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HbA1c, Coronary atheroma progression and cardiovascular outcomes

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ABSTRACT

Background and aims: We tested the hypothesis that on-treatment HbA1c levels independently associate with coronary atheroma progression and major adverse cardiovascular events (MACE: death, myocardial infarction, cerebrovascular accident, coronary revascularization, or hospitalization for unstable angina) rates.

Methods: We performed a *post-hoc* pooled analysis of data from seven prospective, randomized trials involving serial coronary intravascular ultrasonography (IVUS). The percent atheroma volume (PAV) was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque. Using multivariable mixed modeling, we determined the association of on-treatment HbA1c with annualized change in PAV. Cox proportional hazard models were used to assess the association of HbA1c with incidence of MACE.

Results: Among 3,312 patients (mean age 58.6±9years, 28.4%women) average on-treatment HbA1c was 6.2±1.1%. Overall, there was no net significant annualized change in PAV (0.12±0.19%, $p = 0.52$). In a fully adjusted multivariable analysis (following adjustment of age, sex, body mass index, systolic blood pressure, smoking, low- and high-density lipoprotein cholesterol, triglyceride levels, peripheral vascular disease, trial, region, and baseline PAV), higher on-treatment HbA1c levels were independently associated with annualized changes in PAV [beta-estimate (95% confidence interval): 0.13(0.08, 0.19), $p < 0.001$]. On-treatment HbA1c levels were independently associated with MACE [hazard ratio (95% confidence interval): 1.13(1.04, 1.23), $p = 0.005$].

Conclusions: Independent of achieved cardiovascular risk factor control, greater HbA1c levels significantly associate with coronary atheroma progression rates and clinical outcomes. These results support the notion of a direct, specific effect of glycemic control upon coronary atheroma and atherosclerotic events, supporting the rationale of therapies designed to directly modulate it.

Abbreviations: ACS, acute coronary syndrome; AQUARIUS, Aliskiren Quantative Atherosclerosis Regression Intravascular Ultrasound Study; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CVD, cardiovascular disease; GLAGOV, Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity-CRP; IBIS 2, The Integrated Biomarkers and Imaging Study-2; IVUS, intravascular ultrasonography; LDL-C, lipoprotein cholesterol; MACE, major adverse cardiovascular events; NORMALISE, Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation; PAV, percent atheroma volume; PERISCOPE, Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; PVD, peripheral vascular disease; REVERSAL, Reversal of Atherosclerosis With Aggressive Lipid Lowering; SATURN, The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin; STRADIVARIUS, Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabont – The Intravascular Ultrasound Study; TG, triglycerides; UKPDS, UK Prospective Diabetes Study.

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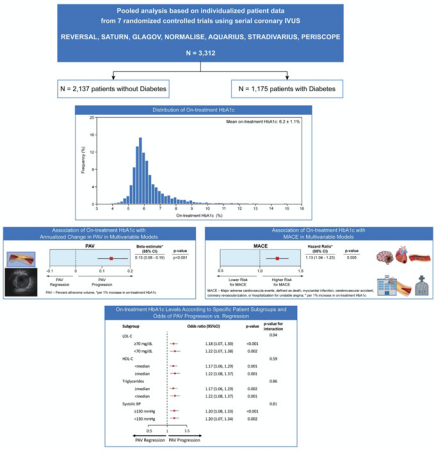
Central illustration



1. Introduction

Hemoglobin A1c (HbA1c) reflects long-term glycemic control and is central to the diagnosis and management of diabetes mellitus [1,2]. Elevated HbA1c is associated with an increased risk of cardiovascular events among diabetic and non-diabetic patients [2–7]; with diabetic atherosclerosis manifesting within the arterial wall with accelerated disease progression and impaired arterial wall remodeling [8]. However, elevated HbA1c-levels are frequently concomitant with multiple other atherogenic risk factors, including dyslipidemia, hypertension, smoking and obesity which are all known drivers of plaque progression [9–11]. In contrast, intense low-density lipoprotein cholesterol (LDL-C) lowering with long-term high intensity statin therapy significantly altered the progressive nature of diabetic coronary atherosclerosis, in some cases promoted disease regression [12]. The impact of HbA1c *per se* upon atheroma progression independent of the presence/absence of diabetes mellitus and other modifiable cardiovascular risk factors such as LDL-C, however, has not been evaluated.

