BMJ Open

Perioperative urinary thromboxane metabolites and outcome of coronary artery bypass grafting: a nested case-control study

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To cite: Liu H, Xu Z, Sun C, *et al*. Perioperative urinary thromboxane metabolites and outcome of coronary artery bypass grafting: a nested case-control study. *BMJ Open* 2018;**8**:e021219. doi:10.1136/bmjopen-2017-021219

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-021219).

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Received 22 December 2017
Revised 8 June 2018
Accepted 19 July 2018

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ABSTRACT

Objective As a marker of in vivo thromboxane generation, high-level urinary thromboxane metabolites (TXA-M) increase the occurrence of cardiovascular events in high-risk patients. To investigate whether perioperative urinary TXA-M level is associated with major adverse cardiac and cerebrovascular events (MACCE) after coronary artery bypass graft (CABG) surgery, we designed a nested case-control study.

Design Observational, nested case-control study.

Setting Single-centre outcomes research in Fuwai Hospital, Beijing, China.

Participants One thousand six hundred and seventy Chinese patients undergoing CABG surgery from September 2011 to October 2013.

Methods We obtained urinary samples from 1670 Chinese patients undergoing CABG 1 hour before surgery (pre-CABG), and 6 hours (post-CABG 6 hours) and 24 hours after surgery (post-CABG 24 hours). Patients were followed up for 1 year, and we observed 56 patients had MACCE. For each patient with MACCE, we matched three control subjects. Perioperative urinary TXA-M of the three time spots was detected in these 224 patients.

Results Post-CABG 24 hours TXA-M is significantly higher than that of patients without MACCE (11 101vs8849 pg/mg creatine, P=0.007). In addition, patients in the intermediate tertile and upper tertile of post-CABG 24 hours urinary TXA-M have a 2.2 times higher (HR 2.22, 95% CI 1.04 to 4.71, P=0.038) and a 2.8 times higher (HR 2.81, 95% CI 1.35 to 5.85, P=0.006) risk of 1 year MACCE than those in the lower tertile, respectively.

Conclusions In conclusion, post-CABG 24 hours urinary TXA-M elevation is associated with an increase of 1 year adverse events after CABG, indicating that the induction of cyclo-oxygenase-2 by surgery-related inflammatory stimuli or platelet turnover may be responsible for the high levels of post-CABG urinary TXA-M.

Trial registration number NCT01573143.

Strengths and limitations of this study

- We used a nested case-control design to analyse the association between perioperative urinary thromboxane metabolite (TXA-M) and major adverse cardiac and cerebrovascular events (MACCE) in a coronary artery bypass graft (CABG) cohort. This CABG cohort was from a randomised controlled trial (STICS), so the cases (56 patients with MACCE) and the 168 controls from the same cohort had the comparable baseline characteristics, which made our results more reliable and powerful.
- We tested the TXA-M levels at different time points before and after surgery establishing more reliable association between the TXA-M levels and adverse events after surgery.
- We have not tested TXA-M levels at later time points beyond the first day after CABG, thus, whether the TXA-M level in this study is a temporary or stable change should be verified in further studies.

INTRODUCTION

Coronary artery disease (CAD) is the leading cause of mortality worldwide. As one of the commonly used revascularisation strategies, coronary artery bypass graft (CABG) surgery is the standard of care for patients with CAD with diabetes or multivessel CAD.[1] In the first year after CABG, thrombotic dysfunction, for example, thrombus occlusion of saphenous vein grafts (SVG),[2] is one of the main reasons increasing the risk of adverse events, including death, myocardial infarction (MI) and repeat revascularisation.[3 4]

