Article

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Ticagrelor Versus Clopidogrel for Post-Operative Inflammation and the CD4/CD8 Ratio After CABG: A Propensity-Score-Matched Cohort Study Stratified by Residual LDL-C

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Background: Coronary artery bypass grafting (CABG) with cardiopulmonary bypass triggers an intense systemic inflammatory response and a transient depression of T-cell responses, both linked to postoperative complications and infection. Patients remaining above the guideline low-density-lipoprotein cholesterol (LDL-C) target retain residual lipid-related risk, which may coexist with residual inflammatory risk. Therefore, we pre-specified residual LDL-C (≥1.4 mmol/L) as a stratification variable rather than an eligibility criterion. Beyond P2Y12 blockade, ticagrelor exerts adenosine-mediated pleiotropic effects that may modulate inflammation and T-cell function. We aimed to examine whether it differs from clopidogrel in early post-CABG inflammation and the cluster of differentiation 4 (CD4)/CD8 ratio and to what extent any difference is paralleled by concurrently measured platelet inhibition.

Methods: In a single-center retrospective cohort undergoing elective isolated on-pump CABG under guideline-directed statin therapy, 1:1 propensity-score matching yielded 258 patients (129 pairs), of whom 179 of 258 (69.4%) had residual high LDL-C (≥1.4 mmol/L). The co-primary outcomes of day-3 C-reactive protein (CRP) and CD4/CD8 ratio were compared using analysis of covariance with adjustment for baseline values and pre-specified covariates. The robustness of the findings was further evaluated using stabilized inverse-probability weighting, cluster-robust inference, E-values, and an exploratory, non-causal decomposition of the between-group difference with respect to adenosine diphosphate (ADP)-induced platelet inhibition.

Results: Ticagrelor was associated with lower day-3 CRP (adjusted difference –20.96 mg/L, 95% confidence interval (CI) –27.74 to –14.18, roughly 12% relative reduction) and a higher CD4/CD8 ratio (+0.117, 95% CI 0.058 to 0.175, both $p < 0.001$). Estimates were robust across weighting, log-scale, and cluster-robust analyses (E-values 3.34 and 2.34). In an exploratory decomposition, the component statistically shared with ADP-induced platelet inhibition corresponded to approximately 34.5% and 41.2% of the respective differences, with the larger part of each difference unexplained by measured platelet reactivity. Because platelet reactivity was measured on days 3–5, that is, concurrently with or after the day-3 outcome, these proportions are descriptive and cannot be interpreted as mediation. Residual LDL-C did not significantly modify the effect.

Conclusion: Among statin-treated patients undergoing on-pump CABG, ticagrelor was associated with lower early inflammation and a higher CD4/CD8 ratio than clopidogrel, differences that were only partly paralleled by concurrently measured platelet inhibition. These hypothesis-generating findings warrant confirmation in a randomized trial.

Keywords: ticagrelor; clopidogrel; coronary artery bypass grafting; C-reactive protein; CD4/CD8 ratio; T-lymphocyte subsets; propensity score

Introduction

On-pump coronary artery bypass grafting (CABG) performed with cardiopulmonary bypass (CPB) provokes a systemic inflammatory response driven by contact activation of blood by the extracorporeal circuit, ischemia-reperfusion, and surgical trauma, with the activation of complement, cytokines, neutrophils, and platelets [1,2]. This response is more pronounced with on-pump than off-pump surgery and is accompanied by transient adaptive immune suppression characterized by postoperative lymphopenia, reduced T-cell receptor signaling, increased T-cell apoptosis, and impaired proliferative capacity, which may increase susceptibility to postoperative infection [1,3,4,5]. The early postoperative window reflects a coupled state of heightened innate inflammation and blunted adaptive immunity; therefore, interventions that favorably shift this balance are of clinical interest.

Inflammation is now recognized as a modifiable determinant of residual cardiovascular risk that operates independently of low-density-lipoprotein cholesterol (LDL-C) [6,7]. Although the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines recommended both a ≥50% reduction from baseline and an LDL-C target of <1.4 mmol/L (<55 mg/dL) for very-high-risk patients, contemporary European registry data indicate that most high- and very-high-risk patients remain above their risk-based LDL-C goals [8]. Elevated high-sensitivity C-reactive protein (hs-CRP) also identifies a higher risk of subsequent cardiovascular events among statin-treated patients with established atherosclerotic cardiovascular disease, including those with LDL-C <1.8 mmol/L (<70 mg/dL) [9]. Randomized trials of long-term low-dose colchicine provide proof of concept that selective anti-inflammatory therapy can reduce recurrent cardiovascular events on top of contemporary lipid-lowering treatment, supporting residual inflammatory risk as a therapeutic target [10,11,12]. However, the neutral CLEAR SYNERGY trial indicated that this benefit is not uniform across clinical settings [13]. Patients who remain above the guideline LDL-C target thus retain residual lipid-related risk, which may coexist with residual inflammatory risk, although the presence of the latter cannot be inferred from LDL-C alone. This is a population in which the anti-inflammatory potential of concomitant therapies is of particular interest.

In patients undergoing CABG for acute coronary syndrome, postoperative dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor has traditionally been guideline-recommended [14]. Clopidogrel and ticagrelor, two commonly used oral P2Y12 inhibitors, differ substantially in their pharmacokinetic and pharmacodynamic properties [15,16]. Clopidogrel is a prodrug requiring cytochrome P450 (CYP)-mediated hepatic bioactivation, yielding variable and often incomplete platelet inhibition [17,18]. Whereas ticagrelor is a direct-acting, reversibly binding antagonist that provides more potent and consistent platelet inhibition [19]. Ticagrelor also inhibits equilibrative nucleoside transporter-1 (ENT1), reducing cellular adenosine uptake and raising extracellular adenosine [20,21]. Through adenosine-receptor signaling, ticagrelor may exert non-P2Y12-mediated effects on neutrophil and other innate immune responses, as well as on endothelial and vasodilatory function [22,23]. The same pathway may contribute to ticagrelor-associated dyspnea, although the mechanism of this adverse effect is probably multifactorial [24,25], providing a mechanistic rationale for an anti-inflammatory and immune-modulating profile beyond platelet inhibition alone.

Some studies report greater reductions in inflammatory biomarkers with ticagrelor than clopidogrel, but these findings have not been consistent across biomarkers or patient populations [26,27]. While the DISPERSE-2 analysis found no significant between-drug difference in CRP, interleukin-6 (IL-6), myeloperoxidase, or soluble CD40 ligand, a substudy of the Platelet Inhibition and Patient Outcomes (PLATO) trial observed marginally lower on-treatment leukocyte counts with clopidogrel but no consistent treatment-related difference in CRP or IL-6 [28,29]. These data predominantly come from the percutaneous-coronary-intervention or acute-coronary-syndrome setting rather than from CABG [27]. The T-cell response to CABG is even less well characterized [30]. The CD4/CD8 ratio is a readily measurable index of T-cell balance, with a low ratio indicating immune activation and immunosenescence [31]. Lower ratios have been associated with increased all-cause mortality in some population cohorts, but their independent prognostic value remains inconsistent [32,33]. It remains unknown whether ticagrelor and clopidogrel differ in their effects on early post-CABG inflammation and the CD4/CD8 ratio, and, if so, whether these differences correspond to differences in on-treatment platelet inhibition or involve pathways beyond platelet inhibition.

We therefore conducted a propensity-score-matched cohort study of patients undergoing elective isolated on-pump CABG across a range of pre-operative LDL-C levels, with residual LDL-C (≥1.4 mmol/L) pre-specified as a stratification variable rather than an entry criterion. The co-primary endpoints were day-3 CRP and the day-3 CD4/CD8 ratio, representing the systemic-inflammatory response and T-cell subset balance. Pre-specified secondary and exploratory analyses examined whether residual LDL-C modified the treatment effect and used an exploratory decomposition to describe how much of any difference was statistically shared with concurrently measured adenosine diphosphate (ADP)-induced platelet inhibition.

Methods

Study Design and Population

We conducted a single-center, retrospective cohort study reported in accordance with the STROBE statement. This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Naval Medical University (Shanghai Changhai Hospital) (approval no. CHEC2025-193, meeting review on 12 November 2025) and conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent was waived by the committee owing to the retrospective nature of the study.