In this *post-hoc* pooled analysis of data from seven prospective, randomized-controlled trials involving serial coronary IVUS, we tested the hypothesis that HbA1c levels would independently associate with coronary atheroma progression on IVUS and major adverse cardiovascular events (MACE) despite the presence of other cardiovascular risk factors.

2. Methods

2.1. Study population

The present analysis included patients participating in one out of seven clinical trials assessing the impact of medical therapies on serial changes in coronary atheroma burden using IVUS. In this analysis, we included trials assessing intensive lipid lowering therapy with statins and the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab [REVERSAL (Reversal of Atherosclerosis With Aggressive Lipid Lowering), SATURN (The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin), and GLAGOV (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound)] [13–16], antihypertensive therapies [NORMALISE (Norvasc for Regression of Manifest Atherosclerotic Lesions by Intravascular Sonographic Evaluation) and AQUARIUS (Aliskiren Quantative Atherosclerosis Regression Intravascular Ultrasound Study)] [17,18], the anti-atherosclerotic efficacy of endocannibanoid receptor antagonist [STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabont – The Intravascular Ultrasound Study)] [19], and the peroxisome proliferator-activated receptor-gamma agonism [PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)] [20]. In the present analysis, patients with on-treatment HbA1c levels (both patients with and without diabetes mellitus) as well as baseline and follow-up IVUS imaging available were included (N = 3,312). For calculation of average on-treatment HbA1c levels, all available assessments (as per protocol as well as available unscheduled assessment) were included on an individual patient level. The frequency of follow-up HbA1c assessments according to study protocols varied between 1 (AQUARIUS and SATURN trials), 2 (REVERSAL, STRADIVARIUS, and NORMALISE trials), and 7 (GLAGOV and PERISCOPE trials). Ethics review board approval was obtained for each of the included trials.

2.2. Acquisition and analysis of serial IVUS images

The acquisition and serial analysis of IVUS images in each of these trials has been previously described in detail [13–21]. Briefly, target vessels for imaging were selected if they contained no luminal stenosis >50% angiographic severity within a segment of at least 30 mm length. Imaging was performed within the same coronary artery at baseline and at study completion, which ranged from 18 to 24 months (18 months for REVERSAL, PERISCOPE, STRADIVARIUS, and GLAGOV trials; 24 months for NORMALISE, SATURN, and AQUARIUS trials). Due to the varying degree of trial duration, changes in IVUS measures were interpolated at 1 year on a patient based level and these annualized changes from baseline were used for analysis purposes. Imaging in all trials was screened by the Atherosclerosis Imaging Core Laboratory of the Cleveland Clinic Coordinating Center for Clinical Research (C5R). Patients meeting pre-specified requirements for image quality were eligible for randomization. An anatomically matched segment was defined at the two time points on the basis of proximal and distal side branches (fiduciary points). Cross-sectional images spaced precisely 1 mm apart were selected for measurement. Leading edges of the lumen and external elastic membrane (EEM) were traced by manual planimetry. Plaque area was defined as the area occupied between these leading edges. The accuracy and reproducibility of this method have been reported previously [22]. The percent atheroma volume (PAV) was calculated as the proportion of the entire vessel wall occupied by atherosclerotic plaque, throughout the segment of interest as follows:

$$PAV = \frac{\sum (EEM\,area - LUMEN\,area)}{\sum EEM\,area} \times 100$$

2.3. Major adverse cardiovascular endpoints

The included clinical trials prospectively collected adjudicated MACE (defined as death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina). For this analysis, events occurring within 24 months after randomization were included.

2.4. Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) when normally distributed and median (interquartile range; IQR) when non-normally distributed. Categorical variables are reported as frequencies and percentages.

Changes from baseline of the average on-treatment biochemical measurements were assessed to see if their means were significantly different from zero using a paired t-test or Wilcoxon signed-rank test for parametric and non-parametric data, respectively. Annualized changes from baseline of PAV was assessed to see if its means was significantly different from zero by using mixed modeling that adjusted for respective baseline IVUS measure and trial. Least-squares mean ± standard error (SE) is reported.