Thromboxane A_2 (TXA_2) is an unstable metabolite of arachidonic acid (AA). Numerous studies have revealed TXA_2 as a culprit of cardiovascular diseases.[5–7] As a platelet agonist, TXA_2 activates adjacent platelets, provokes more platelet-dependent TXA_2 generation, and thus triggers platelet aggregation.[8] Under normal conditions, TXA_2 is dominantly synthesised by platelet via cyclo-oxygenase-1 pathway in humans. Aspirin, inhibiting platelet cyclo-oxygenase-1, has been commonly used as an antiplatelet therapy to reduce TXA_2 generation and prevent secondary vascular thrombotic

events. While, under the condition of acute inflammatory stimuli, such as surgery or cardiopulmonary bypass, the expression level of cyclo-oxygenase-2 can increase dramatically and promote the synthesis of TXA_2, the CABG procedure enhances inflammatory process and platelet turnover, which causes the elevation of TXA_2 by the induction of cyclo-oxygenase-2.[9] Previous studies have reported that TXA_2 generation was an independent risk factor for early SVG thrombosis after CABG.[4]

However, whether perioperative TXA_2 generation is associated with adverse events after CABG is unclear. We hypothesise that enhanced perioperative TXA_2 generation is correlated with poor prognosis after CABG. We studied a cohort of 1670 patients with CABG from the Statin Therapy in Cardiac Surgery (STICS) trial (ClinicalTrials.gov number, NCT01573143)[10] with a nested case-control analysis, to determine whether perioperative TXA_2 generation, measured by urinary thromboxane metabolites (TXA-M), is correlative with major adverse cardiac and cerebrovascular events (MACCE), including all-cause death, non-fatal MI, non-fatal stroke and repeat revascularisation after CABG.

METHODS

Study design

We have complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and/or animals. All patients provided written informed consent to be involved in the study.

Patient enrolment

Patients were selected from the STICS trial.[10] Between September 2011 and October 2013, 1922 patients at Fuwai hospital were randomised, among which 1670 underwent CABG (supplementary methods. For all patients, the medication of ASA stopped at least 5 days before CABG and postoperatively, starting within the first 24 hours postoperation (100 mg). All patients were required to come back for a routine outpatient follow-up visit at 1 month, 6 months and each year after discharge. The medical records of those who reported any adverse events after discharge were reviewed for further confirmation. The primary end point of follow-up was a composite of MACCE (ie, non-fatal stroke, non-fatal MI, repeat revascularisation or death from any cause)[11 12] (supplementary methods). Among the 1670 patients undergoing CABG, 15 (0.9%) were lost during the first year follow-up, and 56 out of 1655 followed-up patients (3.4%) had MACCE. With the use of a nested case-control analysis, we matched each patient with MACCE with three controls from the cohort; matching was based on sex, age, body mass index, hypertension, diabetes mellitus, smoking status, ejection fraction, COPD, previous MI, previous stroke, chronic kidney disease and peripheral vascular disease. Medication use after discharge was recorded at 1 year follow-up; for patients who missed this information we used prescription at discharge instead.

Sample collection and preparation

For every patient enrolled in this study, urinary samples were collected with cryogenic vials at three time spots: 1 hour before CABG (pre-CABG), 6 hours after CABG (post-CABG 6 hour) and twenty-four hours after CABG (post-CABG 24 hours). All urinary samples were stored at −80°C. Before testing, samples were thawed at 4°C for an hour and then centrifuged at 1000 g for 15 min. Finally, 100 ul from the supernatant was collected for further analysis.

Patient and public involvement

All data in this study were from the STICS trial (NCT01573143), so the present study did not involve participants and/or public in the study design and we obtained no more information or biological samples from patients in this study. Results will be disseminated to study participants via this publication.

Measurement of TXA_2 generation

As TXA_2 is an unstable metabolite, we measured urinary TXA-M, including 11-dehydro-thromboxane (TXB_2) and 11-dehydro-2, 3-dinor TXB_2 using the AspirinWorks 11-dehydro-TXB_2 ELISA (Corgenix, Broomfield, Colorado, USA) and expressed as a ratio to urinary creatine as previously described.[13] The measurement was performed during December 2014–Janurary 2015.

