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Association between CK-MB Area Under the Curve and Tranexamic Acid Utilization in Patients Undergoing Coronary Artery Bypass Surgery

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Abstract Myonecrosis after coronary artery bypass graft (CABG) surgery is associated with excess mortality. Tranexamic acid (TA), an anti-fibrinolytic agent, has been shown to reduce peri-operative blood loss without increasing the risk of myocardial infarction (MI); however, no large study has examined the association between TA treatment and post-CABG myonecrosis. In the MC-1 to Eliminate Necrosis and Damage in Coronary Artery Bypass Graft Surgery II trial, inverse probability weighting of the propensity to receive TA was used to test for differences among the 656 patients receiving and 770 patients not receiving TA. The primary outcome was creatine kinase MB (CK-MB) area under the curve (AUC) through 24 h. The secondary outcome was 30-day cardiovascular death or MI. Patients who received TA were more frequently female, had a previous MI, heart failure, low molecular weight heparin therapy, on-pump CABG, valvular surgery, and saphenous vein or radial grafts. The median 24-h CK-MB AUC was higher in TA-treated patients [301.9 (IQR 196.7–495.6) vs 253.5 (153.4–432.5) ng h/mL, $p < 0.001$]. No differences in the 30-day incidence of cardiovascular death or MI were observed (8.7 vs 8.3%, adjusted OR 0.99; 95% CI 0.67–1.45, $p = 0.948$). In patients undergoing CABG, TA use was associated with a higher risk of myonecrosis; however, no differences were observed in death or MI. Future larger studies should be directed at examining the pathophysiology of TA myonecrosis, and its association with subsequent clinical outcomes.

Keywords Myonecrosis · Tranexamic acid · CABG · CK-MB

Introduction

Red blood cell transfusions after coronary artery bypass graft (CABG) surgery are associated with increased morbidity and mortality [1, 2]. Tranexamic acid (TA) is a lysine analogue that mediates its anti-fibrinolytic effect by inhibiting plasminogen binding to fibrin [3]. It is currently recommended by joint practice guidelines (level of evidence 1A) to reduce peri-operative blood loss and the number of blood transfusions in patients undergoing cardiac surgery [4]. Randomized trials and meta-analyses have reported that TA reduces blood loss, number of transfusions, re-operation, and length of stay [5–12].

Post-CABG myonecrosis, quantified using creatine kinase-MB (CK-MB) levels, is a risk factor for both intermediate- and long-term mortality [13–16]. Although TA does not increase the risk of postoperative myocardial infarction (MI), its use has a theoretical risk of vascular thrombosis, and no large study has examined the association between TA treatment and post-CABG markers of

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myonecrosis [9, 12]. Improving our understanding of the interaction between TA use and postoperative CK-MB levels may help improve peri-operative risk stratification. In the MC-1 to Eliminate Necrosis and Damage in Coronary Artery Bypass Graft Surgery II (MEND-CABG II) trial, we evaluated the burden of myonecrosis, MI, and clinical outcomes among patients who did and did not receive perioperative TA.

Methods

Study data

The design and results of the MEND-CABG II trial (NCT00402506) have been previously reported [17, 18]. Briefly, MEND-CABG II was a multicenter, double-blind, randomized controlled trial that compared pyridoxal 5′-phosphate (MC-1) to placebo in 3023 patients who underwent CABG. Patients ≥18 years of age were eligible for enrollment if they were scheduled for an isolated CABG on cardiopulmonary bypass and had ≥2 high-risk features: age ≥65 years, diabetes, recent or current smoker status, recent MI (>48 h to <6 weeks), left ventricular ejection fraction ≤45%, congestive heart failure, stroke, transient ischemic attack, carotid endarterectomy, asymptomatic carotid stenosis (≥50%), peripheral arterial revascularization, or moderate renal dysfunction (creatinine clearance ≥30–60 mL/min). Key exclusion criteria included planned valve or other surgery, cardiogenic shock, papillary or interventricular muscle rupture, uncontrolled diabetes, or creatinine clearance <30 mL/min. Ethics approval was obtained at all study centers, and all participants provided written consent.