Multivariable mixed modeling was used to assess the association of average follow-up HbA1c and annualized change in PAV. A univariate model included adjustments for baseline PAV and trial. A multivariable

Table 1
Clinical baseline characteristics.

Demographic	*N* = 3312
Age, mean (SD), yrs	58.6±9.0
Female, *n* (%)	942 (28.4)
Caucasian, *n* (%)	3104 (93.7)
Body mass index, mean (SD), kg/m^2	30.9±5.9
Current smoker, *n* (%)	910 (27.5)
Metabolic Syndrome	1885 (56.9)
Medical history, n (%)	
Hypertension	2671 (80.6)
Diabetes mellitus	1175 (35.5)
Acute Coronary Syndrome	890 (31.1)
History of MI	985 (29.7)
History of CABG	42 (1.3)
History of PCI	1162 (35.1)
History of CVA	94 (2.8)
History of PVD	146 (4.4)
Medication use during trial, *n* (%)	
Statin (any)	3146 (95.0)
Statin (high-intensity)	1312 (42.8)
ACE Inhibitors	1890 (57.1)
Angiotensin Receptor Blocker	781 (23.6)
Beta Blockers	2563 (77.4)
Calcium Channel Blocker	1206 (36.4)
Aspirin	3019 (91.2)
Insulin	331 (10.0)

Abbreviations: ACE = angiotensin converting enzyme, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CVA = cerebrovascular accident, MI = myocardial infarction, PCI = percutaneous coronary intervention, PVD = peripheral vascular disease, SD = standard deviation.

model included adjustments for baseline PAV, trial, region, age, sex, body mass index (BMI), smoking, peripheral vascular disease (PVD), and average on-treatment systolic blood pressure (SBP), LDL-C, high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG). Log-transforms were used as appropriate. Beta(β)-estimate with 95% confidence intervals (CI) is reported per 1% increase in HbA1c levels.

The association of average follow-up HbA1c and MACE was examined using Cox proportional hazards models. The same adjustments were applied as outlined above for the mixed modeling, except annualized change in PAV was also added as a covariate to the multivariable survival model. Hazard ratio with 95% CI is reported.

Sensitivity analyses were applied to the above multivariable models. In the first scenario, on-treatment C-reactive protein (CRP) and remnant cholesterol were added to the multivariable models. In the second scenario, LDL-C was replaced with non-HDL-C in the multivariable models.

A Forest plot illustrates the association of average on-treatment HbA1c with PAV progression versus regression. Logistic regression modeling was performed with the same adjustments as outlined above in the original multivariable model that treated annualized change in PAV as a continuous variable. Analysis was stratified by the following on-treatment risk factors: LDL-C ≥ or < 70 mg/dL, HDL-C < or ≥ than its median level, TG ≥ or < median, CRP ≥ or < 2.0 mg/L, SBP ≥ or < 130 mmHg, and presence or absence of diabetes mellitus at baseline. Odds ratio with 95% CI is reported.

All tests were two-tailed with a 0.05 significance level. Analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). The Figure was created using Excel (version 16.43, Microsoft, Redmond, Washington).

3. Results

Table 1 describes baseline clinical characteristics and medication use of the pooled study population (N=3,312). Mean overall age was 58.6±9.0 years, 28.4% were women, 35.5% had diabetes mellitus, 56.9% had metabolic syndrome, 27.5% were smokers, and the mean body mass index was 30.9±6.0 kg/m^2. Prior myocardial infarction was present in 985 patients (29.7%), 1,162 (35.1%) had previously undergone percutaneous coronary intervention, and 42 (1.3%) had prior coronary artery bypass surgery. Nearly all patients were treated with a statin (95.0%) and 42.8% were receiving a high-intensity statin. Mean body mass index was 30.9±5.9 kg/m^2 at baseline and did not relevantly change during the duration of the trials (last available follow-up BMI: 30.9±6.0 kg/m^2).