Consecutive patients who underwent elective, isolated coronary artery bypass grafting with at least one saphenous-vein graft between January 2022 and December 2024 were screened. Eligibility required a documented pre-operative LDL-C measured during a stable period under guideline-directed statin therapy (moderate- or high-intensity, taken regularly for ≥4 weeks), together with retrievable postoperative inflammatory, immune and platelet-function values. No LDL-C threshold was imposed at entry. All pre-

operative measurements, including the lipid panel, hs-CRP and the lymphocyte subsets, were drawn during a stable phase in 369 of the 392 on-pump patients. In the remaining 23 patients the draw was taken during the acute phase, and these patients were retained in the primary analysis with a pre-specified sensitivity analysis excluding them (eight of whom entered the matched cohort). Acute-phase sampling was associated with only modestly higher pre-operative hs-CRP (median 3.83 vs 3.02 mg/L, $p = 0.152$) and a similar pre-operative CD4/CD8 ratio (1.88 vs 1.77, $p = 0.120$), and excluding these patients left both co-primary estimates essentially unchanged (Sensitivity and supporting analyses). Clinical, operative, laboratory and one-year follow-up data were extracted from the institutional electronic medical record, and the analytic database was locked on 15 February 2026.

Patients were excluded if they underwent emergency surgery or concomitant valve or other major cardiac/vascular procedures, or had single-vessel disease, left-ventricular ejection fraction (LVEF) <30%, active infection or inflammatory/autoimmune disease, recent immunosuppressant or high-dose glucocorticoid exposure, malignancy or hematological disorder, severe hepatic or renal impairment, recent major surgery or transfusion, perioperative warfarin requirement, active bleeding or platelet disorders, contraindication to either study drug, or missing key clinical variables.

Surgical and Perioperative Management

All operations were performed by the same surgical team using a standardized institutional protocol that did not change during the study period. Anesthesia was induced with midazolam, sufentanil and rocuronium and maintained with propofol and/or sevoflurane combined with a sufentanil infusion. Tranexamic acid was not administered routinely. Cardiopulmonary bypass was conducted with a roller pump and a membrane oxygenator, using heparin-coated tubing and a crystalloid prime with the addition of mannitol. Systemic heparinization used an initial dose of 3 mg/kg targeting an activated clotting time above 480 s, with additional heparin as required, and was reversed with protamine at a ratio of 1:1. Conventional and/or modified ultrafiltration was used routinely, a leukocyte-depleting filter was not incorporated, cell salvage was not used routinely. Myocardial protection was achieved by antegrade delivery of cold blood cardioplegia after aortic cross-clamping. Mild hypothermic bypass was used, with a nasopharyngeal temperature maintained at 32–34 °C and rewarming to 36.5 °C before separation from bypass. Non-pulsatile flow was maintained at 2.2–2.6 L/min/m^2 with a mean arterial pressure of 50–80 mmHg and alpha-stat acid-base management. Red blood cells were transfused for a hematocrit below 24% on bypass or 26% thereafter. Perioperative glucocorticoids were given only for documented allergy or vasoplegia, not as routine anti-inflammatory prophylaxis. Cardiopulmonary-bypass time was recorded for every patient. Aortic cross-clamp time was not consistently documented in the electronic record and could not be retrieved for the full cohort. It was therefore not available as a covariate. These elements of surgical and perioperative care were applied uniformly, independent of the antiplatelet regimen, which was determined post-operatively.

Exposure and Outcomes

Grouping followed the antiplatelet regimen actually received, including aspirin plus ticagrelor (AT) or aspirin plus clopidogrel (AC), with the operative date as the time origin. In accordance with institutional practice, the assigned P2Y12 inhibitor was resumed on the first postoperative day once surgical hemostasis was confirmed and oral intake had been established, at standard maintenance doses (clopidogrel 75 mg once daily or ticagrelor 90 mg twice daily) without a loading dose. Aspirin was co-administered as enteric-coated tablets at 100 mg once daily. Pre-operatively, aspirin was continued up to the day of surgery, whereas the P2Y12 inhibitor was withheld for 5 days before surgery in both groups. Post-operatively, aspirin was restarted on the first postoperative day at the same time as the P2Y12 inhibitor, once surgical hemostasis was confirmed, and was given orally or through a nasogastric tube when oral intake had not yet been established. Both components of dual antiplatelet therapy were prescribed at discharge, with aspirin planned to continue indefinitely and the P2Y12 inhibitor for 12 months. The aspirin dose, its starting day and its planned duration were identical in the two treatment groups by protocol, and no loading dose of aspirin was given. Eligibility criteria did not impose an LDL-C threshold. Residual high LDL-C was pre-specified as a stable-phase pre-operative LDL-C ≥1.4 mmol/L and used as a stratification variable rather than an entry criterion. The two co-primary outcomes were the day-3 CRP concentration and the day-3 CD4/CD8 ratio, representing the systemic inflammatory response and T-cell subset balance, respectively. The corresponding pre-operative values were recorded for covariate adjustment. CRP was measured using a single high-sensitivity, particle-enhanced immunoturbidimetric assay with common calibration and reported across its full analytical range, allowing low pre-operative concentrations and markedly higher postoperative concentrations to be expressed on a continuous mg/L scale and compared within patients. Because postoperative values lie well above the low-concentration window in which the high-sensitivity (hs-CRP) label is clinically meaningful for cardiovascular risk stratification, we used hs-CRP only for the pre-operative (low-range) values and CRP for the postoperative co-primary outcome. The assay and the analyte are identical at both timepoints. Day-3 CRP was approximately symmetric with only mild right skew (skewness 0.89) and homogeneous between-group variance, and was therefore analyzed on its native

scale. A log-transformed (geometric-mean-ratio) analysis was pre-specified as a sensitivity check against residual skewness. Early post-operative on-treatment platelet reactivity, comprising ADP-induced inhibition (%) and ADP-induced maximum clot strength (MA-ADP), measured by thrombelastography on days 3–5 were recorded as concurrent measures of on-treatment pharmacodynamic response. Because both drugs were resumed on the first postoperative day without a loading dose and sampling occurred anywhere within days 3–5, the assay captures on-treatment reactivity at an early and variable point after resumption rather than a formally verified steady state. Ticagrelor reaches maximal inhibition more rapidly and had accumulated for a somewhat different number of doses at the time of testing, so the two groups are not necessarily comparable in terms of time since attainment of steady state. The measure is therefore interpreted as an early post-operative pharmacodynamic snapshot, and this is a further reason for treating the decomposition analysis as descriptive. Because these measures were obtained contemporaneously with or later than the day-3 outcomes, they were not treated as temporally antecedent mediators. Procalcitonin and nosocomial-infection records were used to screen for infection-driven contamination of the inflammatory and immune readouts. One-year vein-graft patency, the components of major adverse cardiovascular events (MACE), Bleeding Academic Research Consortium (BARC) bleeding and ticagrelor-attributed dyspnea were collected as exploratory endpoints.

Laboratory Measurements

Sample Timing

All pre-operative measurements were obtained from a single fasting venous blood draw taken on the morning of the day before surgery, that is, a median of 1 day (IQR 1–2) before the operation, and hs-CRP, the lymphocyte subsets and the lipid panel were assayed from that same draw. Sampling was performed during a clinically stable period, defined as the absence of ongoing chest pain, fever or acute decompensation at the time of the draw and after at least four weeks of uninterrupted guideline-directed statin therapy. Post-operative samples were drawn on the morning of the third postoperative day, so the pre- and post-operative measurements were separated by a median of 4 days and were taken at the same time of day.

Inflammatory Marker

High-sensitivity CRP was measured on a Cobas c702 module (Roche Diagnostics GmbH, Mannheim, Germany) using a particle-enhanced immunoturbidimetric assay (CRPHS). Calibration and internal quality control were performed according to the manufacturer's instructions and the laboratory's standard operating procedures.

Lymphocyte Subsets

Peripheral venous blood was collected into dipotassium ethylenediaminetetraacetic acid (K_2-EDTA) tubes on the morning of postoperative day 3 and processed within 6 h. A lyse-no-wash protocol was used with BD FACS Lysing Solution (349202, BD Biosciences, Franklin Lakes, NJ, USA) and a pre-mixed six-colour reagent (644611, BD Biosciences, Franklin Lakes, NJ, USA). Samples were acquired on a FACSCanto II (BD Biosciences, Franklin Lakes, NJ, USA) with BD FACSDiva CS&T IVD Beads (656047, BD Biosciences, Franklin Lakes, NJ, USA). At least 10000 $CD45^+$ events were collected per sample. Gating proceeded from $CD45^+/SSC^{low}$ lymphocytes to $CD3^+$ T cells and then to $CD3^+CD4^+$ and $CD3^+CD8^+$ subsets, with fluorescence-minus-one controls. The CD4/CD8 ratio was calculated as the ratio of the two subset percentages.

