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MAJOR ARTICLE

Coronary Artery Disease in Persons With Human Immunodeficiency Virus Without Detectable Viral Replication

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Background. We aimed to determine the prevalence of coronary artery disease (CAD) in persons with human immunodeficiency virus (HIV; PWH) and investigate whether inflammatory markers, including interleukin 6, IL-1β, and high-sensitivity C-reactive protein (hsCRP), were associated with CAD.

Methods. From the Copenhagen Comorbidity in HIV Infection (COCOMO) study, we included virologically suppressed PWH who underwent coronary computed tomographic (CT) angiography. Any atherosclerosis was defined as >0% stenosis, and obstructive CAD as ≥50% stenosis.

Results. Among 669 participants (mean age [standard deviation], 51 [11] years; 89% male), 300 (45%) had atherosclerosis, and 119 (18%) had obstructive CAD. The following risk factors were associated with any atherosclerosis and with obstructive CAD: age, male sex, hypertension, diabetes, smoking, dyslipidemia, time with HIV, and current protease inhibitor use. Interleukin 6 (IL-6) and hsCRP levels >2 mg/L were associated with any atherosclerosis and with obstructive CAD in univariable analyses but not after adjustment for traditional risk factors. IL-1β was not associated with CAD.

Conclusions. In a large population of PWH without viral replication, almost half had angiographically verified atherosclerosis. High concentrations of IL-6 and hsCRP were associated with CAD in univariable analyses, but adjustment for cardiovascular risk factors attenuated the association, suggesting that inflammation may mediate the association between traditional risk factors and CAD.

Keywords. CCTA; HIV; comorbidity; coronary artery disease; inflammation.

The clinical presentation of cardiovascular disease (CVD) in persons with human immunodeficiency virus (HIV; PWH) has changed over the last 3 decades [1]. Since the introduction of antiretroviral therapy (ART), myocarditis and cardiomyopathy have become increasingly rare, and the most common CVDs in PWH are now chronic conditions, including heart failure and coronary artery disease (CAD) [1]. The mechanisms leading to CAD in PWH are multifactorial and may include traditional risk factors, ART-associated lipid perturbation, and HIV-associated immune activation and inflammation [2, 3].

Inflammation is lower in well-treated than in untreated PWH, but even in virologically suppressed PWH, markers of systemic inflammation remain elevated compared with uninfected persons, and increased arterial inflammation may be considered a feature of treated HIV infection [4–6]. Evidence for the role of inflammation in the initiation and progression of atherosclerosis has been substantiated by several studies, and the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) unequivocally demonstrated the role of interleukin-1β (IL-1β) in atherogenesis [7]. In PWH, IL-1β has been associated with first-time myocardial infarction and pulmonary disease, and monoclonal antibodies against IL-1β may decrease both circulating markers of inflammation and local arterial inflammation in treated PWH [8–10].

Coronary computed tomographic (CT) angiography (CCTA) has high diagnostic accuracy for detection of CAD, including determination of CAD severity [11–13]. Previous studies have found that 52%–78% of middle-aged PWH have evidence of coronary atherosclerosis. However, although the studies were large and well conducted, some participants in these studies were not using ART and/or were not virologically suppressed [14–17].

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Thus, the distribution of CAD among well-treated PWH remains to be described. We aimed to characterize the burden of CAD and explore factors associated with presence and severity of CAD by CCTA among well-treated PWH. We hypothesized that higher levels of inflammatory markers including high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), and IL-1β would be associated with both the presence and the extent of CAD.

METHODS

Study Population

Participants were recruited from the Copenhagen Comorbidity in HIV Infection (COCOMO) study (NCT02382822), a noninterventional cohort study aiming to assess the burden and pathogenesis of non-AIDS comorbid conditions among the PWH [18]. Inclusion criteria were a positive HIV test result and age >18 years. Between March 2015 and December 2016, 1099 participants were enrolled in the study, representing >40% of the PWH population residing in the area of Copenhagen, Denmark. Participants were offered CCTA at entry. The only exclusion criteria for CCTA were reduced renal function or previous contrast medium–induced anaphylaxis. We included all virologically suppressed PWH (defined as HIV RNA level <50 copies/mL) with a research CCTA scan. We excluded participants with poor-quality CCTA scans.

Patient Consent Statement

All participants provided oral and written informed consent before study inclusion. The COCOMO study (H-8-2014-0004) has been approved by the Ethics Committee of the Capital Region and the Danish Data Protection Agency.

