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ORIGINAL RESEARCH

Examination of Postoperative Changes in Lipid Profile and Glycemic Markers After Coronary Artery Bypass Graft, Percutaneous Intervention Vs Aortic Valve Replacement Demonstrated a Shift in Risk Factors for Coronary Artery Disease

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Purpose: Surgery-related stress may affect the metabolome, leading to abnormal lipid profiles and ineffective glycemic control. Here, we gauge these changes as they may accelerate atherosclerosis, limiting the benefits of interventions aimed at improving coronary artery disease (CAD) progression.

Patients and Methods: Electronic medical records were queried to identify patients undergoing coronary artery bypass grafting (CABG), percutaneous coronary intervention (PCI), or aortic valve replacement (AVR). 7573 records denoted lipid profile (cholesterol, LDL, HDL, VLDL, triglycerides) and glucose metabolism impairment (HbA1c). Pre-procedure lipid and glucose laboratory values were compared with periods representing acute periprocedural inflammation (1–3 months), resolution of acute inflammation (3–6 months), convalescence (6–12 months), and medium- (1–2 years), and long-term periods (2–5 years).

Results: Baseline values differed between groups (AVR: Cholesterol↑↓, LDL↓↑, HDL↓, Triglycerides↑, HbA1c↓; CABG: Cholesterol↓, LDL↓, HDL↓, Triglycerides↓, HbA1c↓; PCI: Cholesterol↑↓, LDL↑↓, HDL↑↓, Triglycerides↓, HbA1c↓). Interestingly, total cholesterol and LDL had opposite trajectories after CABG vs AVR even five years after surgical procedure and the effects were moderate as denoted by *d*-Cohen statistics. HDL declined acutely after CABG and AVR but not after PCI. Triglycerides were elevated for 2 years after AVR but depressed after CABG and PCI. HbA1c remained depressed for up to 5 years after any studied procedure.

Conclusion: Our data suggest surgical procedures result in prolonged lipid profile and glycemic metabolism disturbances, particularly after aortic valve replacement, indicating more aggressive post-surgical treatment of these metabolic abnormalities may be warranted.

Keywords: cardiac surgery, inflammation, lipid profile, glycated hemoglobin

Introduction

Despite advances in care, coronary artery disease (CAD) continues to comprise nearly 20% of mortality in the United States and worldwide.[1] Atherosclerosis is recognized as the main etiopathogenic factor, with dysfunctional cholesterol and impaired glucose metabolism playing synergistic roles.[2] Interestingly, perioperative inflammation profoundly affects the metabolome, but its scope and duration are unknown despite the theoretical impact on the progression of atherosclerosis, thus limiting the long-term benefits of surgery.[2–10]

Progression of CAD necessitates the performance of percutaneous intervention (PCI) or coronary artery bypass grafting (CABG) in symptomatic patients.[4,11] CABG-related surgery is inevitably associated with inflammation, thus affecting lipid

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profile and glucose metabolism.[7,12,13] PCI may also affect inflammation but less than surgical procedures.[14] These differences in perioperative inflammation on changes in lipid profile and glucose metabolism will depend on the duration, magnitude, and nature of the postoperative changes of CAD risk factors. For example, hypocholesterolemia accompanying acute post-surgical inflammation may either retard or accelerate disease progression, depending on whether a post-procedural drop in either LDL or HDL is more profound.[15–17] Postoperative impairment in glucose supports CAD progression.[4,5] In some cases, postoperative variation of VLDL and lipoprotein A remained unexplored despite their effect on atherosclerosis and variation of their level during critical stress.[18,19] On the other hand, increased frequency of pharmacological interventions aimed at atherosclerosis risk reduction is often part of procedural or surgical intervention and may counteract the postoperative increase in risk factors.[16] The complex effect of surgery on lipid and glucose metabolism may explain some of the unexpected outcomes offered by a recent trial comparing PCI vs CABG in diabetic patients.[20] This complex interaction network is inextricably challenging to study, but even small changes in lipid and diabetes profile may have an impact if they persist long-term, as Framingham's study showed.[21–23]

Herein, we hypothesize that the post-procedure inflammatory conditions will result in short-term changes in pro-atherogenic conditions. We hypothesize that changes in lipid profile in the aftermath of CAD-oriented procedure will be signified by a decline in HDL and an increase in LDL. Perioperative hyperglycemia may persist for a short period, further fueling the progression of atherosclerosis.[2,6,24] Furthermore, we hypothesize that these changes will be more exaggerated in patients undergoing CABG than PCI, as the former procedure is more inflammatory and taxing.[14] Patients subjected to aortic valve replacement (AVR) will represent surgical procedures with severe surgical inflammation, but the indication is a degenerative illness, not CAD progression.[25] The duration and nature of glycemic and lipid profile in the post-procedural period will determine the procedure "penalty" of acquired additional risk of accelerated atherosclerosis.[25]

Material and Methods

The Institutional Review Board of the University of Pennsylvania approved this retrospective study of three different cohorts of patients (#834697).

