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# Perioperative diltiazem therapy was not associated with improved perioperative and long-term outcomes in patients undergoing on-pump coronary artery bypass grafting

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## Abstract

**Background**: Diltiazem has been used during the perioperative period in patients undergoing coronary artery bypass grafting (CABG) to prevent arterial graft spasm. However, its long-term outcome effects remain unclear.
**Methods**: Patient records obtained from the Society of Thoracic Surgeons and the Geisinger Clinic electronic health records between October 2008 and October 2018 were screened. Adult patients who had isolated CABG with cardiopulmonary bypass were included. Cohorts of patients who received diltiazem (DILT) and those who did not (non-DILT) were matched by propensity scores based on age, gender, surgical year, Society of Thoracic Surgeons mortality and morbidity scores, and number of arterial grafts. Incidence rate ratios (IRRs) were estimated for DILT *vs* non-DILT on short-term adverse outcomes. Long-term survival over time was compared between DILT *vs* non-DILT using Kaplan–Meier curves.
**Results**: Among the 1004 patients included in the analyses, IRRs for the DILT group relative to the non-DILT group were: 30-day all-cause mortality, IRR: 2.33, 95% confidence interval (CI): 0.91–5.96, $P=0.07$; postoperative myocardial ischaemia, IRR: 1.10, 95% CI: 0.60–2.02, $P=0.75$; new onset atrial fibrillation, IRR: 1.06, 95% CI: 0.78–1.43, $P=0.73$; stroke/transient ischaemic attack, IRR: 0.76, 95% CI: 0.17–3.38, $P=0.71$. For long-term survival, Kaplan–Meier curves stratified by diltiazem revealed no differences in survival rates between DILT and non-DILT groups.
**Conclusion**: For patients undergoing on-pump CABG, perioperative diltiazem therapy did not show significant short- or long-term outcome advantages over those who did not receive diltiazem.

**Keywords**: arterial grafts; calcium channel blocker; cardiopulmonary bypass; coronary artery bypass grafting; mortality

The use of arterial grafts in coronary artery bypass grafting (CABG), most frequently the left internal thoracic artery (LITA, previously internal mamillary artery, LIMA), radial arterial (RA) grafts, or both, has reported advantages over venous grafts.[1] Unlike venous grafts which develop lumen stenosis over time as a result of subintimal fibrosis, arterial grafts have a longer period of lumen patency because of better size adaptability to the native coronary vessels, and greater physiological flow because of the elasticity of the vessel wall and regular lumen.[2] However, arterial graft spasm of LITA and RA conduits may result in graft failure and myocardial ischaemia.[3] In fact, Carpentier and colleagues,[2] the group which originally described the use of RA grafts, reported graft spasm which contributed to an almost two-decade delay in the routine clinical use of RA grafts.[4,5]

Over the past three decades, numerous drugs have been investigated for preventing graft spasm,[6] including calcium channel blockers, such as diltiazem, and nitroglycerine. Diltiazem and nitroglycerine both have selectivity for the coronary vessels and provide reliable symptomatic relief in unstable angina. Data from randomised controlled trials (RCTs), mostly conducted between the 1980s and early 2000s with small

sample sizes of patients with LITA grafts, suggested that both diltiazem and nitroglycerine increased arterial graft blood flow (assessed by direct flow check intraoperatively) when applied locally, systemically, or both. When administered by continuous intravenous (i.v.) infusion perioperatively, diltiazem was superior to nitroglycerine in reducing perioperative myocardial ischaemia and arrhythmias.[7–15] Currently, perioperative continuous i.v. infusion of diltiazem is frequently used to prevent arterial graft spasms, especially for patients with RA grafts. However, its perioperative and long-term benefits remain unconfirmed.

The aim of this single-centre propensity-matched cohort study was to investigate the impact of perioperative systemic application of diltiazem on perioperative and long-term outcomes of adult patients undergoing isolated CABG with cardiopulmonary bypass (CPB) (i.e. on-pump CABG).