Multidetector Computed Tomographic Angiography Image Acquisition

All CCTA was performed using a 320-detector CT scanner (Aquillion One; Canon Medical Systems) and the same scanning protocol. Unless contraindicated, a cardioselective β1-blocker (metoprolol; 25–150 mg) was administered orally approximately 1 hour before the procedure if the heart rate was >55/min unless contraindicated. Participants with inhaler-treated asthma or chronic obstructive pulmonary disease received 15 mg of ivabradin (Corlentor; Servier). Before image acquisition, a 0.4-mg dose of oral spray glyceryl trinitrate (Nitrolingual; Pohl-Boskamp) was administered. An automatic raw data motion analysis tool (PhaseXact; Toshiba) was used to determine the optimal motion free diastolic phase for reconstruction. Images were reconstructed with 0.5-mm section thickness and increments of 0.25 mm.

CCTA Analysis

Coronary artery stenosis on CCTA scans were analyzed using the Society of Cardiovascular Computed Tomography coronary segment model [13]. Reviewers were blinded to clinical characteristics. Dedicated software, Vitrea 6.7 (Vital Images), was used to perform the analyses.

According to clinical practice and the Coronary Artery Disease—Reporting and Data System (CAD-RADS) (Figure 1) [13], participants were categorized according to the most severe coronary artery lesion identified, as follows: CAD-RADS 0, no atherosclerosis (0% maximal coronary stenosis and no atherosclerosis); CAD-RADS 1 minimal, 1%–24% maximal coronary stenosis or atherosclerosis with no stenosis (only positive remodeling); CAD-RADS 2, mild stenosis (25%–49% maximal coronary stenosis); CAD-RADS 3, moderate stenosis (50%–69% maximal coronary stenosis); CAD-RADS 4a, severe stenosis (70%–99% maximal coronary stenosis); CAD-RADS 4b, severe stenosis (>50% LM stenosis or 3-vessel obstructive [≥70% stenosis] disease); CAD-RADS 5, total occlusions (100% maximal coronary stenosis); and CAD-RADS nondiagnostic, >50% CAD cannot be excluded in patient without obstructive disease in remaining segments. If ≥1 coronary segment was nondiagnostic owing to poor image quality (motion artifacts, poor contrast enhancement, image noise or streak artifacts) the scan was deemed nondiagnostic and excluded from the analyses. For statistical analyses, the CAD-RADS groups were further categorized into 3 levels. Any atherosclerosis was defined as CAD-RADS ≥1, and obstructive CAD was defined as CAD-RADS ≥3, previous coronary angioplasty, or coronary artery bypass graft (CABG).

Biochemistry and Inflammatory Markers Variables

Analysis of hsCRP, low-density lipoprotein, and high-density lipoprotein cholesterol, triglycerides, total cholesterol, and plasma glucose was performed at a single laboratory at the Department of Clinical Biochemistry, Herlev Hospital, Copenhagen University Hospital. hsCRP was analyzed with a high-sensitivity assay using latex-enhanced turbidimetry (Dako) or nephelometry (Dade Behring). For analyses of inflammatory markers, plasma samples were collected at baseline and stored at −80°C until use. IL-1β was analyzed with an enzyme immunoassay (Meso Scale V-Plex Human IL-1β kit) and IL-6 with the magnetic multiplex assay kits from R&D systems. All analyses were done according to the manufacturer's instructions. Absorption was read at 450 nm with wavelength correction set to 540 nm, using a Synergy H1 plate reader (BioTek).

Variable Definitions

As outcome variables, we grouped participants into 3 categories based on their CAD-RADS category: no atherosclerosis (CAD-RADS 0), any atherosclerosis (CAD-RADS ≥1), or obstructive atherosclerosis (CAD-RADS ≥3 or previous coronary angioplasty or CABG). Age was defined as age at the time of CT scanning. We categorized body mass index groups according to World Health Organization definitions [19]. Smoking was