Data Set

Electronic Medical Records (EMR) were used to collect all surgeries coded as coronary artery bypass graft (CABG; ICD-10 codes: 021009W, 02100AW, 02100Z9, 021109W, 021209W, 02100Z8), and percutaneous coronary interventions (PCI; ICD-10 codes: 027034Z) as two interventions to improve atherosclerosis progression with dramatically different inflammatory burden.[14] Surgery for aortic valve replacement (AVR; ICD-10 codes: 02RF0JZ, 02RF08Z) was used as a control for invasive surgical interventions but conducted most commonly due to the degenerative illness, not CAD.[11] A total of 7573 patients were identified, and their demographics are present in Table 1 (Figure 1). The database was processed using Python software. Comorbidities were searched using the relevant terms in Electronic Medical Records.

Patient records were reviewed and assessed for lipid abnormalities (cholesterol, LDL, HDL, VLDL, triglycerides) and glycemic control (HbA1c) as critical factors in the progression of atherosclerosis.[2,3,7,20,24] The data were compared to preprocedural baselines and split into periods representing acute periprocedural inflammation (1–3 months), resolution of acute inflammation (3–6 months), convalescence (6–12 months), and medium- (1–2 years), and long-term periods (2–5 years) post-procedure. The values were averaged if multiple values were for a specific test within the allotted time period.

Statistical Analysis

The Shapiro–Wilk *W*-test and distribution plots were used to test the normality of distribution variables.[26] All variables were transformed into Z-score values for inter-lab comparisons. Parametric variables are expressed as mean±SD and compared using *z*- or *t*-test for two-group comparisons if more than two groups were analyzed. Post-hoc comparisons were assessed with the Shaffee test.[26] For non-parametric variables, median (Me) and interquartile ranges (IR) will be shown with the Kruskal–Wallis statistic [dʃ;n] employed to compare such variables. Bonferroni correction was applied for repetitive measurements. *d*-Cohen statistic was utilized to assess the magnitude of the difference, with 0.2 determined as a small, 0.5 as a moderate and 0.8 as a large effect.[26] When possible, we utilized pairwise contrast, with the pre-procedural value being the baseline to the postoperative period. We employed unpaired analysis if the number of pairs was less than 25. Unless a specific hypothesis was formulated, a double-sided adjusted *p*-value less than 0.05 will be

Table 1 Demographic Characteristics of Studied Cohort

Patient Characteristics (N=7573)	CABG N=3359	PCI N=2391	AVR N=2825
Age, mean±SD [years]	66.7±9.69	66.3±12.27	64.8±12.25
Sex - Male no [% of total]	78.8%	66.4%	71.2%
Race [%Caucasian, %Black, % Asian, % Other]	73.7%, 11.1%, 2.8%, 12.3%	66.1%, 22.8%, 2.4%, 8.7%	81.3%, 6.9%, 1.7%, 10.1%
Cerebrovascular Accident (Ischemic)	1.8%	0.90%	2.7%
Diabetes	42.8%	32.8%	22.9%
Atrial fibrillation	37.9%	14.7%	49.9%
Hypertension	50.1%	45.0%	38.3%

considered statistically significant for all tests. This approach was used previously by us. Statistical analyses will be performed with SPSS (IBM, Chicago, IL). Prism (GraphPad; Boston, MA) and Python Seaborn packages were utilized for visualization.[11]

Results

Evolution of Total Cholesterol, LDL, and VLDL After CABG, PCI, and AVR

There was a significant difference between baseline total cholesterol (TChol) levels among all studied groups (KW [2;1514]=14.347; p=0.001). The baseline total cholesterol was significantly higher in both CABG ($TChol_{CABG[baseline]}$ vs $TChol_{AVR[baseline]}$=2.505; p=0.018) and PCI ($TChol_{PCI[baseline]}$ vs $TChol_{AVR[baseline]}$=3.783; p<0.001) groups compared to individuals undergoing AVR (Figure 2A). Total cholesterol levels declined after CABG early and remained lower than the pre-surgical baseline during all observational periods (Figure 2B). In contrast, PCI interventions resulted in an early increase followed by a persistent decline (Figure 2C). In the case of AVR-enrolled individuals, we observed perioperative