Platelet Reactivity

Paired 3.2% sodium-citrate and heparinized whole-blood samples were collected, at 2–4 h after the morning dose, and assayed within 30 min to 2 h on a TEG 5000 Hemostasis Analyzer (Haemonetics Corporation, Boston, MA, USA) using the PlateletMapping™ assay (07-014, Haemonetics Corporation, Boston, MA, USA) with kaolin, heparinase, activator F and ADP 2 µmol/L final concentration. ADP-induced inhibition was calculated as Inhibition (%) = [1 – (MA-ADP – MA-Fibrin) / (MA-Thrombin – MA-Fibrin)] × 100, where MA-Thrombin is the kaolin-activated maximum amplitude and MA-Fibrin the activator-F maximum amplitude. High on-treatment platelet reactivity (HOPR) was pre-defined as MA-ADP >47 mm. A secondary, more stringent definition additionally required ADP-induced inhibition <50%.

Study Drugs

Clopidogrel 75 mg once daily and ticagrelor 90 mg twice daily were dispensed as either the originator or a generic formulation available in the hospital formulary during the study period. Aspirin was dispensed as the enteric-coated formulation available in the hospital formulary during the study period.

Statistical Analysis

Normality of continuous variables was assessed using the Shapiro-Wilk test together with visual inspection of Q-Q plots and skewness. Normally distributed variables are presented as mean (SD) and compared using Student's t test. Non-normally distributed variables are presented as median (IQR) and compared using the Mann-Whitney U test. Categorical variables are presented as n (%) and compared using Pearson's χ^2 test, or by Fisher's exact test when any expected cell count was below 5. All analyses were performed in R (Version 4.5.2, R Foundation for Statistical Computing, Vienna, Austria) using the packages MatchIt (version 4.7.2), cobalt (version 4.6.3), survey (version 4.5), medi-

ation (version 4.5.1, used solely to obtain the regression-based decomposition, with no causal interpretation attached to its output labels) and EValue (version 4.1.4).

For the co-primary outcomes, the relevant assumption was normality of the analysis-of-covariance residuals rather than of the raw variable. Residual Q-Q plots were satisfactory, and day-3 CRP showed only mild right skew (skewness 0.89). With n = 258, the Shapiro-Wilk test was sensitive to trivial departures from normality. We therefore relied on skewness and Q-Q inspection and pre-specified a log-scale sensitivity analysis, which gave a concordant estimate.

Because cardiopulmonary bypass is the dominant driver of post-CABG inflammation, the primary analysis was restricted to on-pump cases. The off-pump cases were set aside rather than retained with forced exact matching on bypass status. A propensity score for receipt of ticagrelor was estimated using logistic regression on pre-specified demographic, clinical, operative and pharmacological covariates, and baseline biomarkers. Perioperative red-blood-cell and platelet transfusion entered the propensity-score model as unit counts. The binary indicators (receipt of ≥2 units of red blood cells; any platelet transfusion) were used for balance display in Table 1 and in the outcome-model adjustment sets. One-to-one nearest-neighbor matching was performed with a caliper of 0.2 SD of the estimated propensity score, with exact matching imposed on perioperative glucocorticoid use. This is a refinement beyond the protocol covariate list, adopted because glucocorticoids strongly depress CRP and perturb the immune readout, and which achieved an standardized mean difference (SMD) <0.001 for this variable. Covariate balance was assessed using the SMD, with <0.10 considered indicative of adequate balance. In the matched cohort, between-group differences in the co-primary outcomes were estimated by analysis of covariance adjusting for the corresponding baseline value and for a pre-specified adjustment set (diabetes, hypertension, smoking status and high-intensity statin use), yielding matching with regression adjustment. The drug-by-LDL-C interaction was tested within these same adjusted models, with LDL-C entered as a continuous modifier. The ≥1.4 mmol/L dichotomy was reserved for display and a threshold sensitivity analysis. The two co-primary outcomes were examined in the pre-specified hierarchical order, CRP first, then the CD4/CD8 ratio, each at a two-sided α of 0.05, with both required to be significant for the primary hypothesis to be regarded as supported. The pair was additionally subjected to Hochberg adjustment. As an exploratory, non-causal analysis, a regression-based decomposition with bootstrap resampling (2000 replicates) was used to quantify how much of the between-group difference in each co-primary outcome was statistically shared with early post-operative on-treatment platelet reactivity, adjusting for platelet count, receipt of ≥2 units of red blood cells (yes/no), perioperative glucocorticoid use, infection and bypass duration. Because platelet reactivity was measured on days 3–5, that is, contemporaneously with or later than the day-3 outcomes, the temporal-ordering condition required for mediation analysis is not satisfied. We therefore report only two descriptive quantities, the component shared with platelet reactivity and the remaining component, and do not report these estimates under their conventional causal-mediation labels or attach any causal interpretation to the resulting proportions. Exploratory endpoints were analyzed within the matched-pair structure by the exact McNemar test on discordant pairs, with Benjamini-Hochberg control of the false-discovery rate. One-year vein-graft failure was the exception. Only patients completing one-year computed-tomographic angiography (CTA) contributed an outcome, so the matched-pair structure was broken (66 of the 129 pairs remained intact), and this endpoint was analyzed among CTA completers by Fisher's exact test. Unpaired Fisher's exact results for all endpoints are shown in **Supplementary Table 1**. These analyses are interpreted as hypothesis-generating only.

Pre-specified and additional robustness analyses included an alternative residual-high-LDL-C threshold (≥1.8 mmol/L) for the interaction test; comparison of infection rates and re-estimation of the co-primary outcomes after excluding patients with documented infection; descriptive comparison of high on-treatment platelet reactivity (HOPR) between groups; estimation of the geometric-mean-ratio for CRP on the log scale; matched-pair cluster-robust standard errors for the co-primary estimates; stabilized inverse-probability-of-treatment weighting with truncation at the 1st/99th-percentile; E-values quantifying the strength of unmeasured confounding required to explain away each co-primary estimate; and sensitivity analysis of the decomposition components to an unmeasured common cause of platelet reactivity and outcome (indexed by the residual correlation ρ). All analyses were performed using complete cases. Eligibility required retrievable day-3 inflammatory, immune and platelet-function values, so patients with missing key variables were excluded during screening (quantified in the participant-flow diagram, Fig. 1), and no imputation was undertaken. Because these measurements are post-operative, this screening step selects partly on post-baseline information. Patients who did not survive to day 3, returned to theatre, or were too unstable to undergo protocol sampling could not enter the cohort. Among the 430 eligible patients these values were complete without exception, so no observations were lost after entry and imputation was not applicable. The analytic sample is therefore a complete-case cohort conditional on survival to and sampling on day 3, and the implications are considered in the Discussion. A two-sided $p < 0.05$ was considered statistically significant.

Results

Cohort Assembly and Covariate Balance

Of the eligible patients, 392 operated on-pump satisfied the analytic criteria and constituted the primary cohort, while 38 off-pump cases were set aside to remove variation attributable to cardiopulmonary bypass (Fig. 1). Ticagrelor- and clopidogrel-based dual antiplatelet therapy had been given to 227 and 165 patients, respectively. Before adjustment, the two arms diverged on several prognostically relevant variables, most strikingly age, pre-operative LDL-C, smoking status and baseline hs-CRP (all |SMD| ≥0.27). This is a configuration characteristic of confounding by indication, with ticagrelor-treated patients being younger and having higher LDL-C and higher baseline inflammation. Despite this separation, the two propensity-score distributions overlapped across essentially their entire range, supporting the positivity assumption required for propensity-score analysis (**Supplementary Fig. 1**). One-to-one nearest-neighbor matching on the propensity score (caliper 0.2 SD of the estimated propensity score, with exact matching on perioperative glucocorticoid use) produced 129 closely overlapping pairs (n = 258). Twenty-one of the twenty-three covariates fell below the 0.10 SMD threshold (Table 1, **Supplementary Fig. 2**), and modest residual differences persisted for smoking (SMD 0.139) and atorvastatin use (0.156). In the matched cohort, 179 of 258 patients (69.4%) met the pre-specified definition of residual high LDL-C (≥1.4 mmol/L) and 79 of 258 (30.6%) fell below it. Pre-operative LDL-C ranged from 0.85 to 2.89 mmol/L, and the two arms were similarly distributed across strata (90 vs 89 patients at or above 1.4 mmol/L). The pre-specified adjustment set (diabetes, hypertension, smoking status and high-intensity statin use), together with the corresponding baseline value, was carried into all outcome models, and the residual imbalances in smoking and atorvastatin use were additionally addressed by the stabilized inverse-probability-weighting analysis, which balanced the full covariate set (maximum |SMD| 0.080) and is reported throughout as a concordant sensitivity framework.