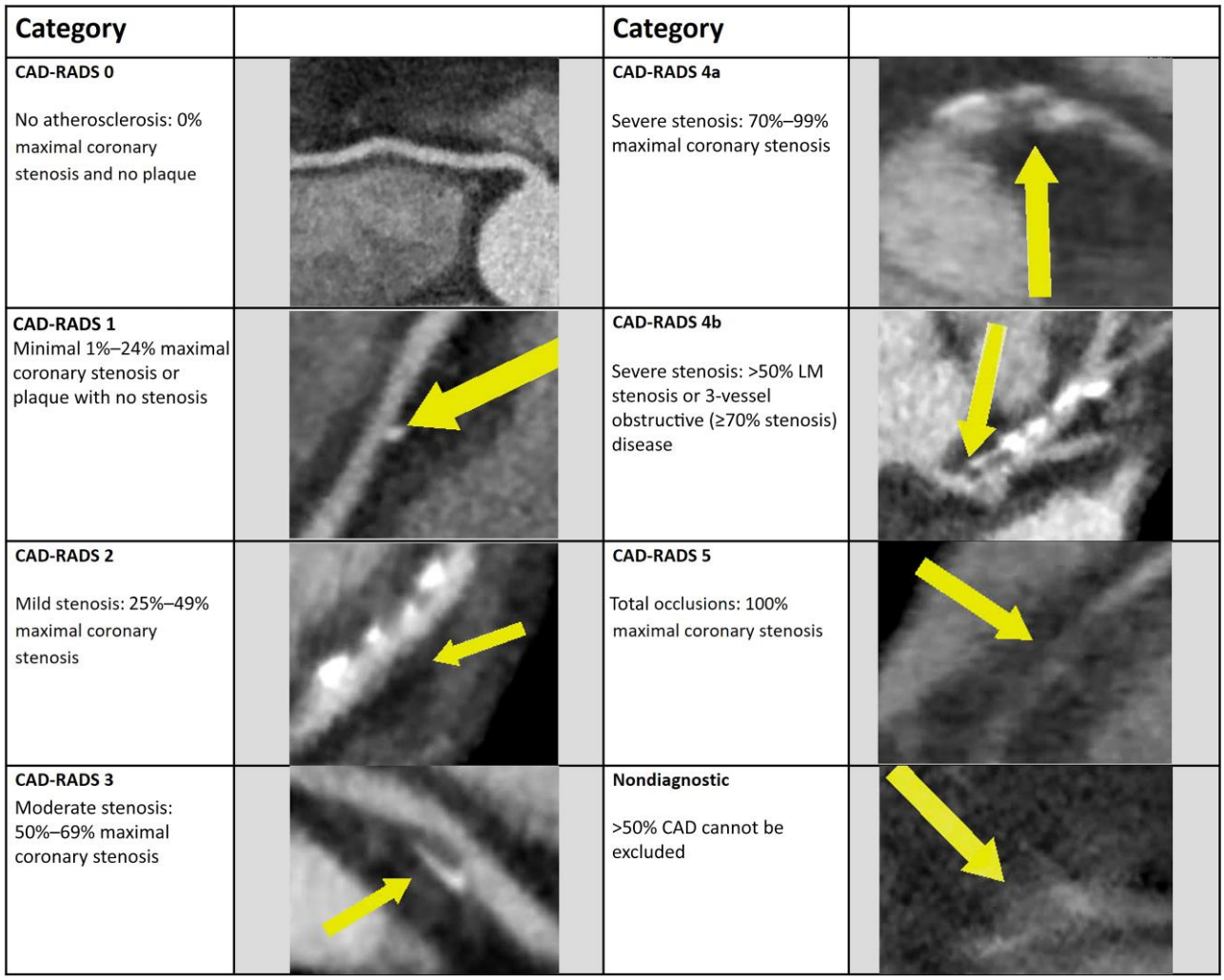

Figure 1. Coronary Artery Disease Reporting and Data System (CAD-RADS) assessment category definitions with examples [13]. The CAD-RADS category is based on the maximum diameter stenosis in coronary segments with diameter ≥ 1.5 mm. Segments were defined according to the segmental anatomy of the coronary arteries outlined by the Society of Cardiovascular Computed Tomography. Abbreviations CAD, coronary artery disease: LM: Left main,.

categorized as never, former, or current smoking. According to guidelines, hypertension was defined as antihypertensive treatment and/or having ≥140 mm Hg systolic and/or ≥90 mm Hg diastolic blood pressure values [20]. Dyslipidemia was defined as low-density lipoprotein levels ≥4.16 mmol/L (160 mg/dL) and/or lipid-lowering treatment (statins) [21]. Framingham risk scores for CVD (10-year risk) were calculated for participants <75 years old; participants with a score of 10% were categorized as low risk, scores of 10%–20% as intermediate risk, and a scores of ≥20% as high risk. High levels of inflammatory markers were defined as values above the 75th percentile for each marker and as >2 mg/L for hsCRP. The CD4 cell count nadir was defined as the lowest recorded CD4 cell count; previous AIDS, as previous AIDS-defining disease; the time since HIV diagnosis, as the time since HIV diagnosis and CT scan; and the use of protease inhibitors, as the use of drugs with the suffix "-navir."