Table 2 describes baseline and average on-treatment laboratory biochemical measurements, systolic blood pressure, and IVUS parameters. Overall, the average follow-up biochemical levels revealed a HbA1c 6.2±1.1%, LDL-C 77.7±32.8mg/dL, remnant cholesterol 22.7 (17.2, 31.0) mg/dL, HDL-C 47.0±12.3 mg/dL, non-HDL-C 103.8±37.4 mg/dL, triglycerides 124.0 (93.1, 167.1) mg/dL, and CRP 1.6 (0.8, 3.6) mg/L respectively. There was no net significant annualized change in PAV (least-squares mean±standard error: 0.12±0.19%, $p = 0.52$).

Table 3 describes the association of average on-treatment HbA1c with coronary atheroma progression and MACE in unadjusted and multivariable adjusted modeling. In the multivariable adjusted analysis, increasing on-treatment HbA1c was associated with PAV progression [beta estimate (95% confidence interval): 0.13 (0.08, 0.19), $p < 0.001$]. Likewise, in the fully adjusted survival analysis, also controlled for annualized change in PAV, on-treatment HbA1c was significantly associated with incidence of MACE [hazard ratio (95% confidence interval): 1.13 (1.04, 1.23), $p = 0.005$].

Fig. 1 describes a multivariable adjusted model illustrating the relationship between on-treatment HbA1c levels and the odds of PAV progression versus regression, stratified according to various patient subgroups of interest. Overall, increasing on-treatment HbA1c associated

Table 2
Baseline and average on-treatment biochemical and intravascular ultrasonography measurements.

Measurements	Baseline	On-treatment	*p*-value[a] μ(Δ)=0
Biochemical measures and blood pressure			
HbA1C, %	6.2±1.1	6.2±1.1	0.002
LDL-C, mean (SD), mg/dL	99.9±32.3	77.7±32.8	<0.001
Remnant Cholesterol, mean (SD), mg/dL	25.0 (19.0, 35.0)	22.7 (17.2, 31.0)	<0.001[NP]
HDL-C, mean (SD), mg/dL	43.5±12.1	47.0±12.3	<0.001
Non-HDL, mean (SD), mg/dL	128.6±37.2	103.8±37.4	<0.001
Triglycerides, median (IQR), mg/dL	131.0 (96.0, 184.0)	124.0 (93.1, 167.1)	<0.001[NP]
CRP, median (IQR), mg/L	2.1 (1.0, 4.7)	1.6 (0.8, 3.6)	<0.001[NP]
Systolic blood pressure, mean (SD), mmHg	130.3±15.8	130.8±13.2	0.06
IVUS			
Percent atheroma volume, mean (SD), %	37.4±8.6	37.1±8.5	0.52[b]

[a] Tests if the mean of the average follow-up change from baseline is statistically different from zero.
[b] Adjusted for baseline PAV and trial.Abbreviations: CRP = high sensitivity C reactive protein, HbA1C = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, IVUS = intravascular ultrasound, LDL-C = low-density lipoprotein cholesterol, Non-HDL =non-high-density lipoprotein cholesterol, PAV = percent atheroma volume, SD = standard deviation.