Study population

The study population included all participants who underwent CABG and compared outcomes between patients who did, and did not, receive intraoperative TA. Patients who received aprotinin (n = 488) or epsilon aminocaproic acid (n = 1059) were excluded from the study to minimize confounding from other anti-fibrinolytic agents available during the study period.

Outcomes

The primary outcome was CK-MB area under the curve (AUC) through 24 h. The secondary outcome of interest was a composite of 30-day postoperative cardiovascular mortality or nonfatal MI. Patients were diagnosed with a postoperative MI using the MEND-CABG II study definition as follows: peak CK-MB ≥ 100 ng/mL through postoperative day 4; a peak CK-MB ≥ 70 ng/mL through postoperative day 4 with new 30-ms Q waves in contiguous leads; peak CK-MB ≥ 25 ng/mL after postoperative day 4; or new 30-ms Q waves in 2 contiguous leads that were not present at postoperative day 4 [18].

Other outcomes of interest were postoperative peak CK-MB, CK-MB AUC through 96 h, all-cause mortality, non-fatal stroke through 30 days, postoperative in-hospital percutaneous coronary intervention, postoperative dialysis, and bleeding endpoints (any intra- or postoperative transfusion, red blood cell, platelet, and plasma transfusion requirements, chest tube drainage in the first 24 h, chest tube number of days, and re-operation for bleeding). All MEND-CABG II outcomes were adjudicated by an independent clinical events committee blinded to the study treatment assignment.

Statistical methods

A statistical analysis plan was developed prior to accessing the data. Continuous variables were summarized as medians (interquartile ranges), and differences were compared using the Wilcoxon rank sum test. Categorical variables were presented as counts (percentages) and differences compared using the Pearson Chi square test when the cell frequencies were sufficient; otherwise, the Fisher exact test was used. Logistic regression models were used to test the relationship between TA use and the outcomes of interest. To account for baseline differences in the likelihood of receiving intra-operative TA, inverse probability weighting (IPW) was used in these models. To calculate the IPW weights, a logistic regression model was fitted to the data to estimate the probability of receiving TA adjusting for multiple covariates. Covariates included in the logistic regression model included age, gender, diabetes, MI ≤ 6 weeks before surgery, prior CABG, New York Heart Association class III/IV heart failure, Canadian Cardiovascular Society (CCS) class III/IV angina, peripheral vascular disease, chronic obstructive lung disease, cerebrovascular disease, cardiac valvular disease, aspirin use within 7 days of surgery, clopidogrel within 7 days of surgery, left ventricular ejection fraction, estimated glomerular filtrate rate, and aortic cross clamp time. Missing values for the covariates were singly imputed using fully conditional specification methods. CK-MB values exhibited a highly skewed distribution; thus, the t-test was used to compare the IPW of the log transformed variables. Statistical significance was set as $p < 0.05$. All analyses were performed at the Duke Clinical Research Institute (Durham, NC) using SAS version 9.4 (SAS Institute, Cary, NC).

Results

The final study population of 1426 patients included 656 (46.0%) who received TA and 770 (54.0%) who did not. A total of 1597 patients from the MEND-CABG II trial were excluded (Fig. 1). The baseline characteristics of patients who did and did not receive intra-operative TA are presented in Table 1.

Patients who received TA were more frequently female and more likely to have a previous history of MI, CCS class III/IV angina, heart failure, lower systolic blood pressure, and a higher incidence of preoperative beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, statin, or low molecular weight heparin therapy. No differences in study treatment (MC-1 vs placebo) were observed. Baseline surgical characteristics are presented in Table 2. Use of TA was more frequent among patient who underwent on-pump cardiopulmonary bypass, incidental valvular surgery, and saphenous vein or radial grafts. Additionally, the mean number of coronary anastomoses was higher in the TA cohort.