Statistical Analysis

Normally distributed continuous variables were reported as mean and standard deviation (SD), and nonnormally distributed continuous variables as median and interquartile range. Categorical variables were reported as frequencies with percentages.

Groups were compared using *t* tests for normally distributed and Mann Whitney *U* tests for nonnormally distributed continuous data. For categorical data, χ^2 tests were used. Simple and multiple logistic regression models with a prespecified model—including age (per 10-year increase), sex, hypertension, diabetes, and smoking status—were used to

analyze the associations of covariates with any atherosclerosis and/or obstructive CAD.

For inflammatory markers, a simple model including age and sex was used. Associations were expressed as crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs). Model fit and assumptions of normality for parametric tests were evaluated graphically. All tests were 2 sided with an α value of 5%.

Table 1. Study Population Characteristics

Variable	PWH, No. (%)[a] (N = 669)
Age, mean (SD), y	51 (11)
Male sex	596 (89)
Former smoker	240 (36)
Current smoker	186 (28)
Hypertension	284 (42)
Diabetes	19 (2.8)
BMI, mean (SD)[b]	24.6 (3.4)
BMI >30[b]	44 (7)
Dyslipidemia	128 (19)
LDL, mean (SD), mmol/L	2.8 (1)
Use of statin	77 (12)
Framingham risk score, median (IQR)	15 (11–20)
Framingham risk score	
Low (<10%)	289 (43)
Intermediate (≥10 and <20%)	172 (26)
High (≥20%)	153 (23)
Current CD4 cell count <500/μL	142 (21)
CD4 cell count nadir <200/μL	270 (40)
Time since HIV diagnosis, mean (SD), y	14 (9)
Protease inhibitor use	200 (30)
hsCRP, median (IQR), mg/L	1.12 (0.55–2.38)
IL-6, median (IQR), pg/mL	3.23 (2.31–4.31)
IL-1β, median (IQR), pg/mL	0.18 (0.07–0.30)

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; IQR, interquartile range; LDL, low-density lipoprotein; PWH, persons with HIV; SD, standard deviation.

[a]Data represent no. (%) of PWH unless otherwise specified. Percentages in some categories do not add to 100%, owing to missing values for that variable.

[b]BMI calculated as weight in kilograms divided by height in meters squared.

RESULTS

Among the 1099 PWH who were included in COCOMO, CCTA was performed in 724, of whom 686 were virologically suppressed (HIV RNA, <50 copies/mL). We excluded 17 participants owing to poor CCTA image quality, leaving 669 who were included.

For the 669 PWH included, the mean age (SD) was 51 (11) years, and 596 (89%) were men. The transmission mode was primarily men having sex with men (76%) or heterosexual transmission (18%). Few (2%) reported ever using intravenous drugs at the time of CT scanning, 664 (99%) were using combination ART, and the mean (SD) current CD4 cell count was 721/μL (277/μL). The mean (SD) time since HIV diagnosis was 14 (9) years, the mean nadir CD4 cell count was 259/μL (18 /μL), and 270 PWH (40%) had a nadir CD4 cell count <200/μL. The median concentrations of IL-6 and IL-1β are listed in Table 1 and stratified by CAD-RADS category in Supplementary Table 1.

CAD According to Severity of Disease

Of the 669 included PWH, 300 (45%) had evidence of atherosclerosis, and 84 (13%) and 97 (14%), respectively, had minimal or mild (nonobstructive) atherosclerosis. Obstructive CAD was present in 119 participants (18%), of whom 53 (44%) had moderate stenosis, 30 (25%) had severe stenosis, 12 (10%) had ≥1 occluded coronary artery segments, and 24 (20%) had previous coronary angioplasty or CABG (Figure 2*A*). Of the included PWH, 65 (10%) were CAD-RADS nondiagnostic (Supplementary Table 2 presents the demographic characteristics