Statistical analysis

For demographic description of patients, we calculated the means (±SD) for continuous variables in both the MACCE and the control groups and compared them using Student's t-test; differences in discontinuous variables were evaluated using χ^2 test. For TXA-M level, we used the median and IQR. Comparison of TXA-M levels between the two groups was conducted by Mann-Whitney analysis because its distribution was non-normally distributed. For survival analysis, pre-CABG, post-CABG 6 hours and post-CABG 24 hours urinary TXA-M were divided into tertiles according to their quantitative levels, respectively. The correlation between MACCE and TXA-M levels were estimated using the Kaplan-Meier method and log-rank test. Univariate and multivariate Cox proportional hazards regression models were used to estimate HRs and 95% CIs. Moreover, we adjusted the model by multiple variables listed in online supplementary table S1, all of which were reported to correlate with the pathogenesis and prognosis of CAD significantly and C-statistic calculations were used for logistic regression. All statistical analyses were done with SPSS V.19.0 for Windows (SPSS, Chicago, Illinois, USA).

RESULTS

Study population characteristics

The STICS trial includes 1670 patients undergoing CABG. During the first year of follow-up after CABG, 15 of them were lost. Among the remaining 1655 patients (99.1%),

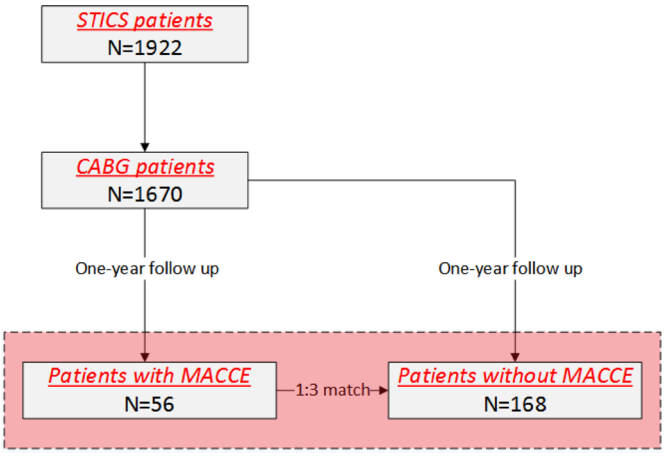

Figure 1 Flow chart of study design. We recruited 1670 patients with CABG from the STICS trial. After 1 year follow-up, 56 patients had MACCE. With the use of a nested case-control analysis, we matched each patient with MACCE with three controls from the cohort; thus, a cohort of 224 patients was established for further study. CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events; STICS, Statin Therapy in Cardiac Surgery.

56 had MACCE (3.4%) (figure 1). For every patient with MACCE, we matched three controls without MACCE for further analysis. The baseline of the MACCE and the control groups has been presented in table 1. The average age of patients with MACCE was 61.7 years, and 44 out of 56 patients with MACCE (78.6%) were male. There were no differences in age, sex, body mass index, hypertension, diabetes mellitus, smoking status, COPD, peripheral vascular diseases, previous MI, chronic kidney diseases and ejection fraction between the MACCE and the control groups. In this nested case-control study, 26 (46.4%) patients in the MACCE group and 84 (50.0%) in the non-MACCE group were treated by perioperative rosuvastatin according to the study protocol of the STICS trial. After discharge, all the secondary preventive medications including aspirin, β-blockers, statins, ACE inhibitors and calcium channel blockers showed no differences between patients with MACCE and controls.

Perioperative TXA-M generation between the MACCE and the control groups

To determine whether the perioperative TXA-M generation was associated with 1 year MACCE after CABG, we tested pre-CABG, post-CABG 6 hours and post-CABG 24 hours urinary TXA-M levels. In both, the MACCE and the control groups, the generation of TXA-M was elevated after CABG. Urinary TXA-M generation before CABG was 5076 pg/mg creatine in the control group, which was slightly higher than that in the MACCE group (4540 pg/mg creatine, P=0.047). The levels of TXA-M post-CABG 6 hours in patients with MACCE and controls showed no significant difference (24016 vs 25681 pg/mg creatine, P=0.727). However, TXA-M post-CABG 24 hours of patients with MACCE was significantly higher than that of patients without MACCE (11101 vs 8849 pg/mg creatine, P=0.007) (table 2).