Outcomes

The median CK-MB AUC through the first 24 h postoperatively was significantly higher among patients who received TA [301.9 (IQR 196.7–495.6) vs 253.5 (153.4–432.5) ng•h /mL, $p<0.001$; Fig. 2]. Peak CK-MB through 96 h was also significantly higher in TA-treated patients [26.2 (16.5–43.2) vs 20.8 (13.3–35.5), $p<0.001$], while CK-MB AUC through 96 h was numerically higher [624.0 (414.1–1019.3) vs 578.6 (381.7–955.2), $p=0.104$].

No differences in the composite outcome of 30-day cardiovascular death or MI were observed between patients with and without TA use [8.7 vs 8.3%, adjusted odds ratio (aOR), 0.99; 95% confidence interval (CI), 0.67–1.45, $p=0.948$]. Similarly, no differences in cardiovascular mortality (1.8 vs 1.2%, aOR, 1.64; 0.67–4.01, $p=0.281$), all-cause mortality (2.3 vs 1.3%, aOR, 1.97; 0.85–4.54, $p=0.113$), nonfatal MI (7.5 vs 7.6%, aOR, 0.93; 0.62–1.40, $p=0.741$), and nonfatal stroke (1.4 vs 1.7%, aOR, 0.81; 0.34–1.94, $p=0.635$) were found through 30 days. The rate of in-hospital postoperative PCI was similar (0.2 vs 0.4%, aOR, 0.29; 0.03–2.87, $p=0.291$); however, dialysis rates were higher (1.9 vs 0.4%, aOR, 4.67; 1.30–16.77, $p=0.018$).

The transfusion and bleeding outcomes according to TA use are provided in Table 3. TA treatment was associated with a lower risk of platelet transfusion, whole blood transfusion, and chest tube days. The unadjusted median number of units of red blood cells, platelets, and plasma was lower in the TA treatment cohort. Chest tube drainage and risk of re-operation for bleeding were numerically lower in the TA treatment cohort. However, the adjusted risk of any transfusion and any red blood cell transfusion was higher among TA-treated patients.

In a post-hoc analysis we compared outcomes in patients who received epsilon aminocaproic acid and no anti-fibrinolytic therapies. The median CK-MB AUC through the first 24 h [263.1 (IQR 172.3–449.1) vs 271.5 (IQR 171.5–459.5) ng•h /mL, $p=0.209$], 96 h [572.8 (IQR 383.2–957.5) vs 600.9 (IQR 395.8–984.5) ng•h / mL, $p=0.102$], and peak CK-MB through 96 h [22.2 (IQR 14.7–36.3) vs 23.1 (IQR 14.7–38.8), $p=0.072$] were not significantly difference between patients who did, and did not, receive epsilon aminocaproic acid, respectively. No differences were observed in the secondary outcomes of 30-day cardiovascular death or MI, cardiovascular mortality, all-cause mortality, nonfatal MI, or non-fatal stroke (Supplemental Table 1). Transfusions of red blood cells and platelets were numerically higher in epsilon aminocaproic acid treated patients (Supplemental Table 2).