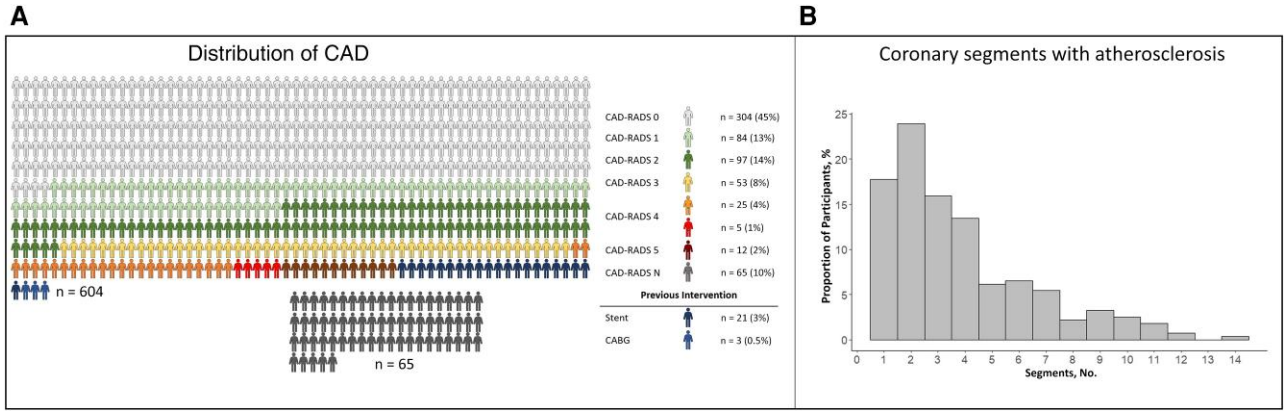

Figure 2. Distribution of coronary artery disease (CAD) among well-treated persons with human immunodeficiency virus. *A,* Coronary Artery Disease Reporting and Data System (CAD-RADS) categories for each of the 669 study participants. *B,* Histogram showing the number of coronary segments with atherosclerosis among participants with atherosclerosis irrespective of stenosis grade (segment involvement score). Segments were defined according to the segmental anatomy of the coronary arteries outlined by the Society of Cardiovascular Computed Tomography [13]. Abbreviation: CABG, coronary artery bypass graft.

of nondiagnostic cases). The median number of coronary segments with atherosclerosis was 3 (range, 1–14; interquartile range, 2–5). Figure 2*B* depicts the number of segments with atherosclerosis among participants who have atherosclerosis, corresponding to the segment involvement score [22].

Traditional Risk Factors and CAD

Estimates for the univariable and multivariable analyses of potential risk factors and CAD are presented in Supplementary Table 3 and Table 2, respectively. In univariable analyses, traditional risk factors for CAD, including age, male sex, hypertension, diabetes, smoking, and dyslipidemia, were all associated both with any atherosclerosis and with obstructive CAD.

In multivariable analyses adjusted for our prespecified model (adjustments for age, sex, smoking status, diabetes, and hypertension), any atherosclerosis was associated with older age, male sex, hypertension, current smoking, dyslipidemia, and body mass index >30 (calculated as weight in kilograms divided by height in meters squared). Obstructive CAD was associated with older age, hypertension, diabetes, current smoking, and dyslipidemia.

Framingham Risk Scores and CAD

Figure 3 depicts the distribution of CAD stratified by Framingham risk scores. Compared with PWH with low Framingham risk scores, those with intermediate scores had ORs of 4.16 (95% CI, 2.76–6.27) for any atherosclerosis and 3.92 (2.11–7.29) for obstructive CAD. Compared with PWH with low Framingham risk scores, those with high scores had ORs of 13.51 (95% CI, 8.12–22.49) for any atherosclerosis and 11.47 (6.34–20.75) for obstructive CAD.

HIV-Related Risk Factors and CAD

Of HIV-related variables, CD4 cell count nadir <200/μL, previous AIDS, time since HIV diagnosis, and use of protease inhibitors were associated with any atherosclerosis and with obstructive CAD in univariable analyses. In multivariable analyses, we found that time since HIV diagnosis, and current protease inhibitor use were associated with obstructive CAD (Table 2). Controlling for dyslipidemia did not change the parameter estimates for the association between protease inhibitor use and CAD significantly. In both univariable and multivariable analyses, higher current CD4 cell count was associated with *lower* odds of any atherosclerosis. No other HIV-related variables were associated with any atherosclerosis or obstructive CAD (Table 2)

Inflammatory Markers and CAD

In univariable analyses, high concentrations of IL-6 and hsCRP values >2 mg/L were associated with any atherosclerosis, and high levels of IL-6 were also associated with obstructive CAD. IL-1β levels were not associated with coronary atherosclerosis (Table 3). In multivariable analyses adjusted for age and sex, high levels of IL-6 were associated with obstructive CAD (adjusted OR, 1.86 [95% CI, 1.13–3.08]; $P = .02$) but not with any atherosclerosis. Levels of IL-1β and hsCRP were not associated with coronary atherosclerosis (Table 4), and no inflammatory markers were associated with CAD indices in models that included traditional cardiovascular risk factors (presented in Table 2). Associations between inflammatory markers and traditional and HIV-related variables are listed in Supplementary Table 4.