Co-Primary Inflammatory and Immune Endpoints

Systemic inflammation on the third postoperative day was substantially lower with ticagrelor. Day-3 CRP averaged 146.88 mg/L under ticagrelor versus 167.19 mg/L under clopidogrel. After adjustment for the baseline value and the pre-specified covariates, the between-group difference was –20.96 mg/L (95% CI –27.74 to –14.18, $p < 0.001$), about a 12% relative reduction (Table 2, Fig. 2A). The T-cell subset balance shifted in the same direction: the day-3 CD4/CD8 ratio was higher under ticagrelor than clopidogrel (0.937 vs 0.817), an adjusted difference of +0.117 (95% CI 0.058 to 0.175, $p < 0.001$) (Fig. 2B). Inverse-probability weighting reproduced both contrasts closely (CRP –19.85 mg/L, 95% CI –26.40 to –13.31; CD4/CD8 +0.096, 95% CI 0.047 to 0.145; untruncated, with 1st/99th-percentile-truncated estimates nearly identical at –18.88 mg/L and +0.104), arguing against residual measured confounding as the explanation.

Effect Modification by Residual LDL-C

With LDL-C modelled as a continuous modifier per protocol, neither co-primary interaction reached significance, and the drug-by-LDL term was $p = 0.244$ for CRP and $p = 0.079$ for CD4/CD8 (Fig. 3). Threshold-based analyses were likewise weak and, notably, inconsistent across specifications. Under a ≥1.4 mmol/L dichotomy, the interaction was borderline for CRP but absent for the CD4/CD8 ratio ($p = 0.054$ and 0.527, **Supplementary Fig. 3**), whereas under the alternative ≥1.8 mmol/L cut-point it was non-significant for both ($p = 0.327$ and 0.237). This cut-point divides the matched cohort into 86 and 172 patients, so the stratum-specific estimates are correspondingly less precise (**Supplementary Fig. 3**). The axis that appeared closest to significance therefore differed between the continuous (CD4/CD8) and dichotomous (CRP) specifications, so no consistent pattern of effect modification by residual LDL-C could be established on either axis. Given the limited power for interaction testing, these isolated borderline signals are interpreted as hypothesis-generating only, and we do not claim that residual LDL-C amplifies the drug effect.

Exploratory Decomposition With Respect to Early Post-Operative On-Treatment Platelet Reactivity

An exploratory decomposition then described how much of the between-group difference was statistically shared with concurrently measured on-treatment platelet inhibition, adjusting for platelet count, receipt of ≥2 units of red blood cells (yes/no), perioperative glucocorticoid use, infection and bypass duration. Because platelet reactivity was measured on days 3–5, this decomposition is cross-sectional and does not identify a pathway. For CRP, the total difference of –19.16 mg/L was partitioned into a component shared with ADP-induced inhibition of –6.60 mg/L (95% CI –10.49 to –2.96), corresponding to 34.5% (95% CI 16.2 to 59.4) of the total, and a remaining component of –12.55 mg/L. MA-ADP returned a concordant but smaller share (shared component –4.74 mg/L; 24.7%, 95% CI 7.8 to 47.7) (Table 3, Fig. 4A). The shared fraction was proportionally larger for the immune endpoint; of the +0.113 total difference in the CD4/CD8 ratio, +0.046 was shared with ADP inhibition (95% CI 0.016 to 0.080; 41.2%, with a wide 15.0–90.1% interval that reflects the limited precision of such proportions when the difference is modest) (Fig. 4B) and +0.044 with MA-ADP (38.9%) (Table 3). Across all models, the shared component excluded zero, but the larger part of each difference was not explained by measured platelet reactivity. Given the concurrent measurement, these two components describe statistical overlap

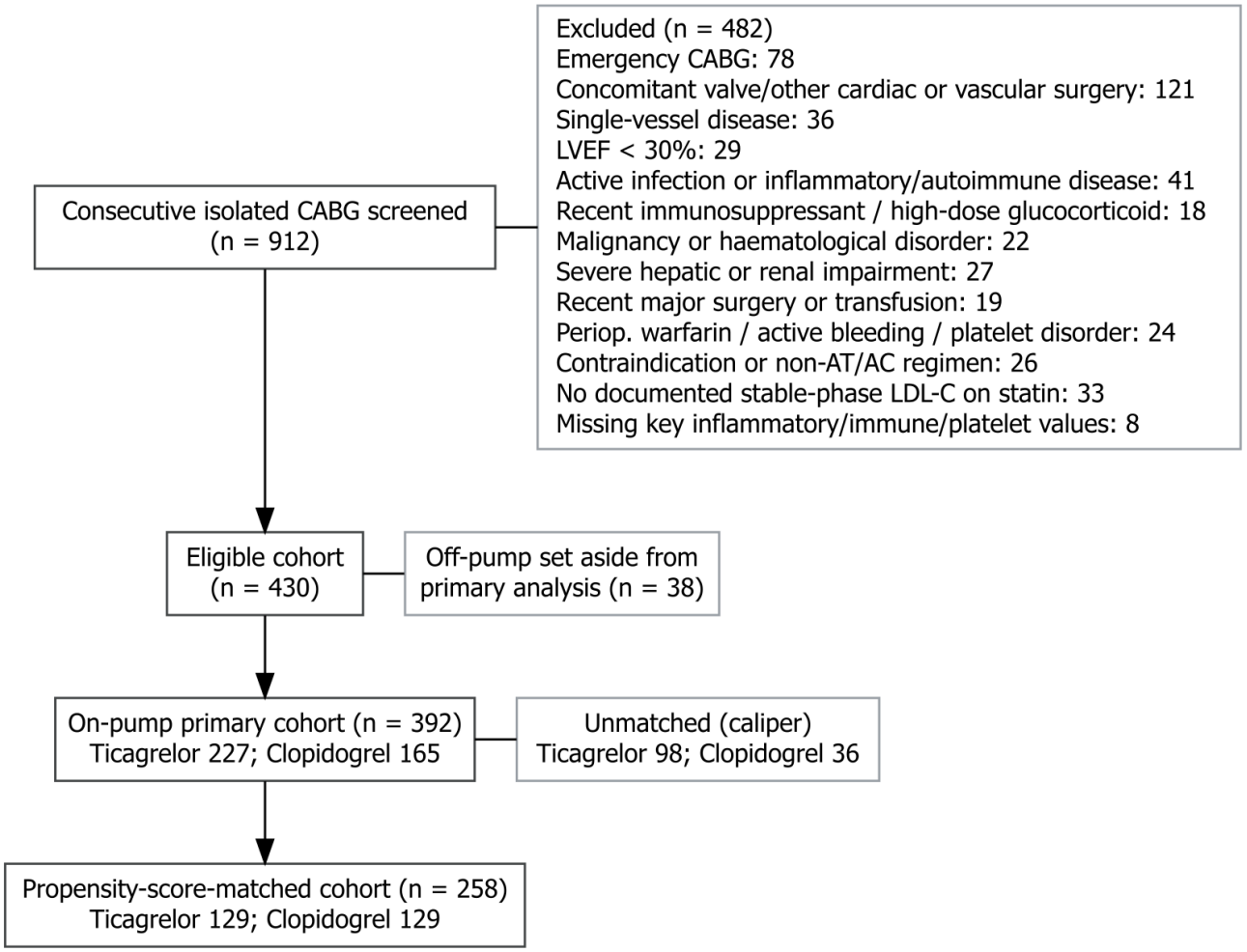

Fig. 1. Participant flow. Of 912 consecutive patients screened after isolated CABG, 482 were excluded for the reasons shown, leaving 430 eligible patients. Thirty-eight off-pump cases were set aside from the primary analysis. The 392 on-pump patients (ticagrelor 227, clopidogrel 165) underwent 1:1 propensity-score matching (caliper 0.2 SD of the estimated propensity score), yielding 258 matched patients (129 per group). CABG, coronary artery bypass grafting; LDL-C, low-density-lipoprotein cholesterol; LVEF, left-ventricular ejection fraction.

only and should not be read as separating pathways that do and do not involve platelet inhibition. The two platelet measures were assessed in separate single-measure models and, because they were strongly correlated, their shared components are not additive. Also, these models adjust for a different covariate set than the primary adjusted using analysis of covariance (ANCOVA), so the total difference here differs marginally from the primary estimate in Table 2.

The shared component was considerably more fragile than the total difference. In the sensitivity analysis, the shared component reached zero at a residual correlation between the platelet-reactivity and outcome models of $\rho = -0.23$ for CRP ($R_M^2 \times R_Y^2 \approx 0.025$) and $\rho = 0.17$ for the CD4/CD8 ratio ($R_M^2 \times R_Y^2 \approx 0.015$). Thus, a modest unmeasured common cause of platelet reactivity and outcome, particularly for the immune endpoint, could abolish the shared component (**Supplementary Fig. 4**). Any contribution of platelet inhibition should therefore be regarded as directional and hypothesis-generating rather than established, notwithstanding the robustness of the total differences.