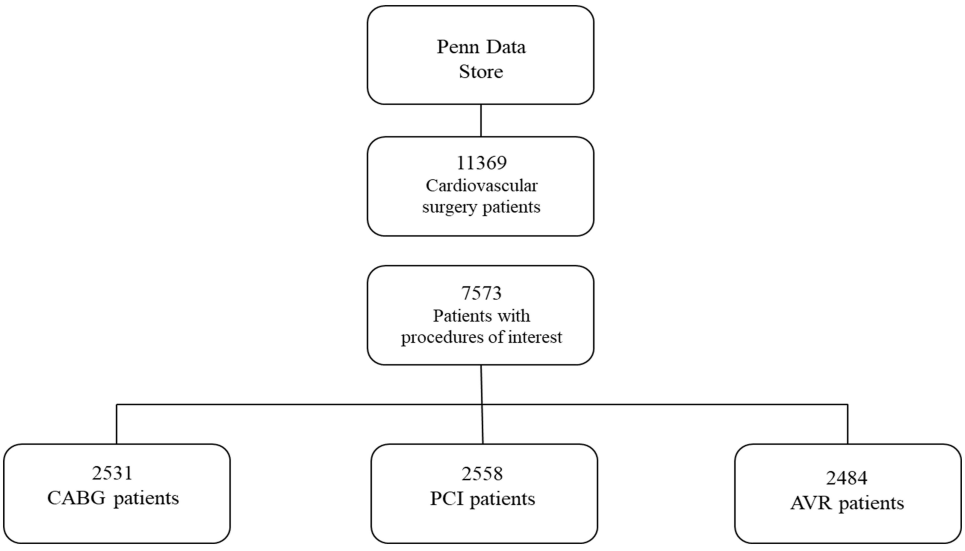

Figure 1 PRISMA graph denoting patient selection. CABG – coronary artery bypass graft, PCI – percutaneous coronary intervention, AVR – aortic valve replacement.

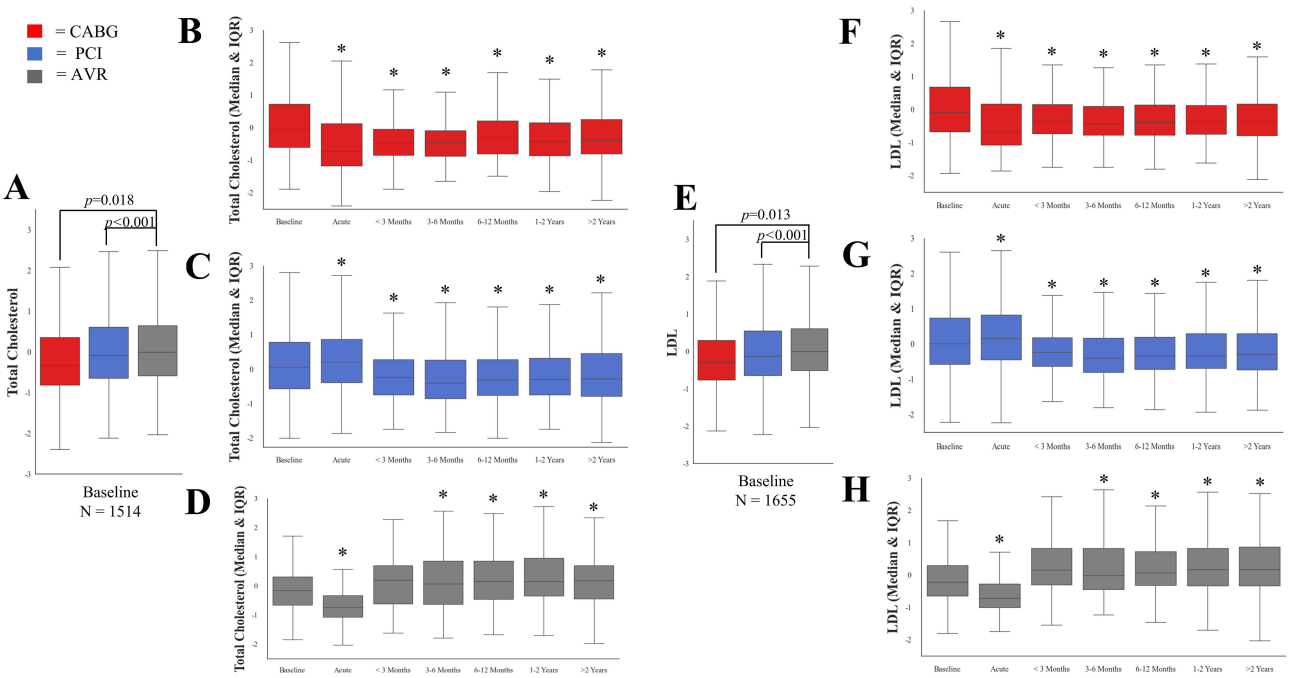

Figure 2 Changes in baseline total cholesterol level were present before surgery (**A**) and compared longitudinally to the postoperative intervals. In the case of the postoperative period of CABG and PCI, serum total cholesterol changed after surgery (B&C), while in the case of patients subjected to AVR, the serum total cholesterol levels increased (**D**). Changes in LDL mimics the difference observed in total cholesterol during pre- (**E**) and postoperative periods across all studied procedures (**F, G, H**).
Notes: *denotes significance CABG or PCI vs AVR, #denotes significance as compared to the pre-procedure level.
Abbreviation: CABG – coronary artery bypass graft, PCI – percutaneous coronary intervention, AVR – aortic valve replacement, LDL – low-density lipoprotein.

decline followed by an increase in total cholesterol (Figure 2D). The main differences were seen between AVR- and PCI-subjected individuals (Table 2).