Table 2. Risk Factors and Adjusted Odds of Any Atherosclerosis or Obstructive Coronary Artery Disease

	Adjusted OR[a] (95% CI); *P* Value	
Variable	Any Atherosclerosis	Obstructive CAD
Age per decade older	3.38 (2.64–4.33); <.001	2.85 (2.19–3.73); <.001
Male sex	2.70 (1.64–5.42); .005	1.20 (.49–2.92); .69
Hypertension	1.57 (1.05–2.37); .03	1.66 (1.01–2.75); .046
Diabetes	2.87 (.80–10.38); .11	2.90 (1.02–8.24); .045
Former smoker	1.39 (.86–2.23); .18	1.95 (.52–1.72); .86
Current smoker	1.71 (1.04–2.82); .04	2.30 (1.24–4.26); .008
Dyslipidemia[b]	1.81 (1.05–3.13); .03	2.01 (1.11–3.67); .02
BMI >30 vs normal BMI[c]	3.37 (1.43–7.93); .005	1.26 (.48–3.32); .64
Current CD4 cell count <500/μL	0.58 (.35–.97); .04	0.93 (.52–1.64); .80
CD4 cell count nadir <200/μL	1.04 (.68–1.58); .87	1.53 (.94–2.47); .09
CD4/CD8 ratio	1.03 (.67–1.58); .90	1.27 (.82–1.99); .29
Time since HIV diagnosis (per 5 y)	1.16 (1.02–1.31); .02	1.34 (1.16–1.55); <.001
Protease inhibitor use	1.49 (.96–2.31); .08	1.73 (1.06–2.84); .03
INSTI use	0.71 (.46–1.10); .12	0.94 (.56 1.58); .82
High level of IL-6	1.02 (.62–1.68); .94	1.56 (.90–2.69); .11
High level of IL-1β	0.95 (.61–1.50); .84	1.01 (.57–1.77); .98
hsCRP >2 mg/L	1.11 (.66–1.86); .70	1.11 (.66–1.86); .70

Abbreviations: CAD, coronary artery disease; BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; INSTI, integrase strand transfer inhibitor; OR, odds ratio.

[a]Adjusted ORs for the associations between risk factors and any atherosclerosis (defined as ≥1% coronary artery stenosis) or obstructive CAD (defined as ≥50% coronary artery stenosis). Adjustments were based on a prespecified model and included age, sex, hypertension, diabetes, and smoking status. High levels of inflammatory marker were defined as the upper quartile for each respective marker and as >2 mg/L for hsCRP.

[b]Only among participants without previous coronary intervention (coronary artery bypass graft or stent).

[c]BMI calculated as weight in kilograms divided by height in meters squared.

DISCUSSION

Among 669 well-treated PWH, almost half had any atherosclerosis, and 18% had obstructive CAD. Traditional risk factors, current protease inhibitor use, and time since HIV diagnosis were associated with both any atherosclerosis and with obstructive CAD in models adjusted for common confounders, including age. We found that high concentrations of IL-6 were associated with obstructive CAD independently of age and sex, but the association was attenuated after further adjustment