Exploratory Clinical Endpoints

Clinical events were sparse, and these comparisons, summarized in Table 4, were designed only to reveal directional signals under false-discovery rate (FDR) control. One-year vein-graft failure occurred in 6/90 (6.7%) ticagrelor versus 13/91 (14.3%) clopidogrel patients (RR 0.47, $p = 0.144$, FDR 0.505), and the composite of death, myocardial infarction, repeat revascularization or stroke was similar between arms (7.8% vs 8.5%; RR 0.91, $p = 1.000$). No individual component reached significance, and a small excess of stroke on ticagrelor (2 vs 0) ran counter to the overall direction. Clinically relevant bleeding (BARC ≥2) was numerically higher with ticagrelor (14.7% vs 7.8%, RR 1.90) but did not reach significance ($p = 0.122$, FDR 0.505).

Table 1. Baseline characteristics of the ticagrelor and clopidogrel groups before and after propensity-score matching.

Characteristic	Before matching			After 1:1 propensity-score matching		
	Clopidogrel (n = 165)	Ticagrelor (n = 227)	SMD	Clopidogrel (n = 129)	Ticagrelor (n = 129)	SMD
Age, years	63.70 (7.74)	60.11 (7.27)	0.479	62.53 (7.51)	62.36 (6.65)	0.024
Male, n (%)	123 (74.5)	174 (76.7)	0.049	96 (74.4)	100 (77.5)	0.073
Body-mass index, kg/m^2	25.39 (2.93)	25.41 (3.20)	0.008	25.63 (3.01)	25.59 (3.25)	0.013
Diabetes mellitus, n (%)	63 (38.2)	76 (33.5)	0.098	47 (36.4)	44 (34.1)	0.049
Hypertension, n (%)	117 (70.9)	158 (69.6)	0.029	97 (75.2)	93 (72.1)	0.070
Smoking status, n (%)			0.332			0.139
Never	65 (39.4)	118 (52.0)		58 (45.0)	55 (42.6)	
Former	50 (30.3)	70 (30.8)		39 (30.2)	47 (36.4)	
Current	50 (30.3)	39 (17.2)		32 (24.8)	27 (20.9)	
Acute coronary syndrome, n (%)	67 (40.6)	107 (47.1)	0.132	58 (45.0)	56 (43.4)	0.031
LVEF, %	54.31 (7.00)	53.38 (7.23)	0.130	53.90 (7.12)	53.85 (7.50)	0.006
eGFR, mL/min/1.73 m^2	79.29 (15.50)	78.02 (15.17)	0.083	78.93 (15.69)	79.46 (15.94)	0.033
Cardiopulmonary-bypass time, min	111.03 (20.39)	113.10 (17.94)	0.108	111.87 (20.63)	111.56 (16.81)	0.016
Number of grafts	3.02 (0.71)	3.01 (0.66)	0.014	3.00 (0.70)	2.96 (0.64)	0.058
High-intensity statin, n (%)	95 (57.6)	128 (56.4)	0.024	74 (57.4)	74 (57.4)	<0.001
Duration of statin therapy, weeks	25.54 (11.22)	27.41 (12.20)	0.159	26.01 (11.25)	26.88 (12.14)	0.074
Atorvastatin, n (%)	84 (50.9)	121 (53.3)	0.048	65 (50.4)	75 (58.1)	0.156
Ezetimibe, n (%)	26 (15.8)	50 (22.0)	0.161	23 (17.8)	26 (20.2)	0.059
PCSK9 inhibitor, n (%)	11 (6.7)	19 (8.4)	0.065	9 (7.0)	8 (6.2)	0.031
Perioperative glucocorticoid, n (%)	34 (20.6)	56 (24.7)	0.097	21 (16.3)	21 (16.3)	<0.001
Receipt of ≥2 U red blood cells (yes/no), n (%)	61 (37.0)	82 (36.1)	0.018	52 (40.3)	48 (37.2)	0.064
Any platelet transfusion, n (%)	18 (10.9)	27 (11.9)	0.031	14 (10.9)	17 (13.2)	0.072
Baseline platelet count, ×10^9/L	217.56 (44.71)	219.36 (44.49)	0.040	220.22 (46.08)	216.95 (45.04)	0.072
Pre-operative LDL-C, mmol/L	1.53 (0.42)	1.72 (0.41)	0.454	1.60 (0.40)	1.63 (0.41)	0.072
Pre-operative hs-CRP, mg/L	2.77 (2.00–3.95)	3.27 (2.38–4.48)	0.273	2.79 (2.00–4.14)	3.06 (2.29–4.17)	0.054
Pre-operative CD4/CD8 ratio	1.81 (0.38)	1.79 (0.40)	0.047	1.79 (0.39)	1.79 (0.42)	0.007

Continuous variables are summarized as mean (SD) if normally distributed and as median (IQR) otherwise, and categorical variables as n (%). Standardized mean differences (SMD) are shown for the full on-pump cohort (left) and for the 1:1 matched cohort (right). An SMD <0.10 was regarded as acceptable balance. Smoking status was coded as never, former or current, and its SMD is the multinomial standardized difference across all three levels. Perioperative red-blood-cell and platelet transfusion were recorded as unit counts with a large mass at zero and marked right skew (skewness 0.78 and 2.89), and are presented here as the binary indicators used in the analysis: receipt of ≥2 units of red blood cells (yes/no) and any platelet transfusion (yes/no). For the red-blood-cell indicator, the reference category is 0–1 unit rather than the absence of transfusion. Pre-operative hs-CRP was right-skewed (skewness 1.17) and is presented as median (IQR). CD4/CD8, CD4-to-CD8 lymphocyte ratio; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-C, low-density-lipoprotein cholesterol; LVEF, left-ventricular ejection fraction; SD, standard deviation; SMD, standardized mean difference.

Table 2. Co-primary outcomes on postoperative day 3 in the matched cohort.

Outcome	Ticagrelor	Clopidogrel	Effect	*p*	IPTW	*p*_IPTW
Day-3 CRP (mg/L)	146.88	167.19	–20.96 (–27.74, –14.18)	<0.001	–19.85 (–26.40, –13.31)	<0.001
Day-3 CD4/CD8 ratio	0.937	0.817	0.117 (0.058, 0.175)	<0.001	0.096 (0.047, 0.145)	<0.001

Group values are observed means. The adjusted effect (ticagrelor minus clopidogrel) is the between-group mean difference from analysis of covariance adjusting for the corresponding baseline value and the pre-specified covariate set (diabetes, hypertension, smoking status and high-intensity statin use). Day-3 CRP was analyzed on its native scale (mg/L), and a log-scale (geometric-mean-ratio) sensitivity analysis is reported in the text. Inverse-probability-of-treatment-weighting estimates shown here are untruncated. The 1st/99th-percentile-truncated values were nearly identical and are reported under Sensitivity and supporting analyses. CRP, C-reactive protein; IPTW, inverse-probability-of-treatment weighting.

Dyspnea attributed by the treating team to ticagrelor was recorded in 20 of 129 ticagrelor-treated patients (15.5%). Because the variable was defined as a ticagrelor-attributed event, it could not, by definition, occur in the clopidogrel arm. No between-group comparison was therefore performed, and the figure represents the incidence of attributed dyspnea in the ticagrelor arm rather than evidence of a difference in the true incidence of dyspnea between drugs. Consistent with the mechanistic focus of the study, these endpoints are framed as hypothesis-generating rather than as evidence of efficacy.

Sensitivity and Supporting Analyses

Several pre-specified and additional analyses reinforced the primary findings. Both co-primary contrasts survived the pre-specified multiplicity control. In the fixed-sequence hierarchy, CRP was significant and opened the gate for the CD4/CD8 ratio, and both remained significant after Hochberg adjustment (both $p \leq 0.001$). Because postoperative C-reactive protein was mildly right-skewed, the inflammatory contrast was re-estimated on the log scale, giving a geometric-mean ratio of 0.879 (95% CI 0.843 to 0.917, $p < 0.001$), a ~12% relative reduction concordant with the native-scale estimate. Accounting for the matched-pair structure with cluster-robust standard errors left both contrasts strongly significant (CRP –20.96, SE 3.50, $p < 0.001$; CD4/CD8 +0.117, SE 0.031, $p < 0.001$). Stabilized inverse-probability-of-treatment weighting, which balanced the full covariate set (maximum |SMD| 0.080, **Supplementary Fig. 5**), reproduced both effects (CRP –19.85 mg/L, CD4/CD8 +0.096), and truncating extreme weights at the 1st/99th percentiles changed nothing materially (CRP –18.88 mg/L, 95% CI –25.44 to –12.32; CD4/CD8 +0.104, 95% CI 0.056 to 0.151), indicating the estimates were not driven by a few influential weights (**Supplementary Fig. 6**). E-values were 3.34 for the CRP estimate (2.53 for its confidence limit) and 2.34 for CD4/CD8 (1.73), so an unmeasured confounder would need to be associated with both treatment and outcome by risk ratios of these magnitudes to explain away the observed differences. The immune contrast is accordingly less robust to unmeasured confounding than the inflammatory one.