## Methods

The protocol of this retrospective cohort study was approved by the institutional review board of Geisinger Clinic and conducted in accordance with the relevant local, state, national, and institutional guidelines, and regulations for human research. A waiver of informed consent was granted by the institutional review board because there was no risk of identity exposure.

Using designated search phrases (see Appendix 1, Supplementary material), the Geisinger electronic health records (EHR) and the Society of Thoracic Surgeons (STS) database were searched. Records from October 2008 to October 2018 were retrieved. We included adult patients, age >18 yr old, who underwent elective or non-elective isolated on-pump CABG with at least one arterial graft. Patients who underwent combined CABG with other open chamber procedures, aortic procedures, or carotid endarterectomy, were excluded. Patients who were on chronic diltiazem or other calcium channel blocker therapy were included. Depending on whether diltiazem was received perioperatively, the patients were assigned to either the diltiazem cohort (DILT) or the control cohort (non-DILT). Propensity score matching (PSM) (1:1) was performed based on the patient's age, sex, year of surgery, STS morbidity and mortality score, and the number of arterial grafts used. The primary outcomes were 30-day and long-term all-cause mortality. Secondary outcomes included postoperative myocardial ischaemia, new onset atrial fibrillation, stroke/transient ischaemic attack (TIA), acute renal failure, multisystem organ failure, cardiac arrest, length of mechanical ventilation, ICU stay, hospital stay, and discharge status (Appendix 2). Two subgroup analyses were conducted—the first analysis identified and included all the patients who had more than one arterial graft, and the second identified and included all patients who had an intra-aortic balloon pump (IABP) inserted before postoperative ICU admission. In both the analyses, patients in the DILT group were compared with those in the non-DILT group.

### Perioperative management and diltiazem administration

Except for oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and oral diabetic medications, all routinely prescribed medications were continued until the day of surgery. I.V. infusions of nitroglycerine, heparin, or both were discontinued after the patients entered the operating room. Patients were premedicated with midazolam. Depending on the patient's ventricular function and the pathology of the coronary vessels, general anaesthesia was induced with the combination of fentanyl and propofol, etomidate, or midazolam, and titrated to maintain haemodynamic stability. General anaesthesia was maintained with isoflurane supplemented with fentanyl and midazolam: neuromuscular block was with rocuronium. Inotropic agents, vasoactive agents, or both were given as needed. Standard protocols were followed for taking down the left, right, or both LITA, and dissection of peripheral arterial segments and saphenous venous segments. The grafts were preserved in Ringer's lactate solution containing verapamil 2.5 mg ml$^{-1}$, nitroglycerine 5 mg ml$^{-1}$, and heparin 1000 units ml$^{-1}$, until they were ready to be sutured onto the target native coronary vessels. During revascularisation, the heart was protected by CPB with hypothermia, and perfusion of cardioplegia solution with high potassium concentration. Continuous i.v. infusion of diltiazem at a dosage of 5 mg h$^{-1}$ was started after successfully weaning off CPB. For patients who were not on calcium channel blockers preoperatively, the i.v. infusion was converted to oral diltiazem 120 mg daily when the patients were able to take medications orally after tracheal extubation. Oral diltiazem was typically discontinued after 30 days for patients with LITA grafts and 6 months for those with RA grafts. For patients who were taking a calcium channel blocker other than diltiazem preoperatively, this drug was resumed, instead of switching to oral diltiazem.

### Statistical analysis

Baseline characteristics were summarised with mean and standard deviation for continuous variables, and frequency for categorical variables. Propensity score-based methods were used to account for covariate imbalance between DILT and non-DILT groups. One-to-one matching using nearest neighbours with calliper of 0.20 was performed using combined propensity scores and exact matching on surgical year (2008–2018). Propensity scores were estimated based on age, sex, number of arterial grafts, and STS morbidity and mortality score. Pearson $\chi^2$ tests for independence were used to test whether the distribution of categorical outcomes differed between groups. Incidence rate ratios (IRRs) with corresponding 95% confidence intervals (CIs) were reported for the treatment effect of DILT *vs* non-DILT on adverse outcomes. Kaplan–Meier curves on survival time were presented for the PSM cohort, stratified by the DILT and non-DILT groups. Statistical analyses were conducted in RStudio (Version 1.3.1093, RStudio, Inc., Boston, MA, USA) using the MatchIt package.[16–18] P-values <0.05 were considered statistically significant.