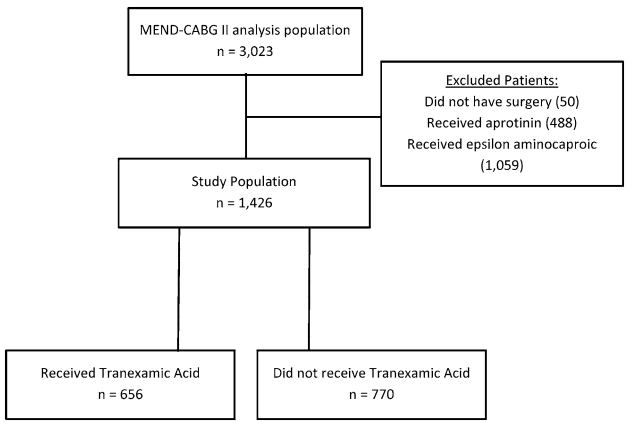

Fig. 1 Flow diagram

Discussion

In a large multinational CABG study with systematically collected markers of myonecrosis and adjudicated clinical endpoints, several important and novel findings emerge. First, the intra-operative use of TA was independently associated with higher postoperative markers of myonecrosis; however no differences in post-CABG MI or cardiovascular mortality were observed. Second, TA use was independently associated with an increased risk of postoperative dialysis. Third, the study reaffirms the efficacy of TA in reducing chest tube days, peri-operative blood loss, and the number of blood product transfusions reported in previous controlled trials; however, TA use was associated with a higher risk of any transfusion.

Table 1 Baseline characteristics by intraoperative tranexamic acid treatment

Characteristic	TA treatment (n = 656)	No TA treatment (n = 770)	*p*
Demographics			
Age (years)	67.3 (58.9, 73.1)	67.0 (59.1, 73.6)	0.950
Female	123/656 (18.8%)	190/770 (24.7%)	0.007
Race			0.001
White	605/656 (92.2%)	720/770 (93.5%)	
Black or African American	16/656 (2.4%)	33/770 (4.3%)	
Other	35/656 (5.3%)	17/770 (2.2%)	
Medical history			
Hypertension	527/654 (80.6%)	625/770 (81.2%)	0.779
Diabetes	288/656 (43.9%)	354/768 (46.1%)	0.407
Hypercholesterolemia	528/642 (82.2%)	608/760 (80.0%)	0.286
Previous myocardial infarction	370/651 (56.8%)	379/765 (49.5%)	0.006
≤6 weeks before surgery	215/370 (58.1%)	200/378 (52.9%)	0.153
CCS angina class			<0.001
No angina	84/583 (14.4%)	165/677 (24.4%)	
Class I/II	165/583 (28.3%)	253/677 (37.4%)	
Class III/IV	334/583 (57.3%)	259/677 (38.3%)	
NYHA class			<0.001
No heart failure	408/627 (65.1%)	564/737 (76.5%)	
Class I/II	121/627 (19.3%)	98/737 (13.3%)	
Class III/IV	98/627 (15.6%)	75/737 (10.2%)	
Previous PCI	174/655 (26.6%)	219/765 (28.6%)	0.386
Previous coronary artery bypass	13/656 (2.0%)	33/769 (4.3%)	0.014
Coronary artery disease ≥70%	633/646 (98.0%)	753/763 (98.7%)	0.300
Left main	112/633 (17.7%)	145/753 (19.3%)	0.456
Left anterior descending	533/633 (84.2%)	636/753 (84.5%)	0.894
Left circumflex	452/633 (71.4%)	505/753 (67.1%)	0.082
Right coronary artery	487/633 (76.9%)	577/753 (76.6%)	0.892
Left ventricular ejection fraction (%)			0.455
Normal (≥50%)	409/612 (66.8%)	493/753 (65.5%)	
Mild (40%-49%)	108/612 (17.6%)	155/753 (20.6%)	
Moderate (25%-39%)	86/612 (14.1%)	92/753 (12.2%)	
Severe (<25%)	9/612 (1.5%)	13/753 (1.7%)	
Atrial fibrillation	35/656 (5.3%)	54/770 (7.0%)	0.192
Cerebrovascular disease	86/651 (13.2%)	126/759 (16.6%)	0.076
COPD	76/649 (11.7%)	110/760 (14.5%)	0.127
Smoking status			0.710
Past	273/656 (41.6%)	334/770 (43.4%)	
Present	176/656 (26.8%)	193/770 (25.1%)	
Never smoked	207/656 (31.6%)	243/770 (31.6%)	
Vitals			
Systolic blood pressure	124.0 (112.0, 140.0)	128.0 (116.0, 140.0)	0.002
Heart rate	67.0 (60.0, 76.0)	68.0 (60.0, 76.0)	0.202
Labs			
Hemoglobin	13.8 (12.7, 14.8)	13.6 (12.4, 14.7)	0.043
Creatinine	1.0 (0.9, 1.2)	1.0 (0.8, 1.1)	0.069
Medications (≤7 days of surgery)			
Beta blocker	535/656 (81.6%)	598/770 (77.7%)	0.070
ACE/ARB	503/656 (76.7%)	512/770 (66.5%)	<0.001
Statin	558/656 (85.1%)	579/770 (75.2%)	<0.001
Aspirin	536/656 (81.7%)	652/770 (84.7%)	0.134

