure that would not be available otherwise.

6. Conclusions

Pre-PPCI point-of-care measurement of renal function biomarkers did not reduce the incidence of CI-AKI in the overall group of STEMI

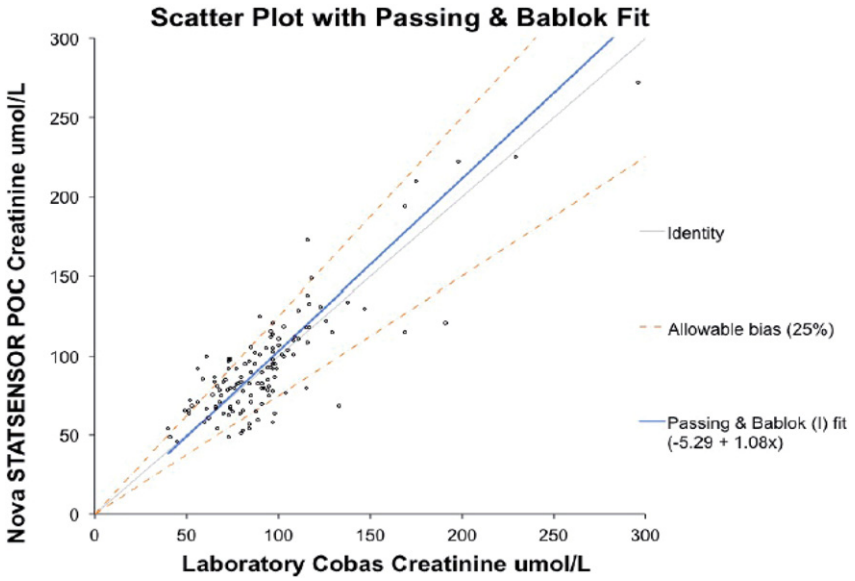

Fig. 1. Scatter plot with passing & Bablok fit for point-of-care and laboratory creatinine measurements.

patients compared to historical controls. In patients who were found to have chronic kidney disease pre procedure, contrast media volume was significantly reduced, but a numerical reduction in the incidence of acute kidney injury did not reach statistical significance. No statistically significant differences were found in the non-CKD group. Larger randomised trials are needed to investigate further the impact of point-of-care creatinine and eGFR testing in clinical outcomes for STEMI patients undergoing PPCI.

Funding

The study was supported by Nova Biomedical, Waltham, MA, USA.

Conflict of interest statement

T. Keeble has received a research grant from Nova Biomedical. G. Karamasis has received travel grants from Nova Biomedical. The other authors have no conflicts of interest to declare.

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