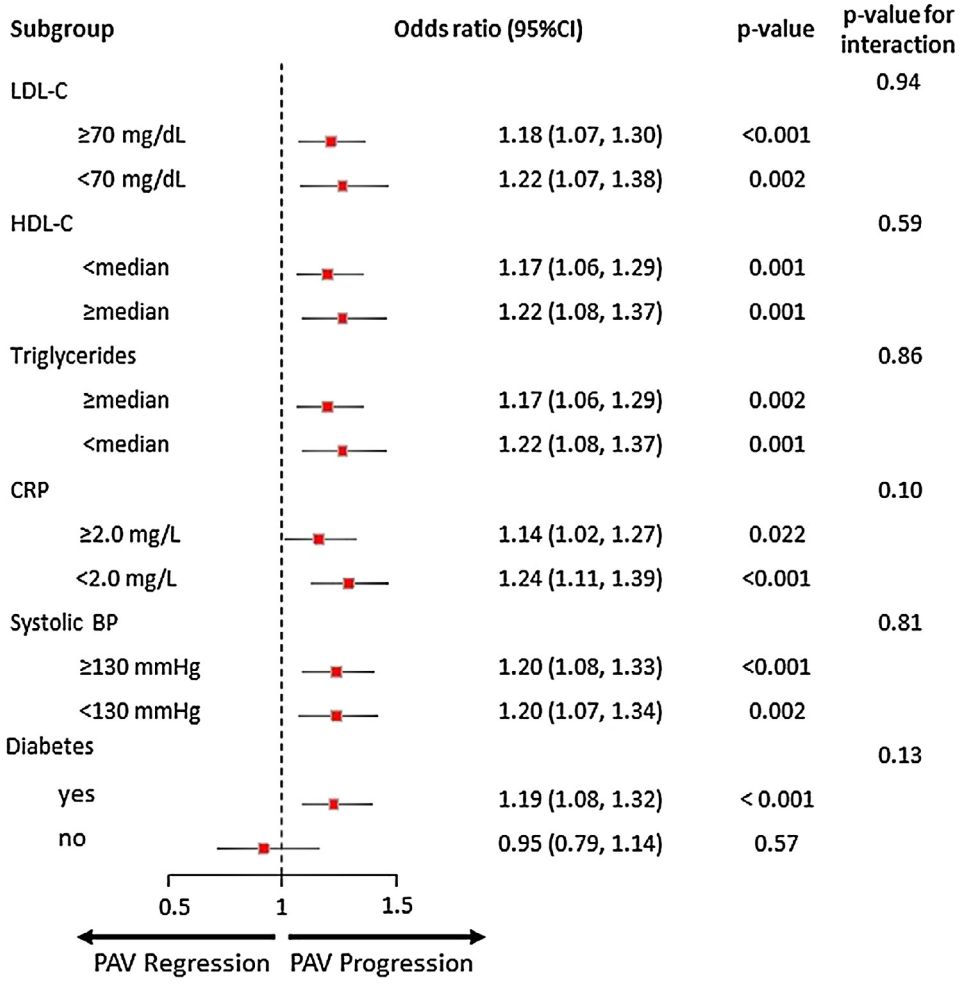


Fig. 1. On-treatment HbA1c levels according to specific patient subgroups and odds of PAV progression vs. regression. Forest plot for the association of on-treatment HbA1c levels and progression vs. regression of PAV across differing patient subpopulations. For on-treatment risk factors, average values were used to create the subgroups. Odds ratio and 95% confidence interval per standard deviation for the on-treatment HbAc1 level was calculated using logistic regression models. Variables adjusted for in each model included baseline PAV, trial, region, age, sex, BMI, smoking, PVD, as well as average on-treatment SBP, LDL-C, HDL-C, and TG. Abbreviations: BMI = body mass index, CI = confidential interval, HbA1C = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PAV = percent atheroma volume, PVD = peripheral vascular disease, SBP = systolic blood pressure, TG = Triglycerides.

with significantly higher chance of coronary atheroma progression, irrespective of on-treatment LDL-C, HDL-C, triglycerides, hsCRP, and systolic blood pressure. The presence or absence of diabetes mellitus did not significantly associate with the propensity for atheroma progression/regression according to HbA1c levels.

Sensitivity analyses were performed to examine if additional adjustment for remnant cholesterol and C-reactive protein as markers of atherosclerotic risk influenced the association of HbA1c with annualized change in PAV and MACE. In these models, the observed associations between average on-treatment HbA1c and outcome measures remained stable and unchanged. Likewise, effect sizes remained stable when controlling for non-HDL-C instead of LDL-C (Table 4).

4. Discussion

In this *post hoc* pooled analysis of data from seven prospective, randomized-controlled trials involving serial coronary IVUS, we demonstrate greater on-treatment HbA1c levels to significantly and independently associate with coronary atheroma progression and clinical outcomes. The strong association of on-treatment HbA1c with PAV progression and MACE was independent of full multivariable adjustment for known cardiovascular risk factors, components of the metabolic syndrome, the presence/absence of diabetes mellitus and trial. These data support the notion of a direct, specific effect of glycemic control upon the natural history of coronary atheroma and atherosclerotic events, supporting further efforts to evaluate diagnostic and therapeutic implications of these findings.