Table 1 (continued)

Characteristic	TA treatment (n = 656)	No TA treatment (n = 770)	*p*
Clopidogrel	179/656 (27.3%)	225/770 (29.2%)	0.419
Warfarin	11/656 (1.7%)	16/770 (2.1%)	0.580
Low molecular weight heparin	183/656 (27.9%)	147/770 (19.1%)	<0.001
Heparin	168/656 (25.6%)	246/770 (31.9%)	0.009
Randomization to MC-1	333/656 (50.8%)	396/770 (51.4%)	0.802

Results are presented as n/N (%) or median (IQR)

ACE angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *CCS* Canadian Cardiovascular Society, *COPD* chronic obstructive pulmonary disease, *MC-1* pyridoxal 5′-phosphate, *NYHA* New York Heart Association, *PCI* percutaneous coronary intervention, *TA* tranexamic acid

Table 2 Surgical variables by intraoperative tranexamic acid treatment

Variable	TA treatment (n = 656)	No TA treatment (n = 770)	*p*
Cardiopulmonary bypass	648/656 (98.8%)	735/770 (95.5%)	<0.001
Aortic cross clamp time, min	57 (42, 76)	55 (42, 75)	0.575
Minimally invasive CABG	53/656 (8.1%)	45/770 (5.8%)	0.096
Valve repair/replacement	9/656 (1.4%)	3/770 (0.4%)	0.043
Graft type			
Left internal mammary	592/656 (90.2%)	672/770 (87.3%)	0.078
Right internal mammary	38/656 (5.8%)	44/770 (5.7%)	0.949
Saphenous vein	617/656 (94.1%)	697/770 (90.5%)	0.013
Composite (vein and artery)	1/656 (0.2%)	9/770 (1.2%)	0.016
Other artery (e.g., radial)	89/656 (13.6%)	58/770 (7.5%)	<0.001
Number of proximal anastomoses			<0.001
0	12/656 (1.8%)	24/769 (3.1%)	
1	128/656 (19.5%)	193/769 (25.1%)	
2	264/656 (40.2%)	347/769 (45.1%)	
3	208/656 (31.7%)	162/769 (21.1%)	
≥4	44/656 (6.7%)	43/769 (5.6%)	
Number of distal anastomoses			<0.001
0	2/656 (0.3%)	4/770 (0.5%)	
1	16/656 (2.4%)	28/770 (3.6%)	
2	91/656 (13.9%)	173/770 (22.5%)	
3	256/656 (39.0%)	294/770 (38.2%)	
4	217/656 (33.1%)	198/770 (25.7%)	
≥5	74/656 (11.3%)	73/770 (9.5%)	
Cell saver use	209/656 (31.9%)	375/768 (48.8%)	<0.001

Results are presented as n/N (%) or median (IQR)