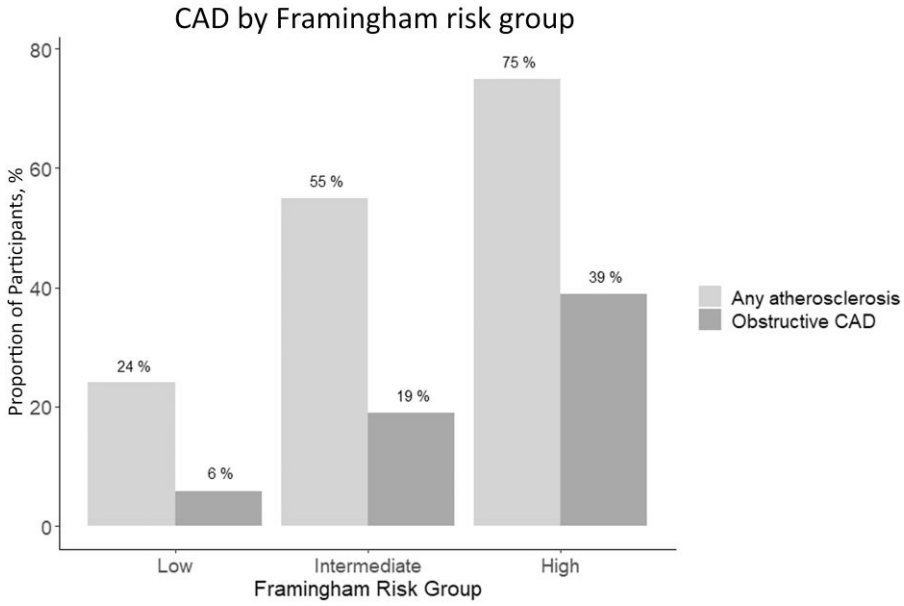

Figure 3. Coronary artery disease (CAD) stratified by Framingham risk scores. Any atherosclerosis was defined as ≥1% coronary artery stenosis; obstructive CAD, as ≥50% coronary artery stenosis. Low risk was defined as <10%, intermediate risk as ≥10% and <20%, and high risk as ≥20%.

Table 3. Inflammation and Crude Odds of Any Atherosclerosis or Obstructive Coronary Artery Disease

	OR (95% CI)[a]	
Variable	Any Atherosclerosis	Obstructive CAD
High level of IL-6	2.57 (1.73–3.81); <.001	2.83 (1.82–4.40); <.001
High level of IL-1β	0.90 (.62–1.29); .56	1.01 (.63–1.63); .96
hsCRP >2 mg/L	1.68 (1.18–2.39); .004	1.45 (.94–2.22); .09

Abbreviations: CAD, coronary artery disease; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; OR, odds ratio.

[a]Crude (unadjusted) association between high levels of inflammatory markers and any atherosclerosis (defined as ≥1% coronary artery stenosis) or obstructive CAD (defined as ≥50% coronary artery stenosis).

Table 4. Inflammation and Adjusted Odds of any Atherosclerosis or Obstructive Coronary Artery Disease

	Adjusted OR (95% CI)[a]	
Variable	Any Atherosclerosis	Obstructive CAD
High level of IL-6	0.96 (.57–1.60); .87	1.86 (1.13–3.08); .02
High level of IL-1β	0.85 (.55–1.33); .48	0.93 (.55–1.58); .79
hsCRP >2 mg/L	1.37 (.90–2.07); .14	1.08 (.66–1.74); .77

Abbreviations: CAD, coronary artery disease; CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; IL-1β, interleukin 1β; IL-6, interleukin 6; OR, odds ratio.

[a]Minimally adjusted association between high levels of inflammatory markers and any atherosclerosis (defined as ≥1% coronary artery stenosis) or obstructive CAD (defined as ≥50% coronary artery stenosis). ORs were adjusted for age and sex.

for cardiovascular risk factors, suggesting that inflammation may mediate the association between traditional risk factors and CAD.

A large metanalysis concluded that the risk of CVD events in PWH were twice that in uninfected persons [23]. This observation has sparked an interest in the study of subclinical or preclinical CAD among PWH using noninvasive cardiac CT [16, 24]. Our prevalence estimates are comparable to data from the Swiss HIV cohort (median age, 52 years; 86% male), which reported that 53% of PWH had atherosclerosis and 13% had obstructive disease [16]. In North American PWH of similar age, the prevalence seems to be higher. Thus, the Canadian HIV and Aging Cohort Study (mean age, 56 years; 92% male) reported that 70% of 155 PWH had atherosclerosis and 20% had obstructive disease, and the Multicenter AIDS Cohort Study (MACS) (mean age, 53 years) reported that 78% of 618 HIV-infected men had atherosclerosis and 17% had obstructive disease [15, 17]. The discrepancies could, at least in part, be attributed to better virological control and lower levels of inflammation and/or differences in CVD risk profiles in the European cohorts. Regardless, our data show that 1 in 5 of middle-aged, well-treated PWH have obstructive CAD, with potential deleterious impact on both survival and quality of life [25, 26].

The pathogenesis of CAD in PWH likely reflects an intricate interplay between both traditional and HIV-related factors that may accelerate the development of atherosclerosis [27]. In line with findings from the Swiss HIV cohort [16], we found that traditional risk factors were associated with higher odds of both having any atherosclerosis and obstructive CAD. Smoking, dyslipidemia, and hypertension, in particular, have been subject to scrutiny as these risk factors are both modifiable and prevalent among PWH [28, 29]. The fact that current

smoking, but not former smoking, was associated with higher odds of CAD, emphasizes the importance of smoking cessation.