## Results

### EHR data

A total of 2916 patients who underwent isolated on-pump CABG from October 2008 to October 2018 were included. Among them, 617 received perioperative diltiazem and 2299 did not. A significantly higher percentage of patients who received diltiazem had two or more arterial grafts (6.3% *vs* 1.6%, P<0.001).

## PSM cohorts

Among the 617 patients who received diltiazem, 502 (81%) were matched to patients not receiving diltiazem based on the propensity scores. Table 1 summarises the patient characteristics before and after PSM. Baseline covariates including age, sex, STS morbidity, and mortality score were well balanced between the DILT and non-DILT PSM cohorts (Appendix 3).

## Perioperative outcomes

Frequency count with corresponding percentages of perioperative outcomes were presented and compared between DILT and non-DILT groups in the PSM cohort (Table 2). The incidence rates of adverse outcomes were compared between the DILT and non-DILT (as reference) groups. Although percentages and computed IRRs were higher for the DILT group in 30-day all-cause mortality (IRR: 2.33, 95% CI: 0.91−5.96, $P=0.07$), postoperative myocardial ischaemia (IRR: 1.10, 95% CI: 0.60−2.02, $P=0.75$), new onset atrial fibrillation (IRR: 1.06, 95%: 0.78−1.43, $P=0.73$), or stroke/TIA (IRR: 0.76, 95% CI: 0.17−3.38, $P=0.71$), these differences were not statistically significant. The incidence rate of postoperative acute renal failure, multisystem organ failure and cardiac arrest were comparable between the matched DILT and non-DILT cohorts.

## Perioperative inotropic agent, vasoactive agent, or both dependency

The differences between the start and end time were estimated for the inotropic agents, vasoactive agents, or both and converted into binary variables using 24 h as the cut-off

**Table 2** Perioperative and long-term outcomes of diltiazem in patients receiving on-pump coronary artery bypass grafting. P-value: based on Pearson $\chi^2$ tests. DILT, diltiazem cohort; non-DILT, control cohort; SD, standard deviation; TIA, transient ischaemic attack.

| | Non-DILT ($n=502$) | DILT ($n=502$) | P-value |
|---|---|---|---|
| Long-term all-cause mortality (%) | 59 (11.8) | 67 (13.3) | 0.505 |
| 30-Day all-cause mortality (%) | 7 (1.4) | 15 (3.0) | 0.131 |
| Atrial fibrillation (%) | 81 (16.1) | 85 (16.9) | 0.799 |
| Myocardial ischaemia (%) | 20 (4.0) | 23 (4.6) | 0.755 |
| Stroke/TIA (%) | 4 (0.8) | 3 (0.6) | — |
| Hours of ICU (mean [SD]) | 47.42 (65.78) | 51.76 (86.83) | 0.372 |
| Inpatient days (mean [SD]) | 8.18 (4.04) | 8.45 (5.41) | 0.36 |

timepoint. $\chi^2$ Analysis suggested that the distributions of being on prolonged inotropic agents, vasoactive agents, or both 24 h postoperatively were statistically different between the matched DILT and non-DILT cohorts ($P<0.0001$).