CABG coronary artery bypass grafting, *TA* tranexamic acid

Elevated myocardial enzymes after CABG have a well-reported association with postoperative mortality [15, 16]. In the large Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial and other small studies, TA was shown to reduce postoperative blood product transfusions and reoperation [8, 12, 19–21]. No large study, however, has examined the association between myonecrosis and TA use in CABG population. We observed that TA was significantly associated with CK-MB AUC through 24 h and peak CK-MB. Given the potential pro-thrombotic risk, widespread clinical use of TA, and post-CABG MI risk previously reported with aprotinin, the results of this analysis suggest a potential subclinical pro-thrombotic risk and raise important questions about the cardiovascular effects of TA [22]. We acknowledge that TA did not increase the risk of MI in the recently published ATACAS trial results (adjudicated based on the third universal MI definition); however, the study did not evaluate measures of myonecrosis [12, 23]. We hypothesize that the comparative lack of incremental myonecrosis associated with epsilon

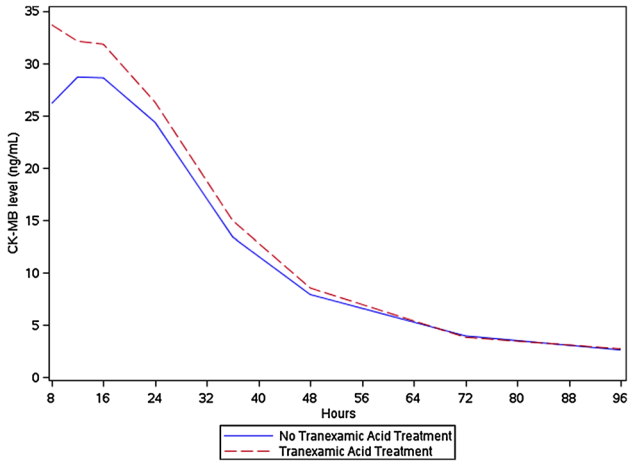

Fig. 2 Average creatine kinase MB (CK-MB) levels in patients treated with and without tranexamic acid over time. The CK-MB area under the curve through the first 24 h after coronary artery bypass surgery was significantly higher among patients who received tranexamic acid

aminocaproic acid treatment may be due to the different in pharmacodynamics and pharmacokinetic properties of TA and epsilon aminocaproic acid. Despite similar mechanisms of action, TA has a 6–10 fold greater affinity for plasminogen and a more sustained tissue level anti-fibrinolytic effect [3, 24]. Importantly, randomized controlled trials and meta-analysis have not reported differences in myocardial infarction rates between TA and epsilon aminocaproic acid treated patients and observational nature of this analysis precludes causal inferences [8, 11]. These findings provide future opportunities to explore the pathophysiology and epidemiologic associations between TA and myonecrosis, and TA's association with subsequent clinical outcomes.

Intravenous TA is eliminated by the kidneys 95% unchanged [3]. Case reports have documented TA-induced acute kidney injury with underlying intra-glomerular capillary and arterial fibrin thrombosis and acute renal cortical necrosis [25, 26]. In patients undergoing cardiac surgery, a meta-analysis by Brown and colleagues evaluated renal dysfunction (defined as ≥0.5 mg/dL rise in serum creatinine) in 4 non-randomized studies with 684 total patients and reported a non-significant increase in the risk of postoperative renal dysfunction (relative risk, 2.02; 95% CI 0.73–5.60) among TA-treated patients [8]. Similarly, an observational analysis by Mangano et al. [22] of 822 patients receiving TA reported a higher point estimate for renal dysfunction or dialysis in patients who underwent complex cardiac surgery (odds ratio 1.47; 95% CI 0.68–3.19). In the ATACAS trial, renal failure (defined as doubling of the serum creatinine or by a rise >2.4 mg/dL) was similar in TA and placebo groups, but the incidence of dialysis was not reported [12, 27]. We acknowledge the potential for residual confounding variables in our observational post-hoc analysis and the lack of postoperative creatine levels to directly compare our results to those of the ATACAS trial; however, the increased risk of dialysis in our study is an important safety signal that merits further evaluation.