To identify individuals who might benefit from risk factor modification, the European AIDS Clinical Society guidelines recommend Framingham risk score evaluation in men with HIV >40 and women with HIV >50 years old [30]. In the well-treated, mainly white participants in COCOMO, Framingham risk scores were able to classify participants reasonably well, and obstructive CAD was uncommon among those with low Framingham scores. In contrast, 39% of participants with high Framingham scores had obstructive CAD, and >4 in 5 had coronary atherosclerosis. This suggests that although Framingham risk scores may underestimate the risk of future cardiovascular events in PWH [31], this tool does identify most individuals with atherosclerosis in a population of PWH without viral replication.

The discrepancy between Framingham risk score and actual risk of major CVD events has been attributed to HIV-related factors, including immune dysfunction, ART toxicity, and chronic inflammation and immune activation [2, 3, 27, 32]. This may be reflected in the association between CAD and time since HIV diagnosis, which may reflect a longer treatment-naive period and/or history of earlier severe immune dysfunction, as prompt initiation of ART for all with newly diagnosed HIV was recommended by guidelines only after 2015.

We found that history of severe immune dysfunction or previous AIDS was associated with CAD only in the univariable analyses and not after adjustment for age and other potential confounders. Current use of protease inhibitors, however, was associated with approximately 50% higher odds of CAD in both univariable and in multivariable analyses. Protease inhibitors, especially first generation, are known to perturb lipid metabolism, but more recent findings indicate that contemporary protease inhibitors may also be associated with higher risk of CVD, and the risk seems to be independent of dyslipidemia [33–35]. The Swiss HIV cohort similarly investigated this in 403 PWH and found a borderline association with atazanavir but not with protease inhibitors as a group [36]. A participant's current ART regimen, however, may reflect management decisions owing to failure of historical therapy, and the effect estimate could be subject to unmeasured confounding. Future prospective studies are needed to clarify whether protease inhibitor use confers an atherogenic effect.

Both hsCRP and IL-6 were associated with CAD in univariable analyses. Chronic inflammation is an established risk factor for atherosclerosis, and unspecific inflammatory markers, including IL-6 and hsCRP, have been associated with CVD in PWH [3]. After adjustment for age and sex, high concentrations of IL-6 remained associated with obstructive CAD, but IL-6 was no longer associated with any atherosclerosis, and adjustment for cardiovascular risk factors further attenuated the association, which may imply that inflammation lies on the causal pathway between traditional cardiovascular risk factors and CAD. This differed from findings in the REPRIEVE trial, in which IL-6 was associated with CAD in multivariable models adjusted for traditional and HIV-related risk factors [37].

IL-1β is an upstream proinflammatory cytokine. Effective inhibition of IL-1β–induced inflammation decreases the risk of cardiovascular events in uninfected individuals with prior myocardial infarction [7, 38]. In the context of HIV infection, a smaller study found that treatment withIL-1β antibodies lowered arterial inflammation in PWH over a period of 12 weeks [10]. As HIV-related factors including immune function have been associated with the IL-1β pathway, the IL-1 family could link HIV infection to CVD [39, 40]. We did not find concentrations of IL-1β to be associated with CAD in well-treated PWH. In contrast, a case-control study found activity of the IL-1 family to predict first time myocardial infarction in PWH [9]. The discrepancy might be explained by differences in risk profile. Moreover, infarction likely represents an entity distinct from stable CAD, and active inflammation may play a more prominent role in plaque rupture and acute coronary events than in stable atherosclerosis.

Our study has strengths, including a large, well-characterized cohort in which data were collected prospectively, but it also has some important limitations. Participants in COCOMO live in Copenhagen and are primarily men of Scandinavian descent. Thus, results may not be applicable to women and to persons from other ethnic groups in other countries. Moreover, the cross-sectional nature of the analyses precludes conclusions regarding causality.

In conclusion, almost half of middle-aged, well-treated PWH had angiographically verified atherosclerosis, and <1 in 5 had obstructive CAD. Traditional cardiovascular risk factors, current protease inhibitor use, and time since HIV diagnosis were associated with both any atherosclerosis and with obstructive CAD. High concentrations of IL-6 and hsCRP were univariable associated with CAD, but adjustment for cardiovascular risk factors attenuated the association, suggesting that inflammation may mediate the association between traditional risk factors and CAD.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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wrote the first draft. All authors contributed to later versions and have read and approved the final manuscript.

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