## Length of care and final discharge location

There was no significant difference in the length of mechanical ventilation, length of ICU stay, and total days of inpatient care. Among the 502 pairs, 427 patients (85%) in the DILT group

**Table 1** Patient characteristics before and after propensity match. ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CPB, cardiopulmonary bypass; COPD, chronic obstructive pulmonary disease; DILT, diltiazem; IABP, intra-aortic balloon pump; IQR, inter-quartile range; PSM, propensity score matching; SD, standard deviation; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack.

| General characteristics | Original cohort | | | PSM cohort | | |
|---|---|---|---|---|---|---|
| | Non-DILT ($n=2298$) | DILT ($n=617$) | P-value | Non-DILT ($n=502$) | DILT ($n=502$) | P-value |
| Age (mean [SD]) | 65.65 (9.92) | 63.90 (10.11) | <0.001 | 64.84 (9.75) | 64.53 (10.26) | 0.618 |
| Male (%) | 1766 (76.8) | 472 (76.5) | 0.9 | 394 (78.5) | 380 (75.7) | 0.33 |
| STS score for mortality (mean [SD]) | 2.09 (3.48) | 1.93 (2.99) | 0.32 | 1.99 (3.91) | 2.10 (3.23) | 0.631 |
| STS score for morbidity *and* mortality (mean [SD]) | 14.99 (12.24) | 14.19 (11.92) | 0.15 | 14.74 (11.99) | 14.80 (12.47) | 0.933 |
| **Major comorbidities** | | | | | | |
| Hypertension (%) | 2061 (89.7) | 524 (84.9) | 0.001 | 442 (88.0) | 426 (84.9) | 0.17 |
| COPD (%) | 580 (25.2) | 223 (36.1) | <0.001 | 111 (22.1) | 189 (37.6) | <0.001 |
| History of smoking (%) | 250 (10.9) | 59 (9.6) | 0.39 | 52 (10.4) | 45 (9.0) | 0.52 |
| Peripheral vascular disease (%) | 344 (15.0) | 98 (15.9) | 0.62 | 65 (12.9) | 81 (16.1) | 0.18 |
| Stroke/TIA (%) | 512 (22.3) | 119 (19.3) | 0.12 | 98 (19.5) | 104 (20.7) | 0.69 |
| **Preoperative medications** | | | | | | |
| ACE-I/ARB (%) | 624 (27.2) | 207 (33.5) | 0.002 | 139 (27.7) | 164 (32.7) | 0.099 |
| Aspirin (%) | 2079 (90.5) | 554 (89.8) | 0.67 | 458 (91.2) | 447 (89.0) | 0.29 |
| β-Blocker (%) | 2105 (91.6) | 571 (92.5) | 0.5 | 472 (94.0) | 462 (92.0) | 0.27 |
| Calcium channel blocker (%) | 269 (11.7) | 79 (12.8) | 0.5 | 49 (9.8) | 68 (13.5) | 0.077 |
| Nitrate (%) | 222 (9.7) | 47 (7.6) | 0.14 | 49 (9.8) | 40 (8.0) | 0.37 |
| **Procedure-related characteristics** | | | | | | |
| Number of arterial graft (mean [SD]) | 0.79 (0.68) | 1.33 (0.84) | <0.001 | 1.13 (0.66) | 1.10 (0.67) | 0.57 |
| IABP (%) | 535 (15.9) | 89 (9.4) | <0.001 | 75 (14.9) | 54 (10.8) | 0.059 |
| Prolonged mechanical ventilation (%) | 204 (8.9) | 44 (7.1) | 0.19 | 32 (6.4) | 40 (8.0) | 0.39 |
| CPB time (median [IQR]) | 83 (65−107) | 92 (75−111) | <0.001 | 83 (65−106) | 91 (74−111) | <0.001 |

and 385 (77%) in the non-DILT were discharged to home (P=0.001, $\chi^2$ test).

### Survival analyses and Kaplan−Meier curves

Among the 502 matched pairs, there were 67 (13.3%) who died in the DILT group and 59 (11.8%) who died in the non-DILT group during the postoperative follow-up period. Kaplan−Meier curves stratified by diltiazem up to 5 yr showed that the curves crossed several times during the follow-up period, indicating that the hazards were not proportional between the matched DILT and non-DILT cohorts (Fig. 1).