We observed that TA was associated with a lower median number of red blood cell, platelet, and plasma transfusions and fewer median chest tube days, results consistent with those reported in previous randomized trials [28]. However, after adjustment, TA use was associated with an increase in any single blood product or red cell transfusions. Given that all other efficacy measures reported in this analysis were consistent with previously published results, we hypothesize that these latter findings

Table 3 Transfusion and bleeding outcomes according to tranexamic acid treatment

Outcome	TA treatment (n = 656)	No TA treatment (n = 770)	Adjusted OR (95% CI)	*P*
Any transfusion	375/646 (58.0%)	385/761 (50.6%)	1.49 (1.20–1.85)	<0.001
Transfusion of red blood cells	353/375 (94.1%)	335/385 (87.0%)	2.31 (1.35–3.95)	0.002
Number of units	2.0 (1.0, 4.0)	2.0 (2.0, 4.0)		0.015
Transfusion of platelets	70/375 (18.7%)	96/385 (24.9%)	0.66 (0.46–0.94)	0.022
Number of units	1.0 (1.0, 3.0)	2.0 (1.0, 6.0)		0.004
Transfusion of plasma	104/375 (27.7%)	84/385 (21.8%)	1.28 (0.91–1.80)	0.161
Number of units	2.0 (2.0, 4.0)	3.5 (2.0, 4.0)		0.094
Transfusion of whole blood	6/375 (1.6%)	33/385 (8.6%)	0.20 (0.08–0.50)	<0.001
Number of units	2.0 (1.0, 3.0)	2.0 (2.0, 4.0)		0.546
Chest tube drainage ≤24 h (ml)	610.0 (430.0, 890.0)	650.0 (440.0, 920.0)		0.218
Chest tube duration (days)	1.0 (1.0, 2.0)	2.0 (1.0, 3.0)		<0.001
Re-operation for bleeding	16/35 (45.7%)	29/51 (56.9%)	0.54 (0.22–1.32)	0.175

Results are presented as n/N (%) or median (IQR)

PCI percutaneous coronary intervention, *TA* tranexamic acid

may reflect that our outcomes were not adjusted for multiplicity or potential residual confounding associated with TA use that was not accounted for by the IPW analysis.

Limitations

Our findings should be interpreted in the context of the study's limitations. First, the study was not randomized, and the indication for TA was not recorded. Although this analysis sought to account for the likelihood of receiving TA using IPW, the results should only be considered hypothesis generating. Second, the case report form did not capture TA dosing information; thus, the association between dosing and outcomes could not be examined. Third, postoperative creatinine levels and indications for dialysis were not recorded in this dataset.

Conclusions

In a secondary analysis of a large trial of patients undergoing CABG, the use of TA was associated with a higher risk of myonecrosis, but no differences were observed in death or MI. Our findings suggest future opportunities to elucidate the cardiovascular effects of TA and explore the pathophysiologic and epidemiologic interactions between TA dosing and myonecrosis, and the association with subsequent clinical outcomes.

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Authors' contributions S.V.D. conception and design, analysis, interpretation of data, drafting the article, final approval of the version to be published, and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; P.D.M.: conception and design, analysis and interpretation of data, drafting the article, final approval of the version to be published, and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; M.C., J.C.T., M.P., J.H.A.: conception and design, acquisition of data, interpretation of data, revisions for critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; R.D.L.: conception and design, analysis and interpretation of data, revisions for critically for important intellectual content, final approval of the version to be published, and agreement to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest J.C.T. has received research support from Amarin, AstraZeneca, DalCor, Eli-Lilly, Hoffmann-LaRoche, Merck, Pfizer, Sanofi and Servier, and honoraria (to his institution) from Hoffmann-LaRoche, Pfizer, Servier and Valeant. Disclosures for J.H.A. and R.D.L. are available at https://www.dcri.org/about-us/conflict-of-interest. The remaining authors have disclosed that they do not have any conflicts of interest.

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