There was a significant difference between baseline LDL levels among all studied groups (KW[2;1655]=12.882; p=0.002). Similarly, the baseline serum LDL was significantly higher in CABG ($LDL_{CABG[baseline]}$ vs $LDL_{AVR[baseline]}$ =2.611; p=0.013) and PCI ($LDL_{PCI[baseline]}$ vs $LDL_{AVR[baseline]}$=3.581; p<0.001) groups than in individuals undergoing AVR (Figure 2E). LDL serum declined after CABG early and remained significantly lower than the pre-surgical baseline during all observational periods (Figure 2F). In contrast, PCI interventions resulted in an early increase followed by a persistent decline (Figure 2G). In the case of AVR-enrolled individuals, we observed perioperative decline followed by an increase in LDL (Figure 2H). The main differences were seen between AVR- and PCI-subjected individuals (Table 2).

There was also a significant difference between baseline VLDL levels across the groups (KW[2;352]=8.828; p=0.012). Baseline serum VLDL was significantly higher in PCI ($VLDL_{PCI[baseline]}$ vs $VLDL_{AVR[baseline]}$=2.895; p=0.006). However, there was no significant difference between CABG and AVR (p=ns).

Evolution of HDL After CABG Vs PCI Vs AVR

There was a significant difference in serum HDL levels at the baseline across all three groups (KW[2;1966]=14.716; p<0.001), with CABG patients having the lowest levels of this lipoprotein (Figure 3A). As stated in our primary hypothesis, the post hoc analysis revealed that CABG individuals had lower serum levels of HDL than AVR individuals ($HDL_{CABG[baseline]}$ vs $HDL_{AVR[baseline]}$ = −3.5; p<0.001) but no difference between AVR and PCI (p=ns).

The postoperative changes were signified by a decrease in HDL in the early perioperative period in CABG and AVR, while we noticed an increase in PCI (Figure 3B–D). However, most of these changes were small statistically speaking, as signified by the d-Cohen statistic (Table 2).

Table 2 Effect Sizes Based on Cohen's d-Statistics

		Acute	Less than 3 months	3 to 6 months	6 to 12 months	1 to 2 years	Greater than 2 years
T cholesterol	CABG	−0.25	−0.59	−0.57	−0.36	−0.39	−0.31
	PCI	−0.15	−0.45	−0.31	−0.35	−0.32	−0.45
	AVR	−1.29	0.13	0.39	0.37	0.26	0.20
LDL	CABG	−0.37	−0.41	−0.40	−0.38	−0.36	−0.27
	PCI	−0.24	−0.32	−0.28	−0.31	−0.27	−0.38
	AVR	−1.08	0.30	0.47	0.32	0.34	0.26
HDL	CABG	−0.03	−0.25	−0.43	−0.22	−0.29	−0.11
	PCI	0.17	−0.13	−0.25	−0.25	−0.30	−0.17
	AVR	−0.68	−0.23	−0.16	−0.22	−0.26	−0.09
TG	CABG	−0.02	−0.17	−0.32	−0.08	−0.09	−0.07
	PCI	−0.26	−0.14	−0.03	−0.18	−0.10	−0.06
	AVR	0.01	0.12	0.27	0.29	0.08	0.01
HbA1c	CABG	−0.49	−0.88	−0.71	−0.55	−0.49	−0.27
	PCI	−0.28	−0.43	−0.54	−0.46	−0.46	−0.33
	AVR	−0.64	−1.07	−0.49	−0.50	−0.28	−0.18

Notes: The effect of time changes in lipid profile components among all three groups is signified by d-Cohen statistics. The effect sizes are defined as follows: 0.2 is small effect, 0.5 is moderate effect, and 0.8 is large effect. Colors were used to display the direction of the effect (blue is greater than 0, red is less than 0).

Abbreviations: CAD, coronary artery disease; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; AVR, aortic valve repair; TChol, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; TG, triglycerides; HbA1c, hemoglobin A1C, glycated hemoglobin.

Triglyceride Changes After Heart Surgery

Triglyceride (TG) levels were significantly different between CABG and PCI vs AVR at the baseline (KW[2;2068] =27.197; $p<0.001$) (Figure 4A). CABG ($TG_{CABG[baseline]}$ vs $TG_{AVR[baseline]}$=5.044; $p<0.001$) and PCI ($TG_{PCI[baseline]}$ vs $TG_{AVR[baseline]}$=4.414; $p<0.001$) had significantly higher levels of TG as compared to patients in the AVR group (Figure 4A). CABG and PCI interventions resulted in a transient decrease in TG levels during the acute periprocedural period, with recovery by three months for the PCI group (Figure 4C) or 6 months for CABG (Figure 4B). Interestingly, the AVR intervention resulted in a steady increase in TG level over the studied period of time (Figure 4D).