### Subgroups analyses

Among the 502 PSM pairs, there were 124 DILT (n=124) and 114 non-DILT patients who received two or more arterial grafts: Table 3 summarises the perioperative outcomes of this subgroup of patients. There were no significant differences in the incidence of 30-day all-cause mortality, long-term all-cause mortality, new onset atrial fibrillation, myocardial ischaemia, stroke/TIA, length of ICU stay, and total inpatient days between the DILT and non-DILT groups. The log-rank test indicated that perioperative diltiazem was associated with increased risk of long-term all-cause mortality (P=0.02) (Fig. 2).

Similar PSM techniques were used in the subgroup of patients with preoperatively inserted IABP: Table 4 presents the perioperative outcomes of the 52 PSM pairs. There were no significant differences in 30-day all-cause mortality, long-term all-cause mortality, new onset atrial fibrillation, myocardial

**Table 3** Perioperative and long-term outcomes of diltiazem in subgroup of patients who received two or more arterial grafts.

| | Non-DILT (n=114) | DILT (n=124) | P-value |
|---|---|---|---|
| Long-term all-cause mortality (%) | 8 (7.0) | 17 (13.7) | 0.141 |
| 30-Day all-cause mortality (%) | 1 (0.9) | 2 (1.6) | − |
| Atrial fibrillation (%) | 16 (14.0) | 15 (12.1) | 0.802 |
| Myocardial ischaemia (%) | 4 (3.5) | 3 (2.4) | 0.91 |
| Stroke/TIA (%) | 0 (0.0) | 1 (0.8) | − |
| Hours of ICU (mean [sd]) | 38.26 (43.11) | 43.30 (56.70) | 0.444 |
| Inpatient days (mean [sd]) | 7.77 (3.43) | 7.61 (4.35) | 0.756 |

P-value: based on Pearson $\chi^2$ tests.
DILT, diltiazem cohort; Non-DILT, control cohort; sd, standard deviation; TIA, transient ischaemic attack.

ischaemia, stroke/TIA, length of ICU stay, and total inpatient days between DILT and non-DILT groups.

Appendix 4 summarises the perioperative outcomes in the subgroups of patients who were on or not on chronic calcium channel blocker therapy. Among the 502 PSM pairs, there were 68 patients in the DILT group and 49 in the non-DILT group who were on chronic calcium channel blockers preoperatively. There were no significant differences in major perioperative outcomes between the subgroups of patients who were taking and those who were not taking calcium channel blockers preoperatively.

### Discussion

We conducted this retrospective study to validate the practice and determine the perioperative and long-term outcome effects of perioperative diltiazem in patients undergoing on-pump CABG involving at least one arterial graft. In this propensity-matched cohort study we found no significant differences in perioperative outcomes when comparing those who received diltiazem with those who did not. There were no significant differences in 30-day all-cause mortality and long-term all-cause mortality. Patients who received preventive perioperative diltiazem required more haemodynamic support using inotropic agents, vasoactive agents, or both 24 h postoperatively. In addition, subgroup analyses revealed that diltiazem may be associated with reduced long-term survival in patients who received LITA with additional arterial grafts, which were mostly RA grafts. Based on these findings, we could not confirm that perioperative diltiazem had significant perioperative and long-term outcome benefits in our studied patient population.