Plaque progression occurs via the complex interplay of numerous effector mechanisms promoted by the presence of various risk factors such as elevated atherogenic lipoprotein levels, systemic inflammation and systemic hypertension to name a few. The specific and independent effect of varying degrees of glycemic control *per se*, upon atheroma progression irrespective of the presence/absence of diabetes mellitus, has been elusive. This has been particularly challenging in patients with diabetes mellitus and the presence of the metabolic syndrome; a population harboring a relatively high overall atherosclerotic cardiovascular disease (ASCVD) risk burden. For the metabolic syndrome, its individual components rather than the metabolic syndrome itself was found to be specifically associated with atherosclerosis progression [9,23]. In a previous analysis, combining data from 5 randomized controlled trials using serial IVUS-imaging, patients with diabetes mellitus had on average greater BMI, and higher prevalence of hypertension, hyperlipidemia, and metabolic syndrome. While the presence of diabetes mellitus was linked with greater atherosclerosis progression, control of other risk factors, most importantly LDL-C, was found to relevantly influence atherosclerosis progression both in diabetic and non-diabetic patients [8]. This was confirmed in a *post-hoc* analysis of the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) trial, where long-term high-intensity statin therapy promoted coronary atheroma regression in patients with diabetes mellitus [12], fundamentally altering the natural history of an otherwise highly progressive atheroma phenotype.

The Integrated Biomarkers and Imaging Study-2 (IBIS 2) trial found HbA1c levels at baseline to significantly associate with baseline plaque burden in a cross-sectional analysis. However, the study failed

Table 3
Association of on-treatment HbA1c with annualized change in PAV and MACE .

	Annualized change in PAV Beta-estimate (95%CI)	*P*-value
Unadjusted[a]	0.13 (0.08, 0.18)	<0.001
MV adjusted[b]	0.13 (0.08, 0.19)	<0.001
	MACE HR (95%CI)	*P*-value
Unadjusted[c]	1.16 (1.07, 1.25)	<0.001
MV adjusted[d]	1.13 (1.04, 1.23)	0.005

[a] Adjusted for baseline PAV and trial.
[b] MV adjusted for baseline PAV, trial, region, age, sex, BMI, smoking, PVD, as well as average on-treatment SBP, LDL-C, HDL-C, and TG.
[c] Adjusted for trial.
[d] MV adjusted for baseline PAV, annualized change in PAV, trial, region, age, sex, BMI, smoking, PVD, as well as average on-treatment SBP, LDL-C, HDL-C, TG.Major adverse cardiovascular event (MACE) indicates death, stroke, myocardial infarction, coronary revascularization or hospitalization for unstable angina.Abbreviations: BMI = Body mass index, CI = confidential interval, HbA1C = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio; IVUS = intravascular ultrasound, LDL-C = low-density lipoprotein cholesterol, MV = multivariable, PAV = percent atheroma volume, PVD = peripheral vascular disease, SBP = systolic blood pressure, SD = standard deviation, TG = Triglycerides.

Table 4
Sensitivity analyses for the association of on-treatment HbA1c with annualized change in PAV and MACE.

	Annualized change in PAV Beta-estimate (95%CI)	*P*-value
Model 1	0.14 (0.08, 0.20)	<0.001
Model 2	0.13 (0.08, 0.19)	<0.001
	MACE Events HR (95%CI)	*P*-value
Model 3	1.13 (1.03, 1.23)	0.008
Model 4	1.13 (1.04, 1.23)	0.006

Model 1: adjusted for baseline PAV, trial, region, age, sex, BMI, smoking, PVD as well as average on-treatment SBP, LDL-C, HDL-C, CRP and remnant cholesterol.
Model 2: adjusted for baseline PAV, trial, region, age, sex, BMI, smoking, PVD as well as average on-treatment SBP, non-HDL-C, HDL-C, TG.
Model 3: adjusted for baseline PAV, annualized change in PAV, trial, region, age, sex, BMI, smoking, PVD, as well as average on-treatment SBP, LDL, HDL, CRP, and remnant cholesterol.
Model 4: adjusted for baseline PAV, annualized change in PAV, trial, region, age, sex, BMI, smoking, PVD, as well as average on-treatment SBP, non-HDL, HDL, and TG.
Major adverse cardiovascular event (MACE) indicates death, stroke, myocardial infarction, coronary revascularization or hospitalization for unstable angina.
Abbreviations: BMI = Body mass index, CI = confidential interval, CRP = high sensitivity C reactive protein, HbA1C = hemoglobin A1c, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio; IVUS = intravascular ultrasound, LDL-C = low-density lipoprotein cholesterol, PAV = percent atheroma volume, PVD = peripheral vascular disease, SBP = Systolic blood pressure, TG = Triglycerides.