Evolution of Glycemic Profile

HbA1c serum levels were significantly different between CABG and PCI vs AVR at baseline (KW[2;4654]=531.57; $p<0.001$) (Figure 5A). CABG ($HbA1c_{CABG[baseline]}$ vs $HbA1c_{AVR[baseline]}$=19.36; $p<0.001$) and PCI ($HbA1c_{PCI[baseline]}$ vs $HbA1c_{AVR[baseline]}$=18.51; $p<0.001$) had significantly higher levels of HbA1c as compared to patients in the AVR group (Figure 5A). There was a persistent decrease in HbA1c across all three groups (Figure 5B–D). Postoperative changes in HbA1c demonstrated a decline in lab values up to one year after surgery, with d-Cohen demonstrating a medium to strong effect (Table 2).

Discussion

Severe peri-surgical inflammation may affect the metabolome for a protracted period.[25] More recently, some researchers have demonstrated the acute effect of surgery on lipid and glycemic risk factors, suggesting that perioperative disturbances may contribute to increased risk of coronary artery illness, thus potentially limiting the benefits of clinical

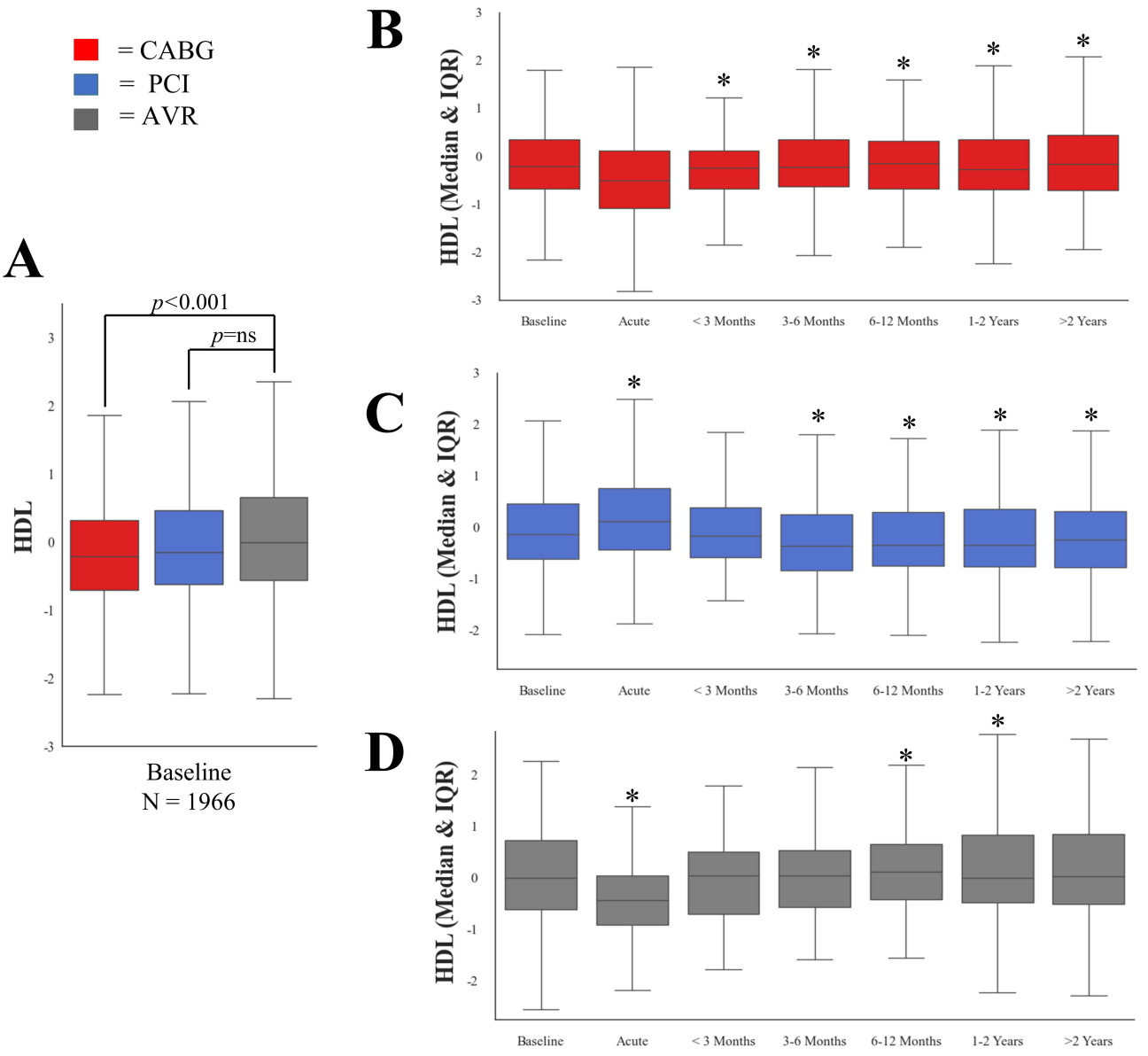

Figure 3 Changes in baseline serum HDL level were present before surgery (**A**) and compared longitudinally to the postoperative intervals. In the case of the postoperative periods of CABG and PCI (B & (**C**), while in the case of patients subjected to AVR, HDL changes were much more temperate (**D**).
Notes: *denotes significance CABG or PCI vs AVR, #denotes significance as compared to the pre-procedure level.
Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; AVR, aortic valve replacement; HDL, high-density lipoprotein.