Furthermore, we compared perioperative TXA-M generation in patients who died, patients with stroke, patients with MI and patients with repeat revascularisation with perioperative TXA-M generation in controls. Pre-CABG and post-CABG 6-hours urinary TXA-M generation showed no differences between patients who died, patients with stroke, patients with MI, patients with repeat revascularisation and controls. Post-CABG 24 hours TXA-M after CABG was significantly higher in patients who died (11993 vs 8849 pg/mg creatine, P=0.039) and patients with stroke (11138 vs 8849 pg/mg creatine, P=0.016). In addition, no differences were detected between patients with repeat revascularisation and controls in post-CABG 24 hours generation of TXA-M (table 3).

Survival analysis of perioperative TXA-M levels and MACCE

Next, we performed survival analysis of perioperative TXA-M levels and MACCE. We divided pre-CABG (tertile 1:~3750; tertile 2: 3750~6150; tertile 3: 6150~, pg/mg creatine), post-CABG 6 hours (tertile 1:~19750; tertile 2: 19750~30300; tertile 3: 30300~, pg/mg creatine) and post-CABG 24 hours (tertile 1:~7000; tertile 2: 7000~12000; tertile 3: 12000~, pg/mg creatine) urinary TXA-M into tertiles according to their quantitative levels.

There were no significant differences of MACCE risk regarding to tertiles of pre-CABG (P_{trend}=0.075) and post-CABG 6 hours urinary TXA-M (P_{trend}=0.755). However, post-CABG 24 hours TXA-M was significantly associated with 1 year MACCE (P_{trend}=0.022). Patients whose post-CABG 24 hours TXA-M was in the intermediate tertile had an elevated HR of 2.22 in comparison to patients generating lower level of post-CABG 24 hours TXA-M (95% CI 1.04 to 4.71, P=0.038), and the higher tertiles of post-CABG 24 hours TXA-M bear an even higher HR of 2.81 (95% CI 1.35 to 5.85, P=0.006). Further, we adjusted the model by multiple variables listed in online supplementary table S1. After adjusting, post-CABG 24 hours generation of TXA-M still exhibited significant association with MACCE (P_{trend}=0.018). MACCE risk of patients who generated intermediate level of post-CABG 24 hours urinary TXA-M was 2.67 (95% CI 1.20 to 5.90, P=0.016) times higher than those who generated low level of post-CABG 24 hours TXA-M, and high tertile of TXA-M generation resulted in a risk 2.86 (95% CI 1.34 to 6.13, P=0.007) times more than the low tertile (table 4, figure 2).

In addition, we calculated the C-statistics of the models. Under logistic regression, the C-statistic of clinical factors containing all variables listed in online supplementary table S1 was 0.64 (95% CI 0.55 to 0.72), the C-statistic of post-CABG 24 hours TAX-M was 0.62 (95% CI 0.54 to 0.70). Combining post-CABG 24 hours TAX-M with clinical factors, the C-statistic increased to 0.68 (95% CI 0.60 to 0.76), which indicated the predictive value was improved by adding post-CABG 24 hours TAX-M (online supplementary table S2).