Effect modification by residual LDL-C was weak and threshold-dependent (continuous-modifier and dichotomous results in the preceding section and **Supplementary Fig. 3**). Infection did not account for the contrasts: nosocomial infection was infrequent and statistically comparable between arms (ticagrelor 5.4% vs clopidogrel 9.3%, $p = 0.341$), procalcitonin was similar (median 0.26 [IQR 0.19–0.38] vs 0.24 [0.18–0.37] ng/mL, $p = 0.394$), and restricting the analysis to the 239 patients without documented infection left both estimates essentially unchanged (CRP –18.03 mg/L, 95% CI –24.56 to –11.49; CD4/CD8 +0.108, 95% CI 0.048 to 0.168). Excluding the eight matched patients whose samples were drawn during the acute phase likewise left both estimates essentially unchanged (CRP –21.81 mg/L, 95% CI –28.70 to –14.93; CD4/CD8 +0.113, 95% CI 0.054 to 0.173; both $p < 0.001$). High on-treatment platelet reactivity was far less common with ticagrelor than clopidogrel (0.8% vs 24.0%, $p < 0.001$), consistent with the markedly greater and more consistent ADP-pathway inhibition observed in the decomposition analysis.

Finally, because platelet reactivity was measured on days 3–5, that is, contemporaneously with or after the day-3 outcome, the decomposition cannot be given a causal interpretation. Its components were additionally probed for sensitivity to an unmeasured common cause of platelet reactivity and outcome. The shared components proved fragile. The shared component reached zero at a residual correlation of $\rho = –0.23$ for CRP and $\rho = 0.17$ for the CD4/CD8 ratio, corresponding to products of platelet-reactivity and outcome partial R^2 values of ~0.025 and ~0.015, respectively (**Supplementary Fig. 4**). These findings indicate that even a weak common cause, particularly for the immune endpoint, could abolish the shared component. The analysis is therefore interpreted as descriptive, exploratory and hypothesis-generating.

Discussion

In a propensity-score-matched cohort of statin-treated patients undergoing on-pump isolated CABG, ticagrelor-based dual antiplatelet therapy was associated with lower early systemic inflammation and a higher CD4/CD8 ratio than clopidogrel-based therapy. Both co-primary contrasts were internally consistent across matching with re-

Table 3. Exploratory decomposition of the between-group difference with respect to early post-operative on-treatment platelet reactivity.

Outcome	Platelet measure	Total difference	Remaining component	Shared component	Shared proportion
Day-3 CRP (mg/L)	ADP inhibition (%)	–19.16 (–25.32, –12.94)	–12.55 (–19.04, –5.81)	–6.60 (–10.49, –2.96)	34.5% (16.2, 59.4)
Day-3 CRP (mg/L)	MA-ADP (mm)	–19.16 (–25.32, –12.94)	–14.42 (–21.02, –7.63)	–4.74 (–8.16, –1.49)	24.7% (7.8, 47.7)
Day-3 CD4/CD8	ADP inhibition (%)	0.113 (0.053, 0.173)	0.066 (0.007, 0.127)	0.046 (0.016, 0.080)	41.2% (15.0, 90.1)
Day-3 CD4/CD8	MA-ADP (mm)	0.113 (0.053, 0.173)	0.069 (0.010, 0.128)	0.044 (0.018, 0.075)	38.9% (15.5, 85.1)

For each co-primary outcome, the total between-group difference is partitioned into the component shared with the platelet measure and the remaining component, for two candidate measures, ADP-induced inhibition and ADP-induced maximum clot strength (MA-ADP), with 95% confidence intervals from 2000 bootstrap replicates. Both measures were obtained on days 3–5, that is, contemporaneously with or later than the day-3 outcomes. The temporal ordering required for mediation analysis is therefore not met, and these components and proportions are descriptive only. Models adjusted for platelet count, receipt of ≥2 units of red blood cells (yes/no), perioperative glucocorticoid use, infection, cardiopulmonary-bypass duration and the corresponding baseline value. Both outcomes were analyzed on their native scales, so CRP effects are expressed in mg/L. The two platelet measures were evaluated in separate single-measure models. Because they are strongly correlated, the shared components are not additive and should not be summed. The shared proportion is the shared component as a fraction of the total difference. Because these models adjust for a different covariate set than the primary ANCOVA, the total difference here differs marginally from the primary between-group difference in Table 2.

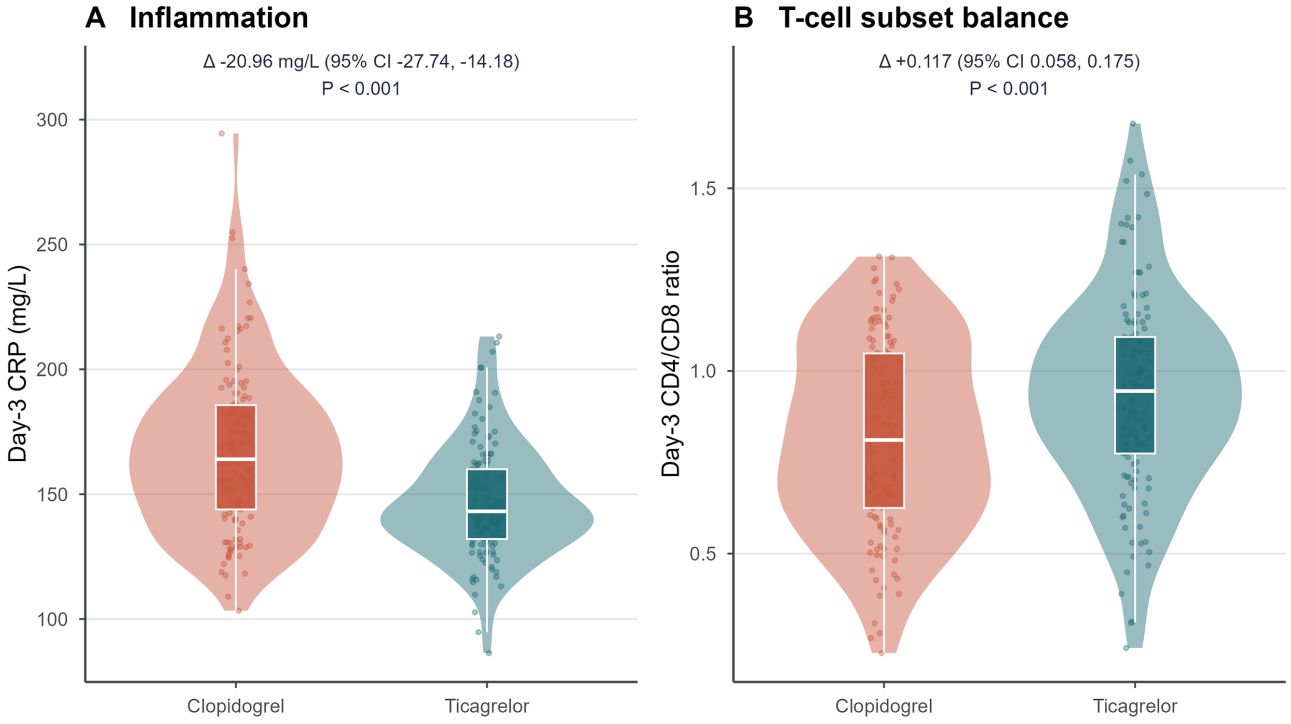

Fig. 2. Co-primary outcomes on postoperative day 3. Distribution of day-3 CRP (A, inflammation) and the CD4/CD8 ratio (B, T-cell subset balance) by treatment group, shown as violin plots with overlaid box plots and individual observations. Annotations indicate the adjusted using analysis of covariance (ANCOVA)-adjusted between-group difference (Δ), with corresponding 95% confidence intervals and *p* value.