interventions.[16,27–29] Therefore, we specifically hypothesize that surgery will result in a transient decrease in lipid profile overall (total cholesterol, HDL, LDL, VLDL) and an increase in HbA1c as part of non-specific inflammatory response, potentially altering long-term benefits of surgery.[28–30] Considering methodological difficulty in conducting long-term follow-ups on surgical patients and the preliminary nature of our research goal, we focused on reviewing electronic medical records to create a database of patients with ICD-10 codes for two of the most common coronary artery disease interventions – CABG and AVR – as interventions addressing the same illness with varied levels of invasiveness and inflammation-driven metabolic disturbances.[31–33] We contrasted surgical CABG-related findings with aortic valve replacement procedure (AVR). AVR is a highly invasive, thus inflammatory, procedure, but it is often done in patients without coronary artery disease due to rheumatoid myxoma degeneration, not necessarily progression of CAD.[33]

In summary, the post-procedure atherogenic profile was characterized by a decline in total cholesterol, LDL, and HbA1c in patients after CABG and PCI. Similar data were published in children undergoing heart surgery or adults

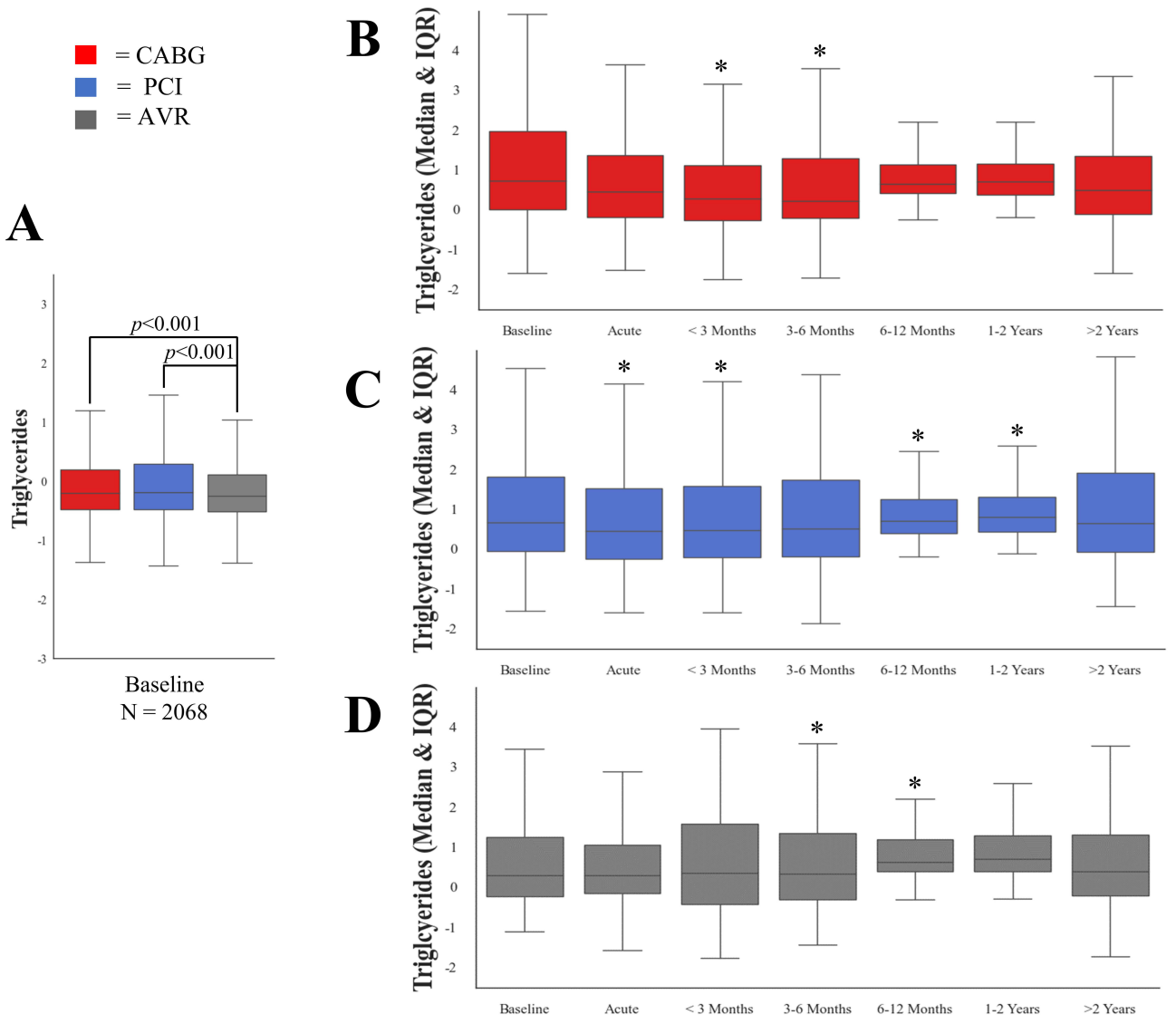

Figure 4 Baseline serum triglyceride levels varied between groups before surgery (**A**) but when compared longitudinally to the postoperative intervals between CABG (**B**), PCI (C and AVR (**D**) a random variability was present.
Notes: *denotes significance CABG or PCI vs AVR, #denotes significance as compared to the pre-procedure level.
Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; AVR, aortic valve replacement.