Table 1 Baseline characteristics of study participants

	All patients (n=224)	MACCE		P values
		No (n=168)	Yes (n=56)	
Age				
Mean - years	61.7 (±7.9)	61.7 (±7.8)	61.7 (±8.2)	0.981
Distribution - no. (%)				
≤60 years	100 (44.6)	75 (44.6)	25 (44.6)	1
>60 years	124 (55.4)	93 (55.4)	31 (55.4)	1
Male sex - no. (%)	180 (80.4)	136 (81.0)	44 (78.6)	0.698
Body mass index (kg/m^2)	25.9 (±2.9)	25.9 (±2.8)	25.9 (±3.2)	0.970
Current smoking - no. (%)	133 (59.4)	103 (61.3)	30 (53.6)	0.307
Medical history - no. (%)				
Hypertension	159 (71.0)	121 (72.0)	38 (67.9)	0.552
Diabetes mellitus	83 (37.1)	59 (35.1)	24 (42.9)	0.299
Chronic obstructive pulmonary disease	2 (0.9)	1 (0.6)	1 (1.8)	0.412
Peripheral vascular disease	7 (3.1)	5 (3.0)	2 (3.6)	0.825
Prior MI	76 (33.9)	55 (32.7)	21 (37.5)	0.515
Chronic kidney disease	3 (1.3)	3 (1.8)	0 (0.0)	0.314
Ejection fraction (%)	60.5 (±7.6)	60.5 (±7.6)	60.4 (±7.9)	0.923
Rosuvastatin use in the STICS trial	110 (49.1%)	84 (50.0%)	26 (46.4%)	0.643
Medication use after discharge - no. (%)				
Aspirin	217 (96.9)	163 (97.0)	54 (96.4)	0.825
β-blocker	163 (72.8)	124 (73.8)	39 (69.6)	0.544
Statins	158 (70.5)	120 (71.4)	38 (67.9)	0.612
ACEI	52 (23.2)	40 (23.8)	12 (21.4)	0.715
Calcium channel blocker	52 (23.2)	36 (21.4)	16 (28.6)	0.273
Scheduled surgery - no. (%)				
On-pump procedure	101 (45.1)	72 (42.9)	29 (51.8)	0.245
Off-pump procedure	123 (54.9)	96 (57.1)	27 (48.2)	0.245

Values are mean (±SD) or n (%).
ACEI, ACE inhibitors; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; STICS, Statin Therapy in Cardiac Surgery.

DISCUSSION

In this study, we used a nested case-control design to analyse the association between perioperative urinary TXA-M and MACCE in a CABG cohort. According to our results, post-CABG 24 hours urinary TXA-M shows significant association of 1 year MACCE. Post-CABG 24 hours TXA-M of patients with MACCE is significantly higher than that of patients without MACCE. In addition, risk stratification according to the post-CABG 24 hours urinary TXA-M level predicts 1 year MACCE after CABG. Patient whose post-CABG 24 hours urinary TXA-M is in the highest tertile bears almost three times higher risk than those in the lowest tertile. These results indicate that post-CABG 24 hours urinary TXA-M has the potential to be a risk predictor of adverse events after CABG in future clinical practice.

TXA_2 originates from AA. The first two steps of AA metabolism are the oxidation catalysed by cyclo-oxygenase-1 or cyclo-oxygenase-2. With these two isoforms

Table 2 Urinary thromboxane metabolite (TXA-M) concentrations pre-CABG, post-CABG 6 hours and post-CABG 24 hours in patients with or without MACCE

	MACCE			Non-MACCE			
	Number	Median	IQR	Number	Median	IQR	P values
Pre-CABG	56	4540	2383~6524	168	5076	3398~7593	0.047
Post-CABG 6 hours	56	24 016	15541~35 965	168	25 681	17612~35 005	0.727
Post-CABG 24 hours	56	11 101	7327~14 624	168	8849	5530~12 552	0.007

CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events.

Table 3 Urinary thromboxane metabolite (TXA-M) concentrations of pre-CABG, post-CABG 6 hours and post-CABG 24 hours in control patients and patients who died, patients with stroke, patients with MI and patients with repeat revascularisation

	Number	Pre-CABG	P values	Post-CABG 6 hours	P values	Post-CABG 24 hours	P values
Patients with MACCE							
Control patients	168	5076 (3398~7593)	–	25 681 (17612~35 005)	–	8849 (5530~12 552)	–
Death	16	4879 (1680~9325)	0.596	26 689 (20423~26689)	0.441	11 993 (8614~23 384)	0.039
Stroke	26	4583 (2713~5875)	0.197	26 156 (13426~36 372)	0.847	11 138 (8764~15 021)	0.016
MI	2	2550 (–)	0.075	17 029 (–)	0.225	13 585 (–)	0.444
Revascularisation	12	3384 (2554~6765)	0.931	21 502 (12965~32 440)	0.335	8059 (6577~13 642)	0.931

Values are median (IQR).
CABG, coronary artery bypass graft; MI, myocardial infarction; MACCE, major adverse cardiac and cerebrovascular events.