to describe a causal relationship of on-treatment HbA1c levels with changes in coronary atheroma burden over time [24]. The present analysis demonstrates that in the setting of multiple risk factor control, glycemic control *per se* remains an independent predictor of coronary atheroma progression, regardless of the presence/absence of diabetes mellitus. Together with prior results from the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial, where treatment with pioglitazone compared with glimepiride led to a significantly greater decline in HbA1c levels and associated with PAV regression [20], our results support the rationale of therapies designed to directly modulate HbA1c to causally alter disease progression and subsequent ASCVD risk.

A wealth of evidence documents the association of greater HbA1c levels with adverse cardiovascular outcome in various cohorts [7]. In the setting of intensified diabetes mellitus therapies, poor glycemic control as reflected by high HbA1c levels was associated with increased all-cause mortality [3]. In addition, the results of the observational long-term follow-up of the UK Prospective Diabetes Study (UKPDS) demonstrated a benefit of improved glycemic control in risk reduction for myocardial infarction and death from any cause [25]. Similarly, a meta-analysis of cardiovascular outcome trials revealed that intensive glycemic control was associated with a 9% reduction in the risk of MACE [26]. In a recent study evaluating patients with and without diabetes mellitus undergoing coronary artery revascularization, the risk for future myocardial infarction was increased in groups with greater HbA1c levels [27]. In addition, a recent large observational cohort of asymptomatic individuals without diabetes mellitus described a strong association between HbA1c and subclinical atherosclerosis, independent of potential confounders [28]. These results are confirmed by our findings of an independent association of HbA1c with incident MACE when controlling for other cardiovascular risk factors, including both patients with and without diabetes mellitus. Our results suggest that the link of glycemic control with the greater risk in cardiovascular outcomes is based on disease progression independent of global ASCVD risk factor control.

4.1. Limitations

Several caveats of the present analysis warrant further consideration. The results of this analysis were obtained by pooling data from various clinical trials. Despite rigorous statistical approaches and relatively uniform inclusion/exclusion criteria in each trial, we cannot disregard unmeasured cofounding that may have biased the results. Second, the population of this study was predominantly male and white, limiting the generalizability of the findings across other groups. Third, residual confounding may contribute to the observed results despite attempts to perform risk adjustment for potential confounders as well as subgroup analyses stratifying by presence and absence of concomitant risk factors. Fourth, as by study design, the mechanisms of increased PAV related to greater HbA1c levels cannot be elucidated from the present analysis. Further investigation is needed to understand mechanisms of coronary atherosclerosis progression related to glycemic control. Despite these limitations, this is the first study to examine the relationship between on-treatment glycemic control *per se* and coronary atheroma progression as well as incident MACE in a large population of patients with and without diabetes mellitus with standardized IVUS protocols, core laboratory adjudication and clinical events committees.

5. Conclusions

Independent of achieved cholesterol levels, ASCVD risk factors and BMI, greater on-treatment HbA1c levels independently associate with coronary atheroma progression and clinical outcomes. These findings support the notion of a direct, specific effect of glycemic control upon the natural history of coronary atheroma and atherosclerotic events, supporting the rationale of therapies designed to specifically modulate it.

Disclosures

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Iryna Dykun: Conceptualization, Methodology, Writing – original draft. **Ozgur Bayturan:** Conceptualization, Validation, Writing – review & editing. **Julie Carlo:** Formal analysis, Writing – review & editing. **Steven E. Nissen:** Resources, Funding acquisition, Supervision, Writing – review & editing. **Samir R. Kapadia:** Resources, Data curation, Supervision, Writing – review & editing. **E. Murat Tuzcu:** Data curation, Validation, Writing – review & editing. **Stephen J. Nicholls:** Data curation, Supervision, Writing – review & editing. **Rishi Puri:** Conceptualization, Methodology, Project administration, Writing – original draft.

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