undergoing emergency surgery.[16,17] In contrast, the AVR group demonstrated a durable increase in total cholesterol and LDL. However, there was no significant difference between CABG and AVR, suggesting the surgery triggers lipid abnormalities. The changes in pro-atherogenic elements of the lipid profile were quite profound, judging by *d*-Cohen statistics and their persistence. We also noted increased HDL in the PCI group during the acute phase, particularly in PCI patients. We believe this is due to the targeted and aggressive implementation of lipid therapy combined with the low periprocedural invasiveness of PCI, culminating in a net increase in serum HDL. One would expect such a change from current guidelines addressing the management of lipid profiles in atherosclerosis. The changes in serum triglycerides and VLDL were relatively minor and random. Consequently, their impact cannot be ascertained. HbA1c decreased across all studied groups over time, suggesting that impairment in glucose metabolism is unlikely to contribute to post-procedure CAD risk factors. These findings nullified a significant part of our original research hypothesis, as we expected a decline in serum HDL, LDL, and total cholesterol with a concomitant increase in HbA1c after surgical procedures (CABG or AVR).

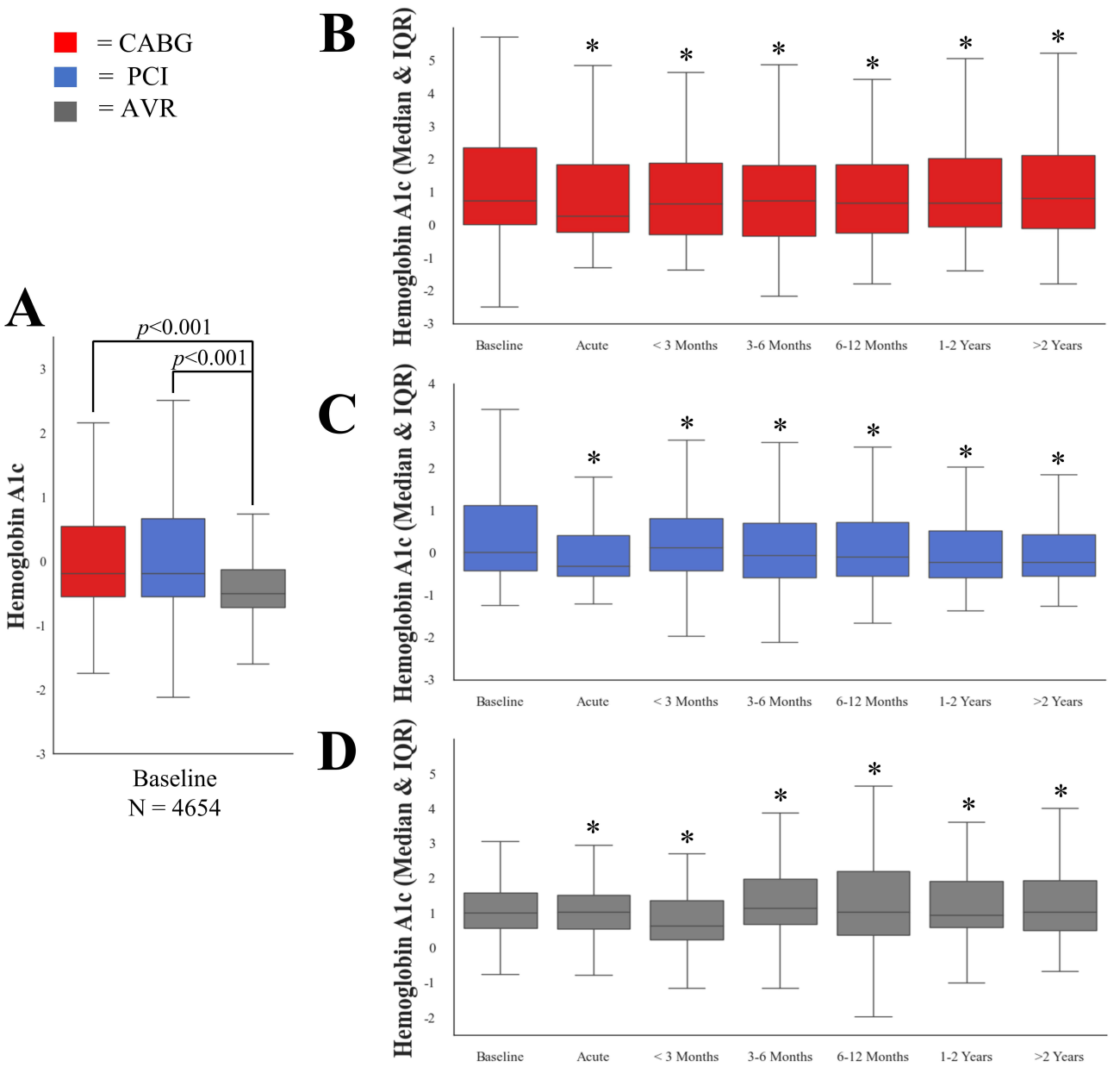

Figure 5 Baseline HbA1c level varied before surgery (**A**) In the case of the postoperative periods of CABG and PCI (B & (**C**), there was a decline in HbA1c while AVR had a variable impact (**D**).
Notes: *denotes significance CABG or PCI vs AVR, #denotes significance as compared to the pre-procedure level.
Abbreviations: CABG – coronary artery bypass graft, PCI – percutaneous coronary intervention, AVR – aortic valve replacement.

Our study has several innovative aspects methodology-wise in order to address a complex hypothesis. Assessing long-term outcomes is complex and financially and methodologically prohibitive. So it is unsurprising that no prior research was published addressing the question of perioperative changes in lipid profile and glucose metabolism. However, previous data from sepsis survivors suggest that the lipid profile can be altered for prolonged periods after severe insults. Concomitantly, the risk of acute coronary events increases over time after sepsis, demonstrating the methodological feasibility of the study.

This research study also has limitations. This is a retrospective review of data obtained from medical records. Consequently, establishing definite causation is not possible. Also, considering the large study sample and potential for systemic error, there is a risk of false positive statistics. However, we analyzed the data in several ways, including pairwise comparisons, randomly checked some of the records for accuracy, utilized estimates of the effect (*d*-Cohen) instead of

p-values, and purposely limited the conclusions to the most prominent ones.[34] We are also aware that there are several sources of bias. Patients in our database were tested for collected variables secondary to implementing recommended AHA's guidelines or because of clinical needs. This may result in patients with more comorbidities and older patients being included. We relied on the lab values provided in the medical records. The testing of blood samples may have evolved during the sampling period. However, after introducing a new technology to measure a given clinical variable, the test results are commonly related to the old ones. We also conducted Z-score standardization using our entire study population, reducing variability related to technological changes. The data could be miscoded, but we randomly reviewed some records to check for accuracy between the data pulled and actual records in the database. Manual coding using ICD-10 