of cyclo-oxygenase, AA is synthesised into hydroperoxy endoperoxide PGG2 and its subsequent reduction to the hydroxy endoperoxide PGH2, which would be transformed by TXA synthase into TXA2.[14] TXA_2 has a very short half-life and undergoes hydrolysis to the inactive TXB_2 without enzyme, then further metabolises to TXA-M (11-dehydro-TXB_2 and 11-dehydro-2,3-dinor TXB_2) and is excreted in the urine. In previous studies, TXA-M has been reported to be associated with increased MI, stroke or cardiovascular death rate in patients with high cardiovascular risk.[15] Moreover, TXA-M also correlates with the increase of cardiovascular events and mortality in patients with atrial fibrillation.[16] For patients with CABG, the urinary TXA-M level is associated with SVG patency.[4] Our study demonstrates that perioperative TXA-M level is associated with adverse events in the first year after CABG for the first time.

In our study, pre-CABG TXA-M has a marginally significant association with 1 year MACCE after CABG; patients who generate high levels of TXA_2 tend to have low risks of MACCE. As the P value of this association is marginal, further study should be undertaken out to confirm this correlation. Urinary TXA-M increases sharply at 6 hours after CABG, which may be caused by the turnover of newly generated platelets and increased inflammation induced by the surgical procedure. At 24 hours after CABG, urinary TXA-M decreases compared with post-CABG 6 hours urinary TXA-M, which is mainly caused by decreased inflammatory response. However, the generation of urinary TXA-M still remains at a relatively high

Table 4 Cox regression analysis of MACCE according to levels of pre-CABG, post-CABG 6 hours and post-CABG 24 hours urinary thromboxane metabolite (TXA-M)

		Unadjusted			Adjusted*		
	Tertile	HR	95% CI	P values	HR	95% CI	P values
Pre-CABG	1	–	–	0.075	–	–	0.066
	2	0.54	0.28~1.01	0.055	0.52	0.27~1.03	0.062
	3	0.55	0.29~1.03	0.062	0.48	0.25~0.95	0.036
Post-CABG 6 hours	1	–	–	0.755	–	–	0.564
	2	1.21	0.64~2.27	0.556	1.33	0.68~2.22	0.404
	3	0.92	0.50~1.88	0.923	0.94	0.46~1.93	0.862
Post-CABG 24 hours	1	–	–	0.022	–	–	0.018
	2	2.22	1.04~4.71	0.038	2.67	1.20~5.90	0.016
	3	2.81	1.35~5.85	0.006	2.86	1.34~6.13	0.007

Adjusted by all the variables listed in online supplementary table S1 (age, sex, body mass index, current smoking, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, prior myocardial infarction, chronic kidney disease, ejection fraction, on-pump procedure, aspirin, β-blocker, statins, ACE inhibitors, calcium channel blocker).
CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events.