The reported incidence of arterial graft spasm with compromised cardiac pump function and haemodynamic stability was between 0.5% and 1.3%.[3,19,20] Nowadays, the commonly accepted perioperative intervention to prevent arterial graft spasm is to locally, systemically, or both apply vasodilators with coronary selectivity. Diltiazem became the preferred antispasmodic agent because, compared with nitroglycerine, it had more favourable perioperative outcome profiles, including a lower incidence of new onset atrial fibrillation and myocardial ischaemia.[7,9,21,22] Notably, these randomised clinical trials also suggested that patients on
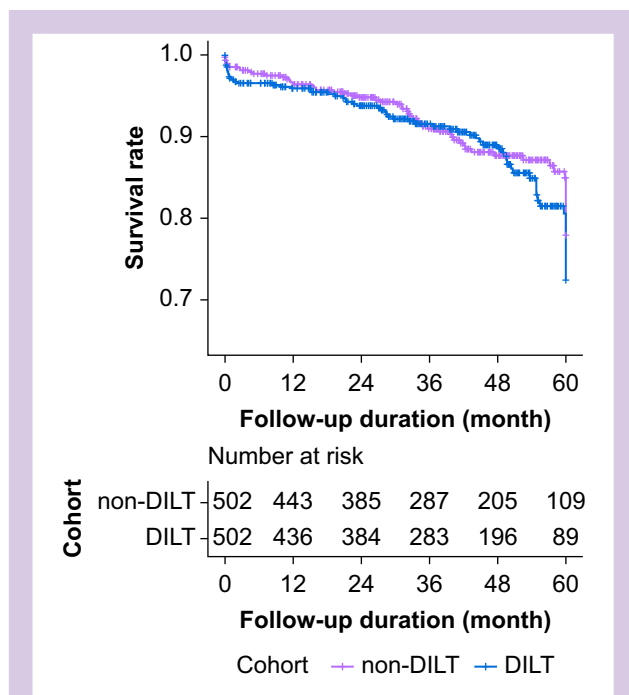


**Fig 1.** Kaplan−Meier survival curve for overall survival of patients in the cohorts of diltiazem (DILT) and non-DILT.
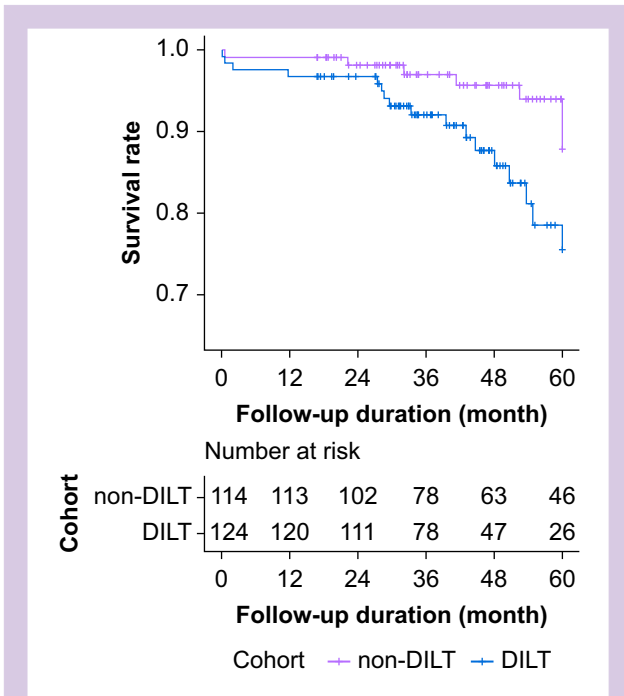
**Fig 2.** Kaplan−Meier survival curve for subgroup of patients who received two or more arterial grafts; diltiazem (DILT) had significantly lower long-term survival (P=0.02).

**Table 4** Perioperative and long-term outcomes of diltiazem in the subgroup of patients who had preoperative inserted intra-aortic balloon pump. P-value: based on Pearson $\chi^2$ tests. DILT cohort, diltiazem; Non-DILT, control cohort; SD, standard deviation; TIA, transient ischaemic attack.