gression adjustment, stabilized inverse-probability weighting, log-scale estimation and cluster-robust inference, and both survived pre-specified multiplicity control. The magnitude of the inflammatory difference, an adjusted –20.96 mg/L, roughly a 12% relative reduction (geometric-mean ratio 0.879), sits at the larger end of what has been reported for antiplatelet effects on C-reactive protein in the percutaneous-coronary-intervention and acute-coronary-syndrome literature, where between-group differences are typically in the single- to low-double-digit mg/L range and the evidence is inconsistent (for example, the neutral DISPERSE-2 experience). We interpret this larger separation as biologically plausible in this particular population rather than as a contradiction of prior work. The pleiotropic, adenosine-mediated anti-inflammatory actions of ticagrelor and the amplification of systemic inflammation by cardiopulmonary bypass may act in the same direction and converge in this surgical population. A contri-

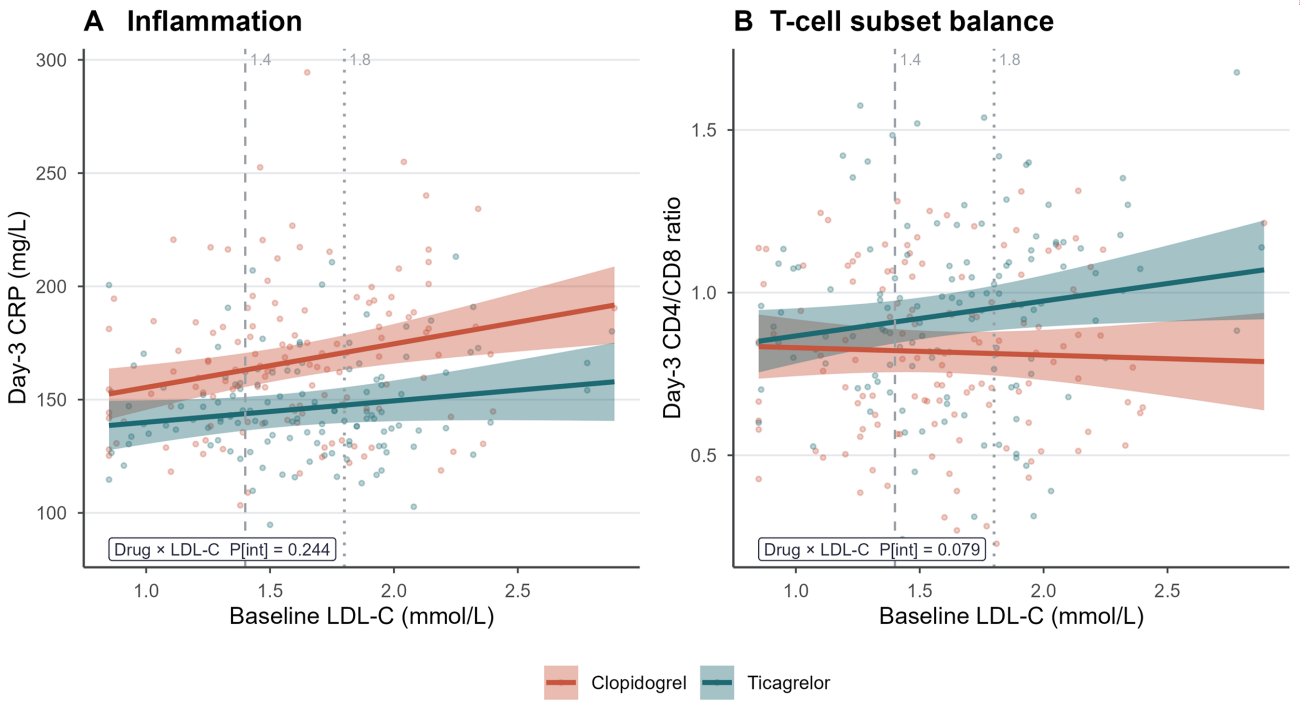

Fig. 3. Effect modification by residual LDL-C. Predicted day-3 CRP (A) and CD4/CD8 ratio (B) across baseline LDL-C for each drug, with 95% confidence bands; points are observed values. Fitted lines are model predictions evaluated at a reference covariate profile (no diabetes, hypertension present, never-smoker, high-intensity statin, baseline value set to the cohort mean). Because the model contains no interaction between drug and these covariates, the vertical separation between the two lines, which is the quantity of interest, is invariant to this choice, and only the absolute level shifts. The vertical dashed line denotes the pre-specified residual-high-LDL threshold (1.4 mmol/L) and the dotted line the alternative 1.8 mmol/L threshold. Both are shown for reference only, as the interaction was modelled with LDL-C on its continuous scale. The *p* value for the drug × continuous-LDL-C interaction is shown in the inset.

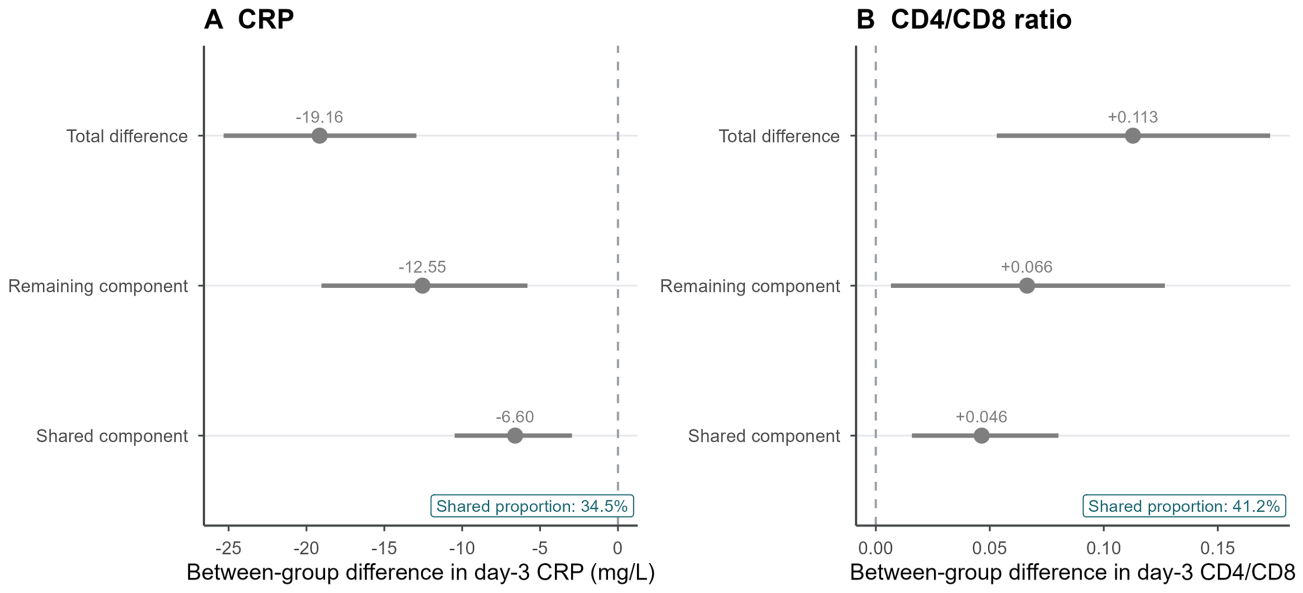

Fig. 4. Exploratory decomposition of the between-group difference with respect to early post-operative on-treatment platelet reactivity. Partition of the total difference into the component shared with ADP-induced inhibition and the remaining component, for CRP (A) and the CD4/CD8 ratio (B). Horizontal bars are 95% bootstrap confidence intervals. The shared proportion is inset in each panel. Because platelet reactivity was measured on days 3–5, these components are descriptive and not causal. Only the decomposition with respect to ADP-induced platelet inhibition is displayed. The corresponding values for ADP-induced maximum clot strength are given in Table 3.

Table 4. Exploratory clinical endpoints in the matched cohort.