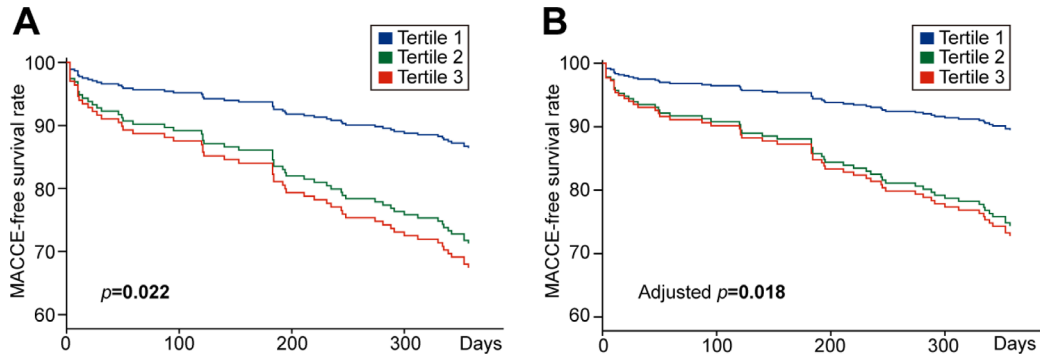

Figure 2 Kaplan-Meier curves of MACCE-free survival rate according to post-CABG 24 hours concentration of urinary thromboxane metabolite (TAX-M). Analysis of MACCE-free survival rate according to concentration tertiles of post-CABG 24 hours urinary TAX-M. (A) Unadjusted curve of MACCE-free survival rate; (B) Curve of MACCE-free survival rate adjusted by variables listed in online supplementary table S1. CABG, coronary artery bypass graft; MACCE, major adverse cardiac and cerebrovascular events.

level 24 hours after CABG compared with the normal status. The main reason for this phenomenon is the cyclo-oxygenase-2-derived thromboxane synthesis. Under normal conditions, an overwhelming majority of TXA_2 is generated by platelet cyclo-oxygenase-1. As an isoform of cyclo-oxygenase, cyclo-oxygenase-2 is mainly activated during the inflammatory process and has been reported to play important roles in the process of atherosclerosis and the progression of CAD. In response to the inflammatory stimuli triggered by the CABG procedure,[17 18] the expression of cyclo-oxygenase-2 is augmented 10–20-fold in nucleated cells.[14 15] Besides, platelet turnover enhanced by the CABG procedure also elevates platelet cyclo-oxygenase-2 expression.[19 20] Aspirin irreversibly inhibits cyclo-oxygenase by acetylating serine 530 of cyclo-oxygenase-1 or serine 516 of cyclo-oxygenase-2,[21–23] but cyclo-oxygenase-2 is ~170-fold less sensitive to inhibition by aspirin than cyclo-oxygenase-1.[24] So the cyclo-oxygenase-2-derived thromboxane synthesis cannot be effectively inhibited by aspirin, which may contribute to the increased MACCE rate after CABG.

Apart from cardiac surgery, TXA-M has also been described as a potential predictive biomarker of MACCE in patients with high cardiac risk and in patients with acute MI. Eikelboom *et al*[15] first found that urinary concentrations of TXM predicted future risk of MI or cardiovascular death. These findings raised the possibility that elevated urinary TXM levels identify patients who are relatively resistant to aspirin and who may benefit from additional antiplatelet therapies or treatments that more effectively block in vivo thromboxane production or activity found in aspirin-treated patients. Then, Eikelboom *et al*[25] suggested that urinary concentrations of TXM are an externally valid and potentially modifiable determinant of stroke, MI, or cardiovascular death in patients at risk for atherothrombotic events. In patients with acute MI, Szczeklik *et al*[26] found that urine TXM could predict 1 year MACCE in patients with acute MI and provide prognostic information on left ventricular performance.

Although, our results indicate urinary TXA-M has the potential to be a risk predictor of adverse events after CABG, this study has several potential limitations. First, the stability of the high urinary TXA-M excretion phenotype is unknown. In other words, we have not tested TXA-M levels at later time points beyond the first day after CABG, thus, whether the TXA-M level in this study is a temporary change or a stable one should be verified in further studies. Second, as a nested case-control study, we did not test TXA-M levels for all patients in the STICS cohort, which mildly reduces the strength of our findings. So a further prospective study focused on this issue should be undertaken to validate our findings.

In summary, in a nested case-control study, we conclude that the perioperative urinary TXA-M level is associated with 1 year adverse events after CABG, which raises the potential possibility that high levels of perioperative TXA-M identify patients with high risk of post-CABG adverse events.

Contributors HL and ZX were involved in data collection, data analysis, writing of manuscript. CS and NB were involved in data verification. WC and QC were involved in the collection of patients' urine and test of TXA-M in patients' urine. ZhoZ, ZheZ and XW were involved in the design of study and student supervision, editing of manuscript.

Funding This study was supported by the Key Project in the National Science and Technology Pillar Programme during the 12th 5-year plan period (2013BAI09B01).

Competing interests None declared.

Patient consent Not required.

Ethics approval Review Board of Fuwai Hospital, Peking Union Medical College (Beijing, China)

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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