| | Non-DILT (n=53) | DILT (n=53) | P-value |
|---|---|---|---|
| Long-term all-cause mortality (%) | 11 (20.8) | 10 (18.9) | — |
| 30-Day all-cause mortality (%) | 1 (1.9) | 4 (7.5) | 0.36 |
| Atrial fibrillation (%) | 6 (11.3) | 14 (26.4) | 0.082 |
| Myocardial ischaemia (%) | 4 (7.5) | 2 (3.8) | 0.674 |
| Stroke/TIA (%) | 2 (3.8) | 0 (0) | — |
| Hours of ICU (mean [SD]) | 64.88 (61.30) | 97.63 (105.58) | 0.054 |
| Inpatient days (mean [SD]) | 8.83 (5.33) | 10.85 (6.39) | 0.082 |

diltiazem may need prolonged haemodynamic support with inotropes, vasoactive support, or both, indicating that the use of diltiazem may have a potential negative perioperative and long-term impact.[22] Because of the limitation of small sample sizes, data on short- and long-term mortality were not reported for these trials. In fact, despite decades of perioperative diltiazem use to prevent graft spasm in CABG, observational data of long-term outcome after hospital discharge were lacking. In our institution, diltiazem has been routinely given to patients who underwent on-pump CABG, especially those who received RA grafts. Despite our findings and because of the limitations of this single-centre retrospective study, it is premature to conclude that diltiazem has no benefit or is harmful for patients undergoing on-pump CABG. However, we think our results have important clinical implications. Our findings are consistent with previous studies that demonstrated that the vasodilatory and negative inotropic effects of diltiazem had significant perioperative haemodynamic consequences, which may negatively affect the perioperative outcomes of patients because of reduced coronary perfusion pressure and perfusion pressure for other end organs. Studies have shown that the length and dosage of perioperative inotropic agents, vasoactive agents, or both predicted poor postoperative outcomes, including mortality, in patients who undergo cardiac surgery.[23] We suspect that the perioperative haemodynamic instability associated with diltiazem may have unfavourable effects on perioperative and long-term outcomes. One speculation for the worse long-term outcome in the subgroup of patients who received two or more arterial grafts is that decreased coronary pressure from the systemic application of diltiazem negated its antispasmodic effect. It may be reasonable to consider the combination of preventive perioperative IABP with perioperative diltiazem, rather than diltiazem alone, for better prevention of myocardial ischaemia caused by arterial graft spasm. A well-designed randomised clinical trial would be necessary to test this hypothesis.

As mentioned above, the preventive application of diltiazem is based on data from RCTs that focused on LITA grafts. The dosage of diltiazem in the current study (0.05−0.1 mg kg$^{-1}$) was based on these studies. However, in practice, patients receiving RA grafts are more likely to be treated with perioperative diltiazem. This assumes that the effect of diltiazem on all types of arterial grafts is the same. This is a plausible confounder, because studies have reported that different arterial grafts have different responses to diltiazem and other vasodilators. Most of these showed that LITA was more responsive to local, systemic, or both applications of diltiazem, exhibiting more graft dilation and increased blood flow.[7 9 11 13 21] Diltiazem showed advantages in perioperative outcomes over nitroglycerine in patients with only LITA grafts.[11,13,24−26] When RA or other arterial grafts were used, diltiazem may not be the best choice. An earlier RCT by Gaudino and colleagues suggested that long-term postoperative calcium channel blockers were not associated with better RA graft patency and may not provide outcome benefits for patients who had RA grafts.[26,27] A more recent study by the same group now argues against their previous conclusion − a *post hoc* analysis of data pooled from six RCTs that compared RA and saphenous vein grafts showed that chronic postoperative calcium channel blocker therapy may improve RA graft patency and reduce the incidence of major cardiovascular events.[28] However, some aspects of their methodology are questionable. *In vitro* and *in vivo* studies of RA sections or similar conduits indicated that nitroglycerine was more effective than diltiazem in preventing the contraction of RA grafts.[11,29,30] Compared with other calcium channel blockers, diltiazem was less effective at preventing graft contraction caused by endothelin-1 and norepinephrine, which affect RA more than LITA.[25] Chanda and colleagues[29] proposed that the combination of nitroglycerine and a calcium channel blocker may be more effective than any single agent at preventing RA graft spasm. In addition, data from recent studies investigating various categories of vasodilators show that the antispasmodic effects depend on the type of vessels and their specific mechanisms of graft spasm.[31−35] Taken together, the

evidence suggests that instead of applying diltiazem to every patient, tailoring the antispasmodic interventions to the type and condition of the arterial grafts and the clinical condition of each individual patient may be more effective. A large-scale, multicentre retrospective outcome study may be warranted to better understand the effects of diltiazem on arterial grafts. If data then suggest that diltiazem use is beneficial, a well-designed and properly powered RCT may be considered to thoroughly investigate if diltiazem improves outcome.