Endpoint	Ticagrelor	Clopidogrel	RR	b/c[c]	*p*	FDR *p*
Graft failure (any vein graft)[a]	6/90 (6.7)	13/91 (14.3)	0.47	—	0.144	0.505
MACE (composite)	10/129 (7.8)	11/129 (8.5)	0.91	7/8	1.000	1.000
All-cause death	3/129 (2.3)	1/129 (0.8)	3.00	3/1	0.625	0.802
Myocardial infarction	2/129 (1.6)	4/129 (3.1)	0.50	2/4	0.688	0.802
Repeat revascularization	3/129 (2.3)	6/129 (4.7)	0.50	3/6	0.508	0.802
Stroke	2/129 (1.6)	0/129 (0.0)	—	2/0	0.500	0.802
BARC ≥2 bleeding	19/129 (14.7)	10/129 (7.8)	1.90	18/9	0.122	0.505
Dyspnea (ticagrelor-attributed)[b]	20/129 (15.5)	—	—	—	—	—

Counts are n/N (%). Risk ratios (RR) are ticagrelor versus clopidogrel. Except where noted, endpoints were analysed within the 129 matched pairs by the exact McNemar test on discordant pairs, with Benjamini-Hochberg control of the false-discovery rate across the seven comparable endpoints. Unpaired Fisher's exact results are given in **Supplementary Table 1**. [a] One-year vein-graft failure was assessed only among patients who completed one-year computed-tomographic angiography, so both members of a pair contributed an outcome in only 66 of the 129 pairs. The matched-pair structure was therefore broken and this endpoint was analysed among CTA completers by Fisher's exact test; the denominators are CTA completers, not matched pairs. [b] Dyspnea was recorded as an adverse event attributed by the treating team to ticagrelor. By the definition of the variable, it cannot occur in the clopidogrel arm, so no between-group comparison was performed and no risk ratio, *p* value or FDR-adjusted *p* value is reported. The figure is the incidence of attributed dyspnea within the ticagrelor arm and does not support any inference about a true between-group difference in the incidence of dyspnea. [c] b = pairs in which the ticagrelor patient had the event and the clopidogrel patient did not, and c = the converse. The exact McNemar test uses these discordant pairs only. BARC, Bleeding Academic Research Consortium; CTA, computed-tomographic angiography; FDR, false-discovery rate; MACE, major adverse cardiovascular events.

bution of coexisting residual inflammatory risk cannot be excluded, but no marker of lipid oxidation or inflammatory priming was measured in this cohort. This mechanistic account is a hypothesis generated by the data rather than a demonstrated pathway.

Modelled continuously, neither interaction was significant, and the dichotomous analyses were weak and inconsistent, with the axis nearest significance differing between the continuous and threshold specifications. We therefore do not claim that residual LDL-C amplifies the effect of ticagrelor. The residual-high-LDL definition should be read as a pre-specified stratification of the cohort, not as an established effect modifier. The interaction analyses were, as pre-specified, underpowered, and these isolated borderline signals are best regarded as hypothesis-generating and warrant confirmation in future adequately powered studies.

The exploratory decomposition indicated that only part of the between-group difference was statistically shared with on-treatment platelet inhibition, approximately one-quarter to one-third of the inflammatory difference and about two-fifths of the immune difference. The larger remaining part was not explained by measured platelet reactivity. Two caveats temper this interpretation. The two candidate platelet measures, ADP-induced inhibition and MA-ADP, are strongly correlated and were modelled separately, so their shared components are not additive, and the shared proportion for the immune endpoint was estimated imprecisely. And more importantly, platelet reactivity (days 3–5) was measured contemporaneously with or even after the day-3 outcome rather than strictly before it, so the temporal-ordering condition required for mediation analysis is not satisfied. We therefore make no claim that platelet inhibition mediates the observed differences, and present the decomposition purely as a descriptive summary of shared variation. Consistent with this, the shared components were fragile to an unmeasured common cause of platelet reactivity and outcome, reaching the null at a residual correlation of $\rho = -0.23$ (CRP) and $\rho = 0.17$ (CD4/CD8). These findings are accordingly descriptive and exploratory.

One-year vein-graft failure and the composite of death, myocardial infarction, repeat revascularization or stroke were numerically lower with ticagrelor but did not approach significance, and a small excess of stroke ran counter to the overall direction. Clinically relevant bleeding (BARC ≥2) was numerically higher with ticagrelor but did not reach significance, and dyspnea, recorded as a ticagrelor-attributed event, plausibly adenosine-mediated, occurred in about one in six treated patients, consistent with its recognized adverse-effect profile and the proposed but not definitive contribution of enhanced extracellular adenosine signaling [24,34]. Because this variable was ascriptive rather than symptom-screened in both arms, the true between-group difference in the incidence of dyspnea cannot be estimated from this cohort. None of these observa-

tions should be read as evidence of clinical efficacy or of a net benefit-risk balance.

Several limitations temper these findings. As a single-center retrospective study, the analysis remains vulnerable to residual and unmeasured confounding. Among the operative variables, aortic cross-clamp time could not be retrieved for the full cohort and was therefore not available for adjustment. Cardiopulmonary-bypass time, with which it is closely correlated and which encompasses the cross-clamp period, was included in the propensity-score model and was well balanced after matching (111.87 vs 111.56 min, SMD 0.016), so residual imbalance in ischemic time is unlikely to be large, although it cannot be excluded. The larger-than-expected inflammatory effect should be weighed against this possibility, and the E-value for the immune contrast in particular was modest (2.34, or 1.73 at the confidence limit), indicating that a moderately strong unmeasured confounder could account for it. Also, although postoperative P2Y12 initiation was standardized to the first postoperative day and did not differ between groups, assignment by the regimen actually received leaves the design only partially protected against residual immortal-time bias. Further, one-year patency was assessed only among patients who completed computed-tomographic angiography; restricting the denominator to CTA completers probably overestimates true patency and may do so differentially. And CRP was measured across both the low (high-sensitivity) and the high (acute-phase) reporting ranges of a single wide-range assay. Although both are expressed on a common mg/L scale and we accordingly reserve the hs-CRP label for pre-operative values, this cross-range bridging should still be interpreted with some caution. The CD4/CD8 ratio indexes T-cell subset balance rather than functional immune competence. Absolute CD4 and CD8 counts, the total lymphocyte count, and functional assays such as lymphocyte proliferation or cytokine responses were not available in the routine record, and the ratio was derived from subset percentages. A higher ratio is therefore not evidence of enhanced cellular immunity. The same ratio can arise from a relative preservation of CD4 cells or from a greater depletion of CD8 cells, and the two cannot be distinguished without absolute counts. The immune endpoint should accordingly be read as a shift in T-cell subset composition of uncertain functional significance. Finally, propensity-score matching retained 129 of 227 ticagrelor- and 129 of 165 clopidogrel-treated patients, discarding a substantial fraction of the ticagrelor arm, so the matched sample may not fully represent the source population, and no finer-grained inflammatory or immune phenotyping was available.

Two further limitations follow from the structure of the data. First, on-treatment platelet reactivity was assayed on days 3–5 as part of routine institutional practice, and no earlier post-operative platelet-function measurement exists in the record. As the cohort is retrospective and the database locked, the measurement cannot be repositioned before the day-3 outcomes. In addition, platelet-function testing was performed anywhere between days 3 and 5, so the number of maintenance doses received before sampling differed across patients and, given the faster onset of ticagrelor, potentially between groups. The assay therefore reflects an early and variable point after resumption rather than a formally verified steady state. We therefore make no claim of mediation and report only a cross-sectional decomposition. Second, eligibility required retrievable day-3 CRP, CD4/CD8 and platelet-function values, so the analytic cohort is a complete-case sample selected partly on post-operative information. Among the 430 eligible patients these variables were complete without exception, so no observations were lost within the analytic cohort and no imputation was applicable; the selection acted entirely at the screening stage. That selection is not neutral. Patients who died before day 3, required reoperation, or were too unstable for protocol sampling could not contribute, so the cohort is enriched for uncomplicated early recoveries, that is, for the patients in whom the inflammatory and immune disturbance is least pronounced. The estimates should accordingly be read as conditional on survival to and sampling on day 3, and they may not generalize to patients with a complicated early post-operative course, in whom both the inflammatory response and the degree of immune suppression are likely to be greater. A comparable caveat applies to one-year patency, although there the completion of computed-tomographic angiography was closely similar in the two arms.

Conclusion

Among statin-treated patients undergoing on-pump CABG, ticagrelor was associated with lower early post-operative inflammation and a higher CD4/CD8 ratio than clopidogrel. These differences were robust across multiple analytic frameworks but only partly paralleled by platelet inhibition, which was measured on days 3–5 and therefore cannot be established as a mediator, and were not clearly modified by residual LDL-C. These mechanistic associations require confirmation in an adequately powered, multicenter prospective randomized trial designed to test whether the inflammatory and T-cell subset differences translate into clinical benefit in this surgical population, with protocol-mandated serial sampling that begins before the outcome window and retains patients with a complicated early post-operative course.

Availability of Data and Materials

The data used or analyzed during the current study are available from the corresponding authors upon reasonable request.

Author Contributions

RJY, BYZ, LH and QX designed the research study. KZ and GXZ performed the research. JL, BLL and XLF analyzed the data. QX drafted the article and all authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This single-center retrospective cohort study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Naval Medical University (Shanghai Changhai Hospital) (approval no. CHEC2025-193, meeting review on 12 November 2025) and conducted in accordance with the Declaration of Helsinki. The requirement for individual informed consent was waived by the committee owing to the retrospective nature of the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638212.218.

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