is subject to omissions and mistakes. An additional critique is that our analysis did not explicitly assess the role of pharmacologic intervention in postoperative lipid metabolome. Future projects should determine the potential confounding influence of such interventions. This is valid as PCI and CABG patients will be aggressively enrolled in pre-and postoperative CAD secondary prophylaxis. However, a significant number of patients are not compliant with medication even in the aftermath of an acute coronary event. Assessing medication intake and compliance is inherently difficult and often myriad in several biases. One specific barrier to evaluating these factors in a longitudinal patient cohort is the variety of patient data obtained from inpatient and outpatient settings and healthcare systems. In the case of our sample, the frequency of medication could not be analyzed beyond the first year after surgery, considering the systematic drop in reported prescriptions. This is most likely an artifact related to patients migrating to another database focused on outpatient data or moving to another healthcare system. However, we did demonstrate an increase in prescription frequency during the first year after surgery, a period when our patients were predominantly under the care of the hospital team. This validates our analysis as one would expect more aggressive secondary CAD prevention after CABG or PCI. On the other hand, our analysis was unique, and our conclusions were robust. Our research is the first of this kind of analysis in a surgical population. The study was intended to be a hypothesis-generating project using already existing data. A more robust project would require an investment in a longitudinal population study, requiring significant resources. Such an investment is premature in the current state of knowledge. Instead, we demonstrate a novel finding that must be confirmed in other large databases. The study spans over ten years. During this time significant changes in perioperative management secondary to changes in guideline but also hospital policies and workflow happened, potentially impacting observed changes.

Several findings validate our data. There were differences in pre-procedural lipid levels. As expected, CABG and PCI patients demonstrated increased LDL and total cholesterol levels as the population more likely presented with CAD-related factors. There was a drop in LDL and HDL after surgical procedures but not after PCI. This phenomenon is well described in the literature. These two observations validate our approach to a certain degree. Our research methodology has been utilized and peer-reviewed beforehand.

Conclusion

Our data suggest that surgical procedures may result in significant and prolonged disturbances in lipid profile proatherogenic components, particularly in the AVR group. This may mean a more aggressive treatment of these disturbances after surgical procedures in patients. However, the next stage in this process should be an establishment of which patients are most susceptible to post-surgery changes in coronary artery disease risk factors.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding authors on reasonable request after the University of Pennsylvania IRB approval.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the University of Pennsylvania (#834697 and the date of approval was 2019.02.06). Considering that the study consisted of a records review, could not be conducted with all patients consenting, and minimal risk to participants the HIPAA and consent waiver were granted. Patient data confidentiality was upheld throughout this study.

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Disclosure

The authors report no conflicts of interest in this work.

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