As secondary outcomes, we compared the duration of ICU stay and hospitalisation and the discharge locations of the patients studied. The duration of ICU and in-hospital care were similar between cohorts, but patients in the DILT group were more likely to be discharged to home instead of cardiac rehabilitation facilities. The association between the use of diltiazem and improved social and economic outcomes would have to be confirmed by a clinical trial.

Our study had some limitations. First, like other retrospective clinical studies, selection bias could not be eliminated even with PSM. Considering the limited sample, we were not able to include every covariate in the PSM. It is possible that other baseline and perioperative characteristics remained unbalanced between matched cohorts and confounded the results. We noted that the DILT cohort had a higher percentage of patients with chronic obstructive pulmonary disease and longer CPB times, both of which are associated with worse perioperative outcomes.[36,37] Although unconfirmed, there might have been a tendency towards more frequent perioperative i.v. diltiazem infusions for patients whose graft condition was deemed a concern based on visualisation and the Doppler flow check. Furthermore, like all the published RCTs, we did not exclude patients who were on chronic calcium channel blockers preoperatively. Second, whereas previous RCTs enrolled elective CABG patients only, we also included patients who received urgent/emergent procedures. Patients who received RA or other arterial grafts in addition to LITA graft and those who required insertion of IABP before planned CABG were included in our study, because the severity of the coronary pathologies rendered these patients more vulnerable to graft spasm. These differences in inclusion criteria may be the reason for our study not reproducing the favourable results of earlier trials. Third, the study may be underpowered. Based on the data, the *post hoc* estimated sample size to detect a difference in perioperative all-cause mortality was 1100 for each cohort. However, after PSM, the number of patients enrolled in each cohort was only 502. Therefore, the study was likely underpowered to investigate certain perioperative outcomes. Fourth, our study spanned 10 yr from 2008 to 2018. The surgical and anaesthetic practice may have changed during this period. However, as the authors can attest, there were very low turnover rates in both cardiac surgery and cardiac anaesthesia teams during this period at Geisinger. In addition, Geisinger had adopted a model to standardise care in cardiac surgery since the beginning of this study period. The changing practice was unlikely to have confounded our results. Fifth, ideally, this study should be conducted in patients who did not have exposure to calcium channel blockers in the past, but this would significantly reduce sample sizes. Therefore, like the cited trials, patients who were on chronic calcium channel blocker therapy were not excluded from our study. The subgroup analyses suggested that preoperative chronic calcium channel blocker therapy had no significant outcome effects in the studied patient population, however, these analyses were limited by the potential high risk of selection bias. Finally, the chosen starting rate of infusion for diltiazem was fixed at 5 mg $h^{-1}$, which was within the range of 0.05–0.1 mg $kg^{-1}$, which is the dosage cited in previous trials. Variations in initial serum diltiazem concentration as a result of the differences in body weight and in the management of the infusion by ICU staff may affect the outcomes.

In conclusion, data from the current retrospective propensity-matched cohort study did not confirm the short- and long-term outcome benefits of perioperative diltiazem. The preventive interventions for arterial graft spasm should be individualised considering the types and conditions of the grafts and the patient's clinical condition.

## Authors' contributions

## Acknowledgements

## Declarations of interest

The authors declare that they have no conflicts of interest.

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## Supplementary data

Supplementary data to this article are presented in Appendices 1–4 that can be found online at https://doi.org/10.1016/j.bjao.